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Research Article

Evaluation of the Effect of *Kigelia africana* Seed Oil on the Antioxidant Status of Cisplatin Treated Wistar Rats

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ABSTRACT

Cisplatin is a well-known chemotherapeutic agent that has been successfully used to treat cancer of the lung, neck, bladder, ovary, and testicle. This medication though an important chemotherapeutic agent, has the potential to induce oxidative stress. The aim of this study was to evaluate the effect of *Kigelia africana* seed oil (KASO) on the antioxidant status and lipid profile of Wistar rats Administered to cisplatin. A total of 48 adult male albino rats were divided into six groups of 8 rats each. Group I (normal control) was fed only rat chow. Groups II–VI were administered 7 mg/kg of cisplatin. Groups III-V were administered 0.5, 1, 1.5 ml/kg of KASO, and group VI was administered 0.5 ml/kg of omega-3 oil. Oil administration lasted for 21 days, after which blood samples were drawn from the animals by cardiac puncture. Biochemical parameters were determined using standard procedures. The results obtained from this study showed that cisplatin markedly lowered antioxidant (superoxide dismutase (SOD), catalase (CAT), and glutathione reductase (GSR)) and raised malondialdehyde (MDA). However, a contrary observation was made following the administration of KASO. In conclusion, it can be deduced that *Kigelia africana* seed oil can mitigate cisplatin induced oxidative stress by enhancing antioxidant enzyme activities and reducing lipid peroxidation. Thus, may be ideal for use as an adjuvant to ameliorate chemotherapy-induced oxidative stress.

Keywords: *Kigelia Africana; Seed; Oil; Antioxidant; Malondialdehyde*

INTRODUCTION

Cisplatin has been clinically proven to be effective in treating various types of cancers, including sarcomas, cancers of soft tissue, bone, muscles, and blood vessels (Desoize and Madoulet, 2002). However, the efficacy of cisplatin as a therapy against solid tumors is significantly hindered by its toxic effects on different tissues, which limits its clinical applications (Rashids *et al*., 2021). One major mechanism through which cisplatin exerts its toxicity is the intensive generation of reactive oxygen species, leading to oxidative stress and its associated consequences, such as hepatic damage (Yen *et al*., 2003; Rashids *et al*., 2021). This suggests that efforts to optimize the clinical use

of cisplatin should prioritize the maintenance of redox homeostasis by incorporating antioxidants as co-adjuvants in cisplatin administration. This strategy can help combat cisplatin-induced oxidative stress.

Compounds that have the ability to stop or prevent the oxidation of a substrate at much lower levels than the substrate itself are called antioxidants. They are broadly classified as natural and synthetic (Jwad and Alkazemi, 2019). Several synthetic antioxidants, such as butylated hydroxytoluene (BHT), n-propyl gallate (PG), and butylated hydroxyanisole (BHA), have been used for this purpose but have failed due to safety concerns, making natural antioxidants a more appealing option (Liang *et al*., 2015). Plants are rich in phytochemicals with impressive antioxidant properties (Nijveldt *et al*., 2001), and *Kigelia africana* is no exception.

Kigelia africana, also known as the sausage or cucumber tree, is a member of the Bignoniaceae family (Saini *et al*., 2009). The *kigelia* plant has a long history of use by rural communities for therapeutic purposes. It has been discovered that all parts of the plant have therapeutic abilities. Oil extracted from the seed of *Kigelia africana* is rich in vitamin E, oleic acid, linoleic acid, α-linolenic acid, protein, and n3-polyunsaturated fatty acids.

The use of oils in drug formulation offers significant benefits, such as improving drug solubility and bioavailability, extending release times, and enabling targeted delivery. They serve as natural emulsifiers, enhance the stability and distribution of active components, and can boost absorption and bioavailability, particularly for lipophilic medications. Furthermore, oil-based formulations can establish controlled release systems and increase therapeutic effectiveness (Thakur *et al*., 2023). Despite all these features for which KASO is known, research effort to evaluate its potential to ameliorate cisplatin-induced oxidative stress is lacking. Thus, the aim of this study is to assess the efficacy of *Kigelia africana* seed oil in mitigating oxidative stress induced by chemotherapy (cisplatin).

MATERIALS AND METHODS

Collection and identification of plant materials

Kigelia africana fruits were collected from a farm in Ikenyi village in the Izzi Local Government Area (6° 40' 41'' N, 8° 12' 57'' E), Ebonyi State. A taxonomist from the Department of Applied Biology at Ebonyi State University identified the fruits of the *Kigelia africana* plant.

Extraction of plant materials

The *Kigelia africana* seeds were ground with a grinder and stored in a secure container. The oil was extracted from the powdered *Kigelia africana* seeds using a Soxhlet apparatus. A round-bottom flask of the Soxhlet apparatus was filled with 150 milliliters of n-hexane. The sample, weighing 61.0 g, was placed into a thimble and inserted into the Soxhlet extractor. The apparatus was assembled, and the solvent was heated to 50 °C. Water was circulated through the extraction setup to condense the vapor. The heating and cooling process was repeated until a sufficient amount of *Kigelia africana* oil was obtained. The percentage oil yield was determined using the following expression:

$$Oil\ yield(\%) = \frac{Weight\ of\ oil\ extracted(g)}{Weight\ of\ sample\ used(g)} \times 100$$

Weight of Oil Extracted (g) is the mass of oil recovered following extraction and adequate solvent evaporation.
Weight of Sample Used (g) is the seed's dry weight from which oil was obtained.
A conversion factor of 100 was used to convert the ratio into a percentage.

Experimental animals

A commercial animal facility provided 48 adult male albino rats for the study. The rats were housed in plastic cages and fed regular pellets (Niger feed). They were acclimatized for three weeks in a well-ventilated chamber with a 12/12-hour light/day cycle at room temperature. The experimental protocols were approved by the Ebonyi State University's Central Institutional Ethical Review Committee (EBSU/BCH/ET/23/024) and followed the guidelines for the welfare and care of experimental animals (Jones-Bolin, 2012).

Experimental design

A total of 48 adult male albino rats were divided into six groups, each consisting of eight rats. Cisplatin (7 mg/kg) was administered to Groups II through VI and treatment was carried out as follows:
Group I (normal control) was fed rat chow and allowed free access to water only.
Group II (negative control) was administered 7 mg/kg body weight of cisplatin only
Group III was given 0.5 ml/kg body weight of *Kigelia africana* seed oil
Group IV was administered 1.0 ml/kg body weight of *Kigelia africana* seed oil
Group V was treated with 1.5 ml/kg body weight of *Kigelia africana* seed oil
Group VI was administered 0.5 ml/kg body weight of Omega-3 oil.
After 21 days of oil administration, the animals' hearts were punctured to draw blood which was then collected in appropriate containers.

Collection of blood sample and preparation

Exactly 2 ml of blood was added to the EDTA tube, spun at 4,000 rpm for 15 minutes, and the plasma was collected for biochemical analysis to assess hepatic and renal health.

Determination of antioxidant enzymes activities

Determination of catalase (cat) activity

Catalase (CAT) activity was determined according to the method of Aebi (1983) with slight modification to enhance

precision and reproducibility. Exactly 2.5 ml of 50 mM phosphate buffer (pH 7.0) and 2.0 ml of freshly prepared 30 mM hydrogen peroxide (H_2O_2) solution were added into a clean test tube. Subsequently, 0.5 ml of the appropriately diluted sample (enzyme source) was introduced to initiate the reaction. The reaction mixture was mixed gently and allowed to proceed at room temperature (25 ± 2°C). At one-minute intervals (0, 1, 2, 3, and 4 min), 1 ml aliquots of the reaction mixture were withdrawn and immediately stopped by adding 2.0 ml of dichromate–acetic acid reagent (prepared by mixing 5% potassium dichromate with glacial acetic acid in a 1:3 v/v ratio). The tubes were heated in a boiling water bath for 10 minutes to develop a stable color, cooled to room temperature, and the absorbance was read at 240 nm against a reagent blank using a UV visible spectrophotometer. Catalase activity was expressed as the amount of H_2O_2 decomposed per minute per milligram of protein, using the molar extinction coefficient of hydrogen peroxide ($\varepsilon = 43.6\ M^{-1}\ cm^{-1}$).

Determination of the superoxide dismutase (sod) activity

Superoxide dismutase (SOD) activity was determined according to the method of Kakkar *et al.* (1984) with slight modifications for improved reproducibility. Exactly 0.5 ml of the appropriately diluted sample (enzyme source) was pipetted into a clean test tube, followed by the addition of 1.7 ml of mixed substrate solution consisting of 0.05 M sodium carbonate buffer (pH 10.2), 0.1 mM EDTA, and 0.1 mM adrenaline (epinephrine) freshly prepared just before use. The mixture was vortexed gently to ensure homogeneity. The reaction was initiated by adding 0.25 ml of xanthine oxidase (0.05 U/ml) solution, and the initial absorbance was recorded after 30 seconds. The final absorbance was taken after 3 minutes at 480 nm using a UV–visible spectrophotometer. A control (without enzyme sample) and a blank (without xanthine oxidase) were also prepared to correct for background oxidation of adrenaline. The SOD activity was determined by comparing the inhibition of adrenaline auto-oxidation by the sample against a standard SOD curve, and expressed as units of SOD activity per milligram of protein (U/mg protein). One unit of SOD activity is defined as the amount of enzyme required to cause 50% inhibition of the auto-oxidation of adrenaline under the assay conditions.

Measurement of glutathione reductase activity

Glutathione Reductase activity was determined using a method described by (Kakkar *et al*., 1984). The reaction mixture consisted of 1.65 ml phosphate buffer: (0.1 mol; pH 7.6), 0.1 ml EDTA (0.5 mM), 0.05 ml oxidized glutathione (1 mM), 0.1 ml NADPH (0.1 mmol) and 0.1 ml of test sample in a total volume of 2 ml. Enzyme activity was determined at 25°C by measuring disappearance of NADPH at 340 nm and was calculated as nM NADPH oxidized/min/mg protein using molar extinction coefficient of $6.22 \times 10^3\ M^{-1}\ cm^{-1}$.

Determination of Malondialdehyde Level

Malondialdehyde (MDA) levels, an index of lipid peroxidation, were determined according to the method described by Janero (1990) with slight modifications to enhance reproducibility. Exactly 0.5 ml of the test sample was mixed with 1.0 ml of 10% trichloroacetic acid (TCA) in a test tube to precipitate proteins. The mixture was vortexed thoroughly and centrifuged at 3,000 rpm for 10 minutes to obtain a clear supernatant. Subsequently, 1.0 ml of the supernatant was transferred into a clean test tube, followed by the addition of 1.0 ml of 0.67% thiobarbituric acid (TBA) solution prepared in 0.05 M glacial acetic acid (pH 3.5). The tubes were tightly covered and incubated in a boiling water bath (95°C) for 15 minutes to allow the formation of the pink MDA–TBA adduct. After heating, the tubes were cooled rapidly in running tap water and centrifuged again at 3,000 rpm for 10 minutes to remove turbidity. The absorbance of the resulting pink supernatant was measured at 535 nm against a reagent blank containing all reagents except the sample, using a UV–visible spectrophotometer. Standard MDA solutions were prepared from 1,1,3,3-tetramethoxypropane (TMP) at concentrations ranging from 0 to 10 µM, and a standard calibration curve was plotted. MDA concentrations in the samples were extrapolated from this standard curve and expressed as nanomoles of MDA formed per milligram of protein (nM/mg protein) using the molar extinction coefficient $\varepsilon = 1.56 \times 10^5\ M^{-1}\ cm^{-1}$.

Statistical analysis

Data generated were expressed as Mean ± Standard Deviation using SPSS (Ver. 23). The data were analyzed using one-way Analysis of Variance (ANOVA). Differences in means were compared using Tukey's Test. p-values less than 0.05 were considered statistically significant.

RESULTS

Table 1. Anti-oxidant Status of Rats Administered *Kigelia africana* Seed Oil

Treatment	SOD ($\mu mol\ min^{-1}mL^{-1}$)	CATALASE ($\mu mol\ min^{-1}mL^{-1}$)	GSR ($\mu mol\ min^{-1}mL^{-1}$)	GPx ($\mu mol\ min^{-1}mL^{-1}$)	MDA (nmol/mL)
Group1(NC)	2.00 ± 0.02^{d}	0.76 ± 0.06^{e}	49.00 ± 1.00^{d}	13.26 ± 0.53^{d}	10.33 ± 0.03^{a}
Group II (-VE Ctrl)	1.10 ± 0.00^{a}	0.17 ± 0.04^{a}	21.33 ± 1.53^{a}	2.89 ± 0.42^{a}	19.24 ± 0.48^{c}
Group III (0.5 ml/kg KASO)	1.92 ± 0.067^{b}	0.61 ± 0.02^{b}	47.33 ± 1.16^{b}	11.40 ± 1.00^{b}	11.52 ± 1.14^{b}
Group IV (1 ml/kg KASO)	1.99 ± 0.02^{c}	0.69 ± 0.14^{c}	48.67 ± 1.53^{c}	12.58 ± 1.00^{c}	11.32 ± 0.74^{b}
Group V (1.5 ml/kg KASO)	1.99 ± 0.01^{c}	0.73 ± 0.07^{d}	48.67 ± 1.53^{c}	12.91 ± 0.61^{c}	10.41 ± 0.53^{a}
Group VI (0.5ml/kg Omega-3 oil)	2.01 ± 0.02^{d}	0.76 ± 0.09^{e}	48.67 ± 1.16^{c}	13.67 ± 1.00^{d}	10.70 ± 0.43^{a}

Results are expressed as mean ± standard deviation. Values with same superscript are significantly ($p<0.05$) different

DISCUSSION

The role of cisplatin in the treatment of cancers such as bladder, head and neck, lung, ovarian, and testicular cancer cannot be overstated (Dasari and Tchounwou, 2024). Despite its critical role as a cancer therapy, its mechanism of action is linked to free radical generation and, consequently, oxidative stress, which adversely impacts non-proliferating cells, suggesting a role for oxidative stress in the pathogenesis of cisplatin toxicities (Ketanic *et al*., 2023). The antioxidant status of cisplatin-treated Wistar rats administered *K. africana* seed oil is shown in Table 1. The results indicate that cisplatin administration significantly ($p<0.05$) reduced the activity of superoxide dismutase compared to the normal control. However, oral administration of *K. africana* seed oil significantly ($p<0.05$) increased SOD activity, though significantly ($p<0.05$) lower than that of the normal control. SOD activity in groups administered 1 ml/kg and 1.5 ml/kg was not significantly different ($p>0.05$) but was significantly higher than that in group III administered 0.5 ml/kg KASO and significantly ($p>0.05$) lower that group VI administered 0.5 ml/kg omega-3. There was a significant ($p<0.05$) reduction in catalase activity in Wistar rats administered cisplatin, which was significantly ($p<0.05$) increased following oral administration of KASO in a dose-dependent manner. Oral administration of 0.5 ml/kg omega-3 oil increased CAT activity to a level that was not significantly different ($p<0.05$) from the normal control. The negative control showed a significantly ($p<0.05$) reduced glutathione activity, which was markedly increased following oral administration of KASO. The 1 ml/kg and 1.5 ml/kg doses of KASO achieved a level of glutathione reductase activity that was significantly ($p<0.05$) higher than that given 0.5 ml/kg but lower than that administered omega-3 oil. The activity of glutathione peroxidase showed a similar trend, with the activity following oral administration of 0.5 ml/kg omega-3 oil not significantly different ($p<0.05$) from the normal control. Cisplatin administration significantly increased malondialdehyde (MDA) levels ($p>0.05$). However, the administration of 1 ml/kg and 1.5 ml/kg KASO significantly reduced MDA levels ($p<0.05$), with no significant difference between the two doses ($p<0.05$).

Phenolic compounds reportedly inherent in the seed oil of *K. africana* could be responsible for the declined level of malondialdehyde (MDA) and impressive activity of antioxidant enzymes by directly mopping up reactive oxygen species and indirectly upregulating the antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione reductase (GR) (Pandey and Rizvi, 2009). The enhanced synthesis of the antioxidant enzymes is orchestrated by the phenolic compounds through their involvement in the activation of the Nrf2–ARE (nuclear factor erythroid 2–related factor 2–antioxidant response element) signaling pathway, translating to transcriptional upregulation of antioxidant genes and consequently enhancing the synthesis of the said antioxidant enzymes (Nguyen *et al*., 2009; Zhang *et al*., 2019). Furthermore, the generation of hydroxyl radicals mediated by Fenton-type reaction is impeded by the chelation of redox-active metal ions such as Fe^{2+} and Cu^{2+} (Rice-Evans *et al*., 1997). The observed decline in MDA levels in our study lends credence to the hypothesis that oil derived from the seed of *K. africana* has the potential to ameliorate peroxidation through its ability to scavenge ROS. The outcome of this study is in tandem with the results of a study by Abdu *et al*. (2023), who established the antioxidant property of methanol root extract of *K. africana*. Owing to the antioxidant potential of KASO, it may be considered not only as a complementary therapy for ROS-inducing medications but also in the management of oxidative stress-related disorders, including hepatic injury, nephrotoxicity, diabetes, and cancer (Halliwell and Gutteridge, 2015). However, it is imperative to deepen research efforts to isolate, characterize, and standardize the bioactive constituents responsible for these protective effects.

CONCLUSION

This study investigated the ameliorative effects of *K. africana* seed oil on cisplatin-induced oxidative stress. The findings revealed that oral administration of *K. africana* seed oil significantly enhanced the activities of key antioxidant enzymes while effectively lowering malondialdehyde (MDA) concentrations. These outcomes indicate that *K. africana* seed oil confers protective antioxidant benefits and can mitigate lipid peroxidation and oxidative damage associated with cisplatin therapy. This implies that KASO could serve as an ideal adjuvant or complementary agent to cisplatin, suggesting that incorporating KASO into cisplatin formulation could improve treatment outcomes and impede medication-induced oxidative stress. Further studies

focused on an in-depth analysis of KASO's safety on long-term use should be conducted.

AUTHORS' CONTRIBUTIONS

Conceptualization. CEO: Supervision. EEU: Formal analysis. IOI: Supervision. FO: Supervision. AEO: Writing – Review & Editing. AON: Methodology. OFO: Writing – Review & Editing. EO: Writing – Original Draft. EDC: Project administration. AkA: Writing – Review and Editing. All authors read and approved the manuscript for submission

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No application to this study

CONFLICT OF INTEREST

The authors declare that no conflict of interest

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