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Effect of a Dual-Formula of *Picralima nitida* and *Cymbopogon citratus* Extract on Expression of APC and P53 Genes in Benzene-Induced Haematotoxicity in Wistar Rats

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ABSTRACT: The leaves of *Picralima nitida* and *Cymbopogon citratus* are potential therapeutic agents; studies have explored their role in modulating gene expression. Therefore, this study aims to determine the effect of a dual formula of *Picralima nitida* and *Cymbopogon citratus* extracts on p53 and APC genes in benzene-induced haematotoxicity in Wistar rats. 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 p53 and APC 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. Polymerase Chain Reaction was used to measure gene expression. The result showed that groups B and C exhibited elevated p53 expression compared to the control, with Group C showing a higher increase than Group B. Regarding APC expression, Group C had higher levels than Groups A and B. In contrast, Groups D, E, and F exhibited reduced APC expression compared to Groups A and C (p <0.05). In conclusion, the dual-formula extract demonstrated therapeutic potential by modulating p53 and APC gene expression and alleviating oxidative stress.

Keywords: Adenomatous Polyposis Coli Gene, Tumour Protein-53 Gene, *Picralima nitida* leaves, *Cymbopogon citratus* leaves, Benzene.

Introduction

Haematotoxicity is a condition characterised by toxic effects on the blood and bone marrow, which can result in severe haematological disorders, including anaemia, leukopaenia, thrombocytopaenia, and even haematologic malignancies (Zandee *et al*., 2019). One of the major environmental and occupational toxins linked to haematotoxicity is benzene, a widely used industrial solvent and chemical precursor (Elsayed, 2015). Chronic exposure to benzene has been well documented to cause oxidative stress, genetic mutations, and disruptions in normal haematopoiesis, ultimately leading to bone marrow suppression and increased susceptibility to haematological malignancies, including leukaemia (Spatari *et al*., 2021; Lu *et al*., 2020). Benzene exerts its toxic effects primarily by generating reactive oxygen species (ROS), which induce oxidative damage to critical biomolecules such as DNA, lipids, and proteins (D'Souza *et al*., 2024). Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen, such as superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH) (Ozougwu *et al*., 2016). These molecules cause oxidative stress by overwhelming the body's natural antioxidant defence mechanisms, leading to structural and functional damage at the cellular and molecular levels (Sahoo *et al*., 2022). In the haematopoietic system, excessive ROS production disrupts the delicate balance required for normal blood cell development, leading to cytotoxicity, genomic instability, and increased apoptotic cell death (Ghaffari, 2008).

Beyond direct cytotoxicity, benzene-induced oxidative stress can also lead to dysregulation of tumour suppressor genes like Adenomatous Polyposis Coli (APC) and Tumour Protein p53 (P53). These genes are

essential for maintaining genomic integrity and preventing malignant transformation. The APC gene is a regulator of the Wnt signalling pathway, which controls cellular proliferation, differentiation, and apoptosis (Hoenerhoff *et al*., 2009). This pathway is important for normal haematopoietic cell development and renewal (Staal and Luis, 2010). However, oxidative stress induced by benzene can inactivate or mutate the APC gene, leading to aberrant activation of the Wnt pathway. This results in uncontrolled cell proliferation, loss of differentiation, and increased susceptibility to leukemogenesis (Lu *et al*., 2020). Additionally, APC dysfunction can impair apoptosis, allowing the survival of genetically damaged hematopoietic cells that would otherwise be eliminated (Warr er al., 2011). The P53 gene, widely regarded as the "guardian of the genome," plays a role in maintaining cellular homeostasis. It acts as a transcription factor that responds to DNA damage by activating genes involved in cell cycle arrest, DNA repair, and apoptosis (Feroz and Sheikh, 2020). Under normal physiological conditions, p53 prevents the accumulation of mutations by eliminating cells with severe genetic damage (Speidel, 2015). However, oxidative stress can suppress P53 expression, induce mutations, or promote post-translational modifications that impair its function. As a result, cells with damaged DNA escape apoptosis and continue to divide, increasing the risk of leukemogenesis (Cordani *et al*., 2020; Dai and Gu, 2010).

Given the increasing concerns about benzene-induced haematotoxicity, there is a need for effective interventions that can reduce its toxic effects. Natural phytochemicals have gained significant attention due to their antioxidative, anti-inflammatory, and cytoprotective properties (Forni *et al*., 2019). *Picralima nitida* (commonly known as the "Akuamma plant") and *Cymbopogon citratus* (commonly known as "Lemongrass") are two medicinal plants that have been traditionally used for their therapeutic benefits, including antimicrobial, analgesic, anti-inflammatory, and antioxidant activities. *Picralima nitida* is rich in alkaloids, such as akuammine and akuammicine, which exhibit potent antioxidative and anti-inflammatory properties (Erhauyi *et al*., 2014). These bioactive compounds have been shown to modulate oxidative stress pathways and enhance haematopoietic function (Obazelu and Gaius-Igboanugwo, 2024). Similarly, *Cymbopogon citratus* contains flavonoids, phenolic compounds, and essential oils, such as citral, which are known for their free radical scavenging ability, cytoprotective effects, and role in enhancing DNA repair mechanisms (Oladeji *et al*., 2019).

Despite the extensive individual studies on these two plants, there is limited research on the combined (dual-formula) therapeutic effect of *Picralima nitida* and *Cymbopogon citratus* against benzene-induced haematotoxicity, particularly concerning their impact on APC and P53 gene expression. Investigating this dual-formula approach may provide insights into its potential to restore haematopoietic integrity, reduce oxidative DNA damage, and modulate critical tumour suppressor genes involved in benzene toxicity. Therefore, this study aims to evaluate the effects of a dual-formula of *P. nitida* and *C. citratus* extract on APC and P53 genes in benzene-induced haematotoxicity in Wistar rats.

Materials and methods

Animals used: Sixty healthy albino Wistar rats were obtained from the Anatomy Department at the University of Benin in Benin City, Nigeria, and subsequently housed in their animal facility.

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 the Ovia Northeast area on August 23, 2024. Identification and authentication of the leaves were carried out by Prof. A.O. Akinnibosun from the Department of Plant Biology and Biotechnology at the University of Benin.

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, 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 h) to ensure complete dryness. Once dried, the leaves were ground using an industrial 1000A high-speed grinder. The precise weight of 250 g was measured for each leaf type for further use.

Preparation of plant extract: About 2.5 L of distilled water were mixed with 250 g of the pulverised plant powder. After that, the combination was left to steep for a full day under carefully monitored storage conditions. Thereafter, 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.

Care of animals: 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, with a 12-h light/dark cycle. Before the experiment started, the rats were allowed to acclimatise for two weeks.

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

Research design and administered doses of the dual-blend of C. citratus and P. nitida leaves extract: 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 was given standardised feed and clean water only. Group B was exposed solely to benzene solution through intraperitoneal injections every 48 h. Group C received benzene intraperitoneally along with treatment using the standard drug solution, cyclophosphamide. Group D was administered benzene intraperitoneally and treated orally with a low dose of *C. citratus* and *P. nitida* leaves extract. Similarly, Group E received benzene intraperitoneally but was treated orally with a higher dose of the herbal formulation, while Group F was exposed to benzene intraperitoneally and received the highest dosage of the herbal preparation.

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 h. The cyclophosphamide group (C) was administered 0.2 mL of 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 a 48-h 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-h intervals 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-h intervals for 28 days and was administered 0.6 mL of a 400 mg/kg of *C. citratus* and *P. nitida* leaves extract orally daily through a gavage tube (Obazelu and Olorunda, 2024).

Preparation of benzene solution: Distilled water, 2-propanol, and benzene were combined in a 1:5:5 ratio to prepare the benzene solution. Over the course of 28 days, each animal weighing around 150 g received a dosage of 0.2 mL of this solution every 48 h.

Preparation of 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 0.3 mL of this solution orally. The administration was carried out every 48 hours for a duration of 28 days.

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 min, then at 42 °C for 1 h, and finally at 80 °C for 5 min. 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 visualised on an agarose gel, and gene expression was normalised to GAPDH. The intensity of the bands on the gel was quantified using ImageJ software (Elekofehinti *et al*., 2020). The primers used for amplification were as follows: p53 (Forward: ACATGACTGAGGTCGTGAGA, Reverse: GATTTCCTTCCACCCGGATAAG), APC (Forward: GCAAGTTGAGGCCCTGAAGA, Reverse: GCAGCTGCTTAAGTACTTCCTTC), and GAPDH (Forward: AGACAGCCGCATCTTCTTGT, Reverse: CTTGCCGTGGGTAGAGTCAT).

Statistical analysis: GraphPad Prism software was used to analyse the data and generate bar charts depicting mRNA gene expression. P-value of less than 0.05 was considered significant.

Results

Figure 1 illustrates expression levels of p53 in all the groups studied, with each group's p53 expression represented by a specific bar on the bar chart. Groups B (Benzene) and C (Benzene + Cyclophosphamide) had higher p53 expression compared to the control (Group A), with Group C also showing a higher expression than Group B. Groups E (Benzene + 200 mg/kg of *P. nitida* and *C. citratus* leaves extract) and F (Benzene + 400

mg/kg of *P. nitida* and *C. citratus* leaves extract) had lower p53 expression than Group B, while Group F also had lower expression compared to the control. Additionally, Groups D (Benzene + 100 mg/kg of *P. nitida* and *C. citratus* leaves extract), E, and F had lower expression compared to Group C, with Group F showing significantly lower expression than Group E ($p < 0.05$).

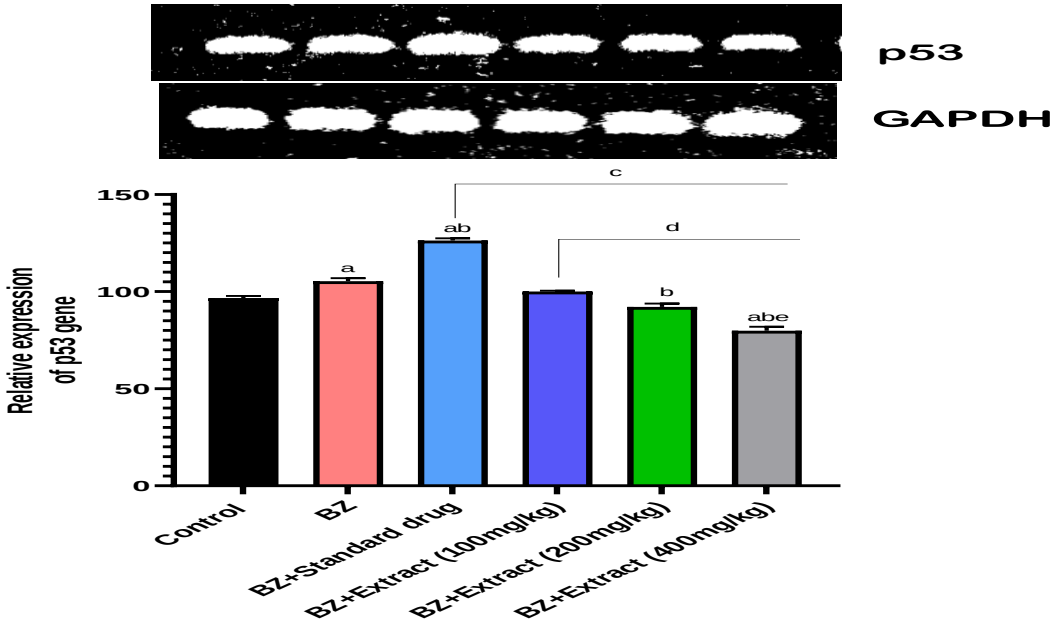

Figure 1: mRNA expression of p53 in the studied groups with error bars representing the mean ± SEM. BZ is used to denote the benzene group. Statistical significance was determined at $p < 0.05$. The letters a, b, c, d, and e indicate significant differences when compared to groups A, B, C, D, and E, respectively.

Expression levels of APC in all the groups studied is depicted in Figure 2. Group C (Benzene + Cyclophosphamide) had higher expression of APC when compared to groups A (Control) and B (Benzene). Groups D (Benzene + 100 mg/kg of *P. nitida* and *C. citratus* leaves extract), E (Benzene + 200 mg/kg of *P. nitida* and *C. citratus* leaves extract) and F (Benzene + 400 mg/kg of *P. nitida* and *C. citratus* leaves extract) had lower expression of APC when compared to groups A and C. Group E and F had lower expression of APC compared to group B ($p < 0.05$).

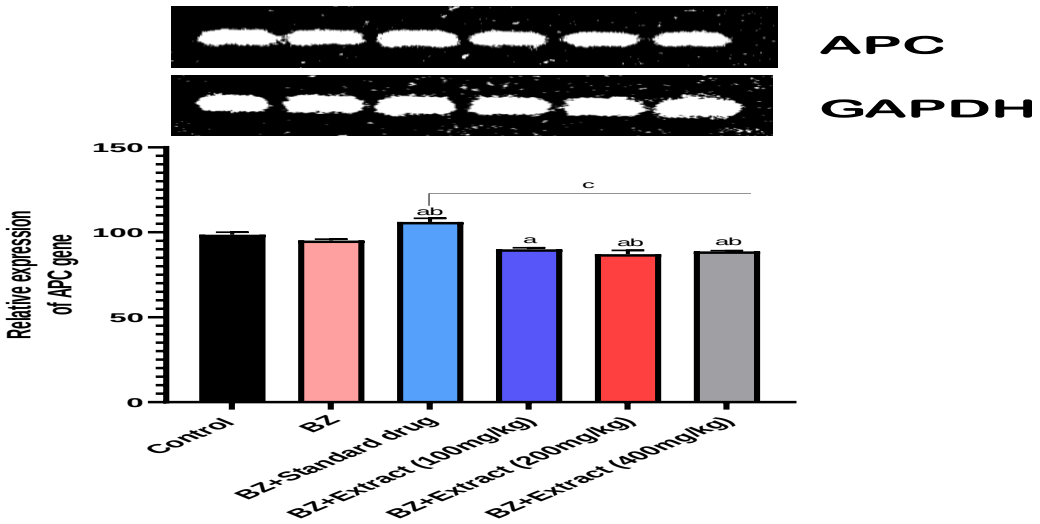

Figure 2: mRNA expression of APC in the studied groups, with error bars representing the mean ± SEM. BZ is used to denote the benzene group. Statistical significance was determined at $p < 0.05$. The letters a, b, c, d, and e indicate significant differences when compared to groups A, B, C, D, and E,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

Discussion

Benzene, a widely recognised environmental and occupational toxin, poses a significant threat to human health, particularly affecting the hematopoietic system (Galbraith *et al*., 2010). Chronic exposure has been linked to hematotoxicity, characterised by bone marrow suppression, anaemia, leukopenia, and an increased risk of haematological malignancies (Snyder, 2012). At the molecular level, benzene-induced toxicity is associated with DNA damage, oxidative stress, and disruptions in key regulatory genes, including Adenomatous Polyposis Coli (APC) and Tumour Protein 53 (P53). These genes play important roles in cell cycle regulation, apoptosis, and tumour suppression, making them essential biomarkers for evaluating the impact of toxic insults and potential therapeutic interventions (Badham *et al*., 2010).

In recent years, there has been growing interest in the use of natural compounds as protective and therapeutic agents against chemically induced toxicities (Altomare *et al*., 2022). *Picralima nitida* (commonly known as *Akuamma*) and *Cymbopogon citratus* (*Lemongrass*) are two medicinal plants with well-documented pharmacological properties, including antioxidant, anti-inflammatory, and cytoprotective effects (Obazelu and Ogiza, 2024). *Picralima nitida* contains alkaloids with potential haematopoietic and anti-cancer properties, while *Cymbopogon citratus* is rich in flavonoids, phenolics, and essential oils known for their free radical scavenging and anti-apoptotic activities (Obazelu and Gaius-Igboanugwo, 2024). The combination of these two botanicals may offer a synergistic protective effect against benzene-induced haematotoxicity by modulating oxidative stress and preserving genetic integrity (Obazelu and Williams, 2024). This study investigates the effect of a dual formula of *Picralima nitida* and *Cymbopogon citratus* extract on APC and P53 gene expression in benzene-induced hematotoxicity in Wistar rats. The research aimed to determine whether this herbal formulation can mitigate the toxic effects of benzene by restoring normal gene expression patterns, thereby preserving haematopoietic function and preventing genomic instability.

In this study, the expression pattern of p53 offers information on the cellular response to benzene-induced haematotoxicity and the potential protective role of *P. nitida* and *C. citratus* extracts. Since p53 is a well-established regulator of apoptosis and DNA repair, changes in its expression reflect the extent of cellular damage and the effectiveness of potential therapeutic interventions (Amaral *et al*., 2010). Benzene administration led to a significant increase in p53 expression compared to the control group. This is expected, as benzene is a well-documented haematotoxicant that generates oxidative stress and DNA damage, triggering a p53-mediated response to counteract the cellular injury. The body responds to benzene-induced genotoxicity by activating p53 to promote either DNA repair or apoptosis to remove severely damaged cells, thus preventing malignant transformation (Haschek *et al*., 2004). This finding is in agreement with previous studies that have linked the upregulation of p53 expression to benzene exposure (Uzma *et al*., 2010; Boley *et al*., 2002).

It was also observed that an even higher p53 expression was observed in the group administered benzene and cyclophosphamide, more than in the group administered only benzene. Cyclophosphamide is a well-known chemotherapeutic and immunosuppressive agent that induces DNA crosslinking, leading to heightened genomic stress (Rehman *et al*., 2012). Its combined effect with benzene likely worsens DNA damage, thereby needing a stronger activation of p53 to initiate apoptosis or cell cycle arrest. This also confirms the role of p53 as a sensor of cellular damage and highlights the compounded toxic effects of benzene and cyclophosphamide (Achanta and Huang, 2004). However, the groups that received different doses of the dual extract formulation showed a progressive reduction in p53 expression compared to benzene-only exposed groups. The most notable reduction was observed in the group administered the highest dose of the extract, where p53 expression was not only lower than in benzene-exposed groups but also lower than in the control group. This pattern suggests a protective effect of *P. nitida* and *C. citratus* extracts in mitigating benzene-induced stress. This finding aligns with previous research that has linked both these plants to oxidative stress mitigation (Obazelu and Williams, 2024). The reduction in p53 expression implies that the extracts may be counteracting oxidative damage, thereby reducing the need for p53 activation. Since p53 is primarily upregulated in response to cellular distress (Lazo, 2017), its lower expression in extract-treated groups suggests that the extract formulation might be enhancing antioxidant defences and DNA repair mechanisms, thereby preventing significant cellular damage that would otherwise need p53-mediated apoptosis.

The APC gene plays a role in regulating cell proliferation, differentiation, and apoptosis, primarily through its involvement in the Wnt signalling pathway (Hankey *et al*., 2018). A decrease or dysregulation in APC expression has been linked to increased cell survival and potential malignant transformation, making it a key marker in evaluating hematotoxicity (Zhang and Shay, 2017). In this study, the group administered benzene and cyclophosphamide had the highest APC expression compared to both the control and the group administered benzene only. This suggests that the combination of benzene and cyclophosphamide induced significant cellular stress, leading to an upregulation of APC as part of a mechanism to reduce excessive cell proliferation or DNA damage. Cyclophosphamide, known for its cytotoxic effects (Rehman *et al*., 2012), likely triggered a heightened APC response to suppress abnormal cell growth and promote apoptosis, similar to its role in various

chemotherapy-induced cellular responses. The groups that received the dual formula of *P. nitida* and *C. citratus* had lower APC expression compared to the control group and the group administered benzene and cyclophosphamide. This might mean the extract may have a regulatory effect on APC expression, possibly by reducing oxidative stress and DNA damage, thereby lowering the need for APC activation. Since APC is often upregulated in response to cellular distress, its lower expression in extract-treated groups could indicate a reduction in hematotoxicity, reinforcing the protective effect observed with p53 expression (Catalano *et al*., 2021).

Another observation was that the groups administered 200 mg/kg and 400 mg/kg had significantly lower APC expression compared to the group administered benzene only. This suggests that the herbal extract not only mitigated the harmful effects of benzene but also downregulated APC to levels lower than those observed in benzene-exposed rats. This aligns with the hypothesis that the extract exerts a protective, possibly antioxidant-mediated, effect in counteracting benzene-induced toxicity (Obazelu and Williams, 2024).

Conclusion

The study indicates that benzene exposure leads to an upregulation of p53 expression, reflecting a cellular response to genotoxic stress. The administration of a combined extract of *Picralima nitida* and *Cymbopogon citratus* results in a dose-dependent reduction of p53 expression. Benzene combined with cyclophosphamide led to an increase in APC gene expression, while treatment with the combined extracts of *Picralima nitida* and *Cymbopogon citratus* resulted in a dose-dependent decrease in APC expression.

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