Cardioprotective Effects of Virgin Coconut Oil and Carvedilol Against Doxorubicin-Induced Cardiotoxicity in Male Mice: Biochemical and Histopathological Evaluation

**Abstract**

Background: Doxorubicin (DOX) is a widely used chemotherapeutic agent known for its potent anticancer effects but also for its dose-limiting cardiotoxicity, primarily driven by oxidative stress and myocardial degeneration.

Objective: This study aimed to evaluate the cardioprotective effects of virgin coconut oil (VCO) and carvedilol (CARV) against DOX-induced cardiac injury in mice, using biochemical and histopathological Parameters.

Methods: Thirty two adult mice were randomly assigned to four groups: control, DOX-only (3.75 mg/kg/week, i.p.), DOX+VCO (5 ml/kg/day, orally), and DOX+CARV (5 mg/kg, orally, thrice weekly) for 28 days. At the end of treatment, heart tissues were analyzed for malondialdehyde (MDA) and superoxide dismutase (SOD) levels, and examined histologically.

Results: The DOX only group showed a significant increase in malondialdehyde (MDA) levels indicating oxidative cardiac damage. The DOX + CARV group had significantly decreased MDA levels, whereas the DOX + VCO group exhibited a mild, non-significant decrease. SOD levels decreased further in both DOX + CARV and DOX + VCO groups. Histopathological analysis revealed severe cardiac damage in the DOX group, which was markedly attenuated in the DOX + CARV group and moderately reduced in the DOX + VCO group.

Conclusion: Virgin coconut oil and carvedilol conferred notable histological protection against doxorubicin-induced cardiac injury, preserving myocardial structure and function. Despite limited antioxidant effects biochemically, their cardioprotective potential may involve alternative mechanisms beyond enzymatic restoration, including non-enzymatic scavenging and anti-inflammatory pathways. These findings underscore the complexity of redox regulation in cardiotoxicity and support further exploration of combination therapies and time-dependent antioxidant responses

Keywords: Doxorubicin, Cardiotoxicity, Virgin Coconut Oil, Carvedilol, Oxidative Stress.

**Introduction**

Cardiotoxicity arising from cancer treatment remains a significant clinical concern, particularly among survivors of pediatric and adolescent malignancies. Notably, it stands as the third leading cause of treatment-related mortality in this population (National Institute for Cancer, 2014). In adult cancer survivors, the pattern persists; for instance, a recent study in the United States revealed that cardiovascular disease surpasses cancer itself as the leading cause of mortality in women over 50 who were diagnosed with breast cancer (Siegel et al., 2023).

Anthracyclines, particularly doxorubicin, are among the most potent and widely used chemotherapeutic agents. These drugs are employed in treating a broad spectrum of malignancies, including leukemia, Hodgkin’s lymphoma, and cancers of the breast, lung, thyroid, stomach, bladder, and soft tissues (Rawat et al., 2021). Despite their effectiveness, the clinical utility of doxorubicin is often hindered by its dose-limiting toxicities, notably cardiotoxicity, as well as hepatotoxicity, nephrotoxicity, and neurotoxicity (Kalyanaraman, 2020). Given the increasing incidence of chemotherapy-related cardiac dysfunction (CRCD), there is a pressing need to prevent or mitigate these life-threatening complications without compromising the therapeutic efficacy of doxorubicin (Ezeh Chiamaka et al., 2023).

Doxorubicin-induced cardiotoxicity (DIC) manifests in both acute and chronic forms. Acute DIC, which occurs in approximately 11% of cases, mimics acute myocarditis, presenting within days of drug administration. It is typically reversible and characterized by transient myocyte injury (Schirone et al., 2022). Conversely, chronic DIC may emerge months or even years post-treatment, and is associated with a persistent decline in left ventricular ejection fraction exceeding 10%, often progressing to symptomatic heart failure (Curigliano et al., 2016). Current perspectives in cardio-oncology suggest that acute and chronic DIC represent a continuum rather than discrete entities. The underlying pathophysiology is believed to begin with subclinical myocardial injury, followed by progressive functional deterioration that ultimately culminates in overt cardiac failure (Fabiani et al., 2021).

Although the precise mechanisms driving doxorubicin-induced cardiotoxicity remain under investigation, several pathways have been proposed. These include oxidative stress through free radical generation, the formation of anthracycline-iron complexes, and DNA double-strand breaks, all of which contribute to cardiomyocyte dysfunction and death (Kalyanaraman, 2020). The risk of cardiotoxicity is known to increase with cumulative doxorubicin dosage and may become apparent during or after treatment (Mitry and Edwards, 2016, as cited by Elsayed et al., 2024). Additional exacerbating factors include mitochondrial damage, apoptosis, and necrosis, with these processes also implicated in chemotherapy-associated cognitive decline (Kong et al., 2022; Wu et al., 2022; Ezeh Chiamaka et al., 2023).

Currently, there are no definitive therapies to prevent or reverse doxorubicin-induced cardiotoxicity. However, several preventive strategies have been proposed, such as dose limitation, utilization of liposomal drug formulations, administration of cardioprotective agents, and routine cardiac monitoring (Chaulin, 2023). Edible medicinal substances, especially plant-based products, are gaining traction for their role in cardiovascular disease prevention and therapy (Syahputra et al., 2022). The immunomodulatory and antioxidant properties of medicinal plants have inspired their investigation as adjuncts in mitigating chemotherapy-related toxicities (Singh et al., 2016; Song, 2014, as cited by Ezeh Chiamaka et al., 2023).

Among these natural agents, carvedilol and virgin coconut oil (VCO) have shown promise in combating doxorubicin-induced toxicity. Carvedilol, a β-blocker, exhibits neuroprotective effects by increasing nitric oxide (NO) levels, inducing vasorelaxation, and inhibiting sympathetic nervous activity. It also reduces oxidative stress through its unique carbazole moiety (Jhorawat et al., 2016, cited by Ezeh Chiamaka et al., 2023). On the other hand, VCO extracted through fermentation from fresh coconuts contains medium-chain fatty acids, antioxidants, and high levels of vitamin E. These components have demonstrated therapeutic potential in various diseases including diabetes, hypertension, hepatitis, and coronary heart disease (Teo et al., 2013, cited by Ningsih et al., 2020).

VCO do not only attenuates the biochemical markers of neuroinflammation but also reduces the expression of inducible nitric oxide synthase (iNOS), suggesting its dual role in ameliorating neurotoxicity and preventing its onset (Ezeh Chiamaka et al., 2023). The cumulative evidence of doxorubicin’s neurotoxic, hepatotoxic, and cardiotoxic effects underscores the critical need for effective protective interventions. The chronic cardiovascular complications associated with this chemotherapeutic agent, including life-threatening conditions such as heart failure, necessitate the exploration of adjunctive therapies. Given the reported antioxidative and neuroprotective effects of both carvedilol and VCO, this study aims to evaluate their potential in attenuating doxorubicin-induced cardiotoxicity.

**MATERIALS AND METHODSMaterials**Materials used for this research include 32 mice, syringes, soaps/sanitisers, cages, mice feed, canula, hand gloves, towels, face mask**Equipment:** Analytical weighing balance, digital weighing balance, refrigerator, water bath, incubator, centrifuge and spectrophotometer.**Purchase of drugs:** Doxorubicin and carvedilol were purchased from Octova Pharmacy in Abakaliki, Ebonyi state.

**Collection and extraction of Virgin coconut oil (Cold Pressed):** Coconut kernel was obtained from a local market in Abakaliki. The coconut meat detached from its shell and blended with lukewarm water. The coconut milk was then strained using a cheese cloth, and the coconut milk was kept in a container and allowed to ferment for some days, such that the oil, the curd, and the water separated and the oil was carefully scooped from the top layer

**Reagents and chemicals:** 0.1 M phosphate buffered saline, 10% formalin, Distilled water, Normal saline, and 0.25 M sucrose buffer solution.**MethodsExperimental Design:**

Thirty-two (32) adult mice were procured from the animal house of the Department of Physiology, Alex Ekwueme Federal University, Ndufu-Alike, Ebonyi State, and housed in the same facility. The animals were acclimatized for two weeks under standard laboratory conditions, fed with ad libitum and water. During the study, the mice were maintained in a controlled environment with alternating light and dark cycles, a room temperature of 35 ± 2°C, and appropriate humidity levels. After acclimatization, the animals were randomly assigned into four groups of eight mice each(n=8), with the following treatment and administration.

**Table 1 . Animal Grouping**

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| Group | Treatment |
| 1 | Normal saline |
| 2 | Doxorubicin |
| 3 | Dox. + VCO |
| 4 | Dox + CARV. |

**Treatment dosage**1. Group 1 (Normal control): received normal saline (2 ml/kg b.w).2. Group 2 (DOX): received Doxorubicin (3.75 mg/Kg b.w i.p) weekly as a single dose on days 5, 12, 19 and 26 only to make up 15 mg/kg b.w administered for 28 days and normal saline.3. Group 3 (DOX + VCO): received virgin coconut oil (5ml/kg b.w, orally) daily + Doxorubicin as group 2.4. Group 4 (DOX + CARV): received 5 mg/kg b.w of carvedilol weekly for three days (day 5-7 weekly, for four weeks) after DOX administration as group 2.Carvedilol and virgin coconut oil were administered orally. All administration lasted for 28 days (4 weeks).

The administered dose of Dox + VCO and Carv + Dox was 5mg/kg.b.w orally and Doxorubicin (3.75 mg/Kg b.w i.p) weekly as a single dose (Ezeh chiamaka et al., 2023).

The dosage selection for Doxorubicin (3.75 mg/kg/week I.p) was based on Ezeh Chiamaka et al. (2023), which established a cumulative dose of 15 mg/kg over 28 days as optimal for inducing chronic cardiotoxicity. VCO (5 ml/kg/day orally) and CARV (5 mg/kg orally, 3 times weekly) were selected based on previous literature demonstrating their cardioprotective and antioxidant properties in rodent models. The choice of 5ml/kg is consistent with prior preclinical studies assessing antioxidant and cardioprotective effects in studies like Nevin and Rajamohan (2006) and Famurewa et al. (2019). The selected Carvedilol (5 mg/kg, 3x/week orally) dosage is a therapeutic range dose for carvedilol in murine models.

Animal Sacrifice: After the 28-day treatment period, the animals were humanely sacrificed. Blood samples were collected directly from the heart using cardiac puncture. Following a blood sample collection, mice were euthanized using a cervical dislocation method, which was in accordance with the American Veterinary Medical Association, (2020) guidelines for the euthanasia of animals, and approved by the faculty ethical committee. The heart was carefully removed and fixated in 10% formalin in phosphate buffer saline and embedded in paraffin blocks. Sections of 5 μm thick were serially sliced with a microtome and stained with hematoxylin and eosin.The harvested samples and tissues were transported to the Central Research Laboratory, University of Uyo, Akwa Ibom State, Nigeria for biochemical and histopathological evaluation. The microscopic observation of the longitudinal section of the heart tissue was performed by a veterinary pathologist, especially in the area of the ventricles, using a light microscope (Olympus®) at 40X magnification.

**Determination of Superoxide Dismutase (SOD) Activity in Heart Tissue**

Superoxide dismutase (SOD) activity was measured in heart tissue using the pyrogallol autoxidation method described by Marklund and Marklund (1974) This method is based on the inhibition of pyrogallol autoxidation by SOD.

**Sample Preparation**

Heart tissue was homogenized in 50 mM Tris-HCl buffer (pH 8.2) containing 1 mM EDTA. The homogenate was centrifuged at 10,000 x g for 15 minutes, and the supernatant was collected for SOD activity measurement.

**SOD Activity Measurement**

The reaction mixture consisted of 2.5 ml of 50 mM Tris-HCl buffer (pH 8.2), 0.1 ml of 1 mM EDTA, 0.5 ml of 1 mM DTPA, and 0.1 ml of 0.02 mM pyrogallol. The reaction was initiated by adding 0.1 ml of the tissue homogenate supernatant. The change in absorbance at 420 nm was measured kinetically for 3 minutes using a spectrophotometer.

**Calculation of SOD Activity**

SOD activity was calculated using the formula:

SOD activity (U/mg protein) = (ΔA420/min) x (1/ε) x (1/protein concentration)

where ΔA420/min is the change in absorbance at 420 nm per minute, ε is the extinction coefficient of pyrogallol (4.02 x 10^3 M^-1 cm^-1), and protein concentration is the concentration of protein in the sample.

**Determination of Malondialdehyde (MDA) Levels in Heart Tissue**

Malondialdehyde (MDA) levels were measured in heart tissue using the Thiobarbituric Acid (TBA) assay described by Ohkawa et al. (1979) This method is based on the reaction between MDA and TBA to form a pink-colored chromophore.

**Sample Preparation**

Heart tissue was homogenized in 50 mM phosphate buffer (pH 7.4) containing 1 mM EDTA. The homogenate was centrifuged at 10,000 x g for 15 minutes, and the supernatant was collected for MDA measurement.

The reaction mixture consisted of 0.5 ml of the tissue homogenate supernatant, 2.5 ml of 20% trichloroacetic acid (TCA), and 1.0 ml of 0.67% TBA. The mixture was incubated at 95°C for 30 minutes, and then cooled to room temperature. The absorbance was measured at 532 nm using a spectrophotometer.

**Calculation of MDA Levels**

MDA levels were calculated using the formula:

MDA (nmol/mg protein) = (Absorbance at 532 nm) x (Sample volume) / (Extinction coefficient x 10^6 x Protein concentration).where the extinction coefficient for the TBA-MDA complex is 1.56 x 10^5 M^-1 cm^-1.

**Data/Statistical Analysis**Results obtained were expressed as Mean±SEM (Standard error of the mean). One-way analysis of variance (ANOVA) was used to compare the mean differences between the control and other treatment groups in this study. P-value less than 0.05 (P≤0.05) was considered statistically significant.

**RESULTS AND DISCUSSION**

EFFECT OF VIRGIN COCONUT OIL AND CARVEDILOL ON TOTAL MALONDIALDEHYDE CONCENTRATION OF THE HEART

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**Figure 1 – Bar charts comparing the effects of DOX, virgin coconut oil and carvedilol on heart Malondialdehyde (MDA) levels of doxorubicin-treated miceKey**: \*significant when compared to normal control (p≤0.05); # significant when compared to the DOX group (p≤0.05)

EFFECT OF VIRGIN COCONUT OIL AND CARVEDILOL ON SUPEROXIDE DISMUTASE CONCENTRATION OF THE HEART



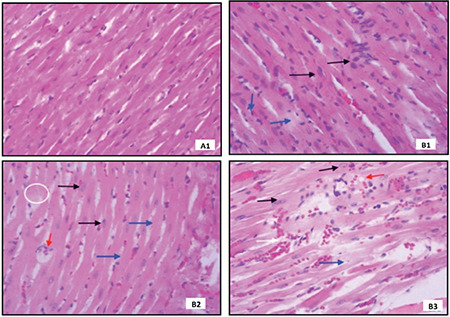
**Figure 2 – Bar charts showing the effects of DOX, virgin coconut oil and carvedilol administration on superoxide Dismutase in doxorubicin-treated mice**

**Key:** \*significant when compared to normal control (p≤0.05). # significant when compared to negative control (p≤0.05).

**Histopathological examination**

“The normal control that was not subjected to the DOX injection showed regular cardiac myocyte shapes and structures (Figure 3A1). The bands and nucleus of cardiac myocytes and the myofibrils were clearly clear. There were barely inflammatory cells or necrotic damage found in the area of myocytes. In contrast, the DOX group experienced mild-to-moderate histopathological injuries. Histopathological changes in the heart muscle cells were evident and profound in the area of myocytes. Moderate damage was observed in most DOX-treated mice, which was characterized by hyper-eosinophilic cytoplasm and necrotic cell nuclei, myocardial cell atrophy, loss of nuclei, myolysis, infiltration of inflammatory cells, and hemorrhagic area (Figure 3B1-B3)” (Utari, A. U., et al., 2022).

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**FIG 3. Representative of microscopic images of cardiac tissues in the control and DOX-treated rats. The control (A1) showed normal architecture of myocytes. cells with a normal structure with a magnification of 40X. The DOX group (B1, B2, and B3) showed necrotic cells (black arrow), myocardial muscle atrophy (blue arrow), vacuolar degeneration and hemorrhage (red arrow), and myolysis (white) (Source: Utari, A. U., et al., 2022)**

Figure 4 shows the representative microscopic images of cardiomyocyte histopathological changes found in mice treated with Dox + VCO, In the Dox+ VCO-treated rats (Figure 4C1, C2), most cardiac sections showed necrotic cells and cardiomyocyte atrophy. “The degree of myocardial injury was found mild to moderate With Carvedilol pre-treatment, the injection of DOX still resulted in mild-to-moderate damage, shown by the presence of necrotic cells, atrophy of cardiomyocytes, and inflammatory cells in cardiac tissue of mice (Figure 4D1, D2). Furthermore, In this group, some histopathological changes were found, including hemorrhage and necrotic cells, but the degree was minimal (Figure 4E1, E2)” (Utari, A. U., et al., 2022).

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**FIG 4. Representative of microscopic images of cardiac tissues in DOX treated rats that received pre-treatment with Dox + VCO (C1-2), Dox + VCO (D1-2), Necrotic myocardial cells (black arrow), muscle atrophy (blue arrow), inflammatory cells (white circle), and hemorrhagic area (red arrow) (Source: Utari, A. U., et al., 2022)**

Doxorubicin (DOX) is a potent chemotherapeutic agent whose clinical use is limited by its cumulative cardiotoxicity, cause by reactive oxygen species (ROS)-induced oxidative stress and mitochondrial dysfunction. Various antioxidant-based interventions have been investigated to mitigate this cardiotoxicity, including pharmacologic agents such as carvedilol and natural products like virgin coconut oil (VCO). In the present study, we explored the comparative cardioprotective effects of VCO and carvedilol in DOX-induced cardiac injury, with a focus on oxidative stress markers, enzymatic antioxidant responses, and histopathological outcomes.

MDA concentration serves as a direct indicator of lipid peroxidation and oxidative stress. In the DOX-only group, MDA levels were elevated compared to the normal control group, although the difference was not statistically significant. This suggests a moderate oxidative insult, consistent with doxorubicin’s known mechanism involving reactive oxygen species (ROS) generation and lipid membrane damage (Carvalho et al., 2009; Octavia et al., 2012; Takemura & Fujiwara, 2007). The finding is in line with Utari et al., (2022) findings that submaximal doses of DOX can disrupt redox balance and initiate lipid peroxidation, contributing to cardiomyocyte degeneration

In the DOX + VCO group, there was a non-significant decrease in MDA levels compared to the DOX group. This modest attenuation may be attributed to the antioxidant compounds in virgin coconut oil particularly lauric acid, tocopherols, and phenolic acids which have been previously reported to reduce lipid peroxidation in cardiovascular and neurotoxic models (Nevin & Rajamohan, 2004; Arunima & Rajamohan, 2013; Ezeh Chiamaka et al., 2023). The outcome may reflect limitations in VCO’s potency at the administered dose, the timing of administration, or the intensity of ROS generation by DOX.

MDA levels were significantly increased in DOX + CARV group compared to the DOX-only group. Despite carvedilol’s antioxidant and cardioprotective roles, a paradoxical finding was observed in the DOX + CARV group and this finding may be linked to several complex biochemical phenomena, pro-oxidant effect of carvedilol metabolites under sustained oxidative conditions has been reported to transiently increase lipid peroxidation through mitochondrial membrane interactions or metal-catalyzed redox cycling (Kumar et al., 2016; Atalay et al., 2022). Additionally, ROS rebound mechanisms may be involved, whereby initial scavenging of ROS by carvedilol could result in compensatory oxidative signaling or mitochondrial stress, particularly if redox homeostasis is not fully restored (Yu et al., 2021). The paradoxical increase in MDA, do not negate carvedilol’s therapeutic benefit. On the contrary, this phenomenon may represent a hormetic response, wherein low-level oxidative stimulation triggers cytoprotective pathways such as Nrf2 activation, upregulating survival genes and bolstering mitochondrial defense (Calabrese et al., 2015). Thus, while elevated MDA indicates ongoing lipid peroxidation, it may coexist with functional histological recovery, as evidenced in our findings.

SOD is an essential enzymatic antioxidant that catalyzes the dismutation of superoxide radicals into oxygen and hydrogen peroxide. From the result, SOD level significantly decreased across both the DOX + VCO and DOX + CARV groups, even more than in the DOX-only group. This paradoxical reduction challenges conventional expectations that antioxidant therapy enhances endogenous enzymatic defenses. This finding novel finding may be due a negative feedback regulation through redox-sensitive transcription factors such as Nrf2, that may have downregulated SOD expression in response to perceived ROS quenching by exogenous antioxidants (Fang et al., 2002; Halliwell, 2012). This mechanism aligns with other studies where therapeutic agents paradoxically suppressed SOD while activating other protective systems (Zhou et al., 2021). Importantly, the timing of sample collection may also influence enzymatic readings SOD activity often peaks early in stress responses and may decline as redox balance is partially restored.

Furthermore, recent studies suggest that doxorubicin-induced oxidative stress may cause post-translational modifications or proteasomal degradation of SOD enzymes, leading to functional exhaustion despite the presence of exogenous antioxidants (Singh et al., 2016). This is supported by findings from Kumar et al. (2016), who demonstrated that carvedilol's antioxidant effects were primarily mediated through catalase and glutathione pathways, rather than SOD restoration. This phenomenon suggests an adaptive antioxidant remodeling, where the organism prioritizes non-enzymatic or alternative enzymatic systems to neutralize ROS. Such adaptive responses may explain why SOD activity remains suppressed even as overall tissue damage is reduced, as also reported by Santos et al. (2020)

Despite the suppressed SOD activity, both treatment groups showed improved myocardial structure upon histological examination. DOX caused classic cardiac injury characterized by widespread necrosis, atrophy, and inflammatory infiltration consistent with previous findings (Sawyer et al., 2010). DOX + VCO group showed mitigation of some of this damage, reducing necrosis and cellular degeneration. This aligns with prior studies documenting VCO’s ability to enhance membrane integrity and modulate inflammatory pathways (Arunima & Rajamohan, 2013; Ezeh Chiamaka et al., 2023). Nevertheless, the residual signs of damage suggest that VCO alone may be insufficient under intense oxidative assault. Carvedilol-treated animals, by contrast, exhibited near-normal myocardial architecture, with minimal signs of degeneration or inflammation, confirming its multifaceted protective mechanisms involving β-blockade, anti-inflammatory modulation, and mitochondrial stabilization.

The DOX + CARV group, however, exhibited near-normal myocardial architecture, with minimal signs of necrosis or inflammation. This aligns with carvedilol’s multi-pronged protective mechanisms, including β-blockade, anti-inflammatory activity, and mitochondrial stabilization (Hanawa et al., 2008;Gonzalez et al., 2007 ). Despite elevated MDA and suppressed SOD, the preserved tissue structure suggests that non-enzymatic and mitochondrial-targeted mechanisms were effectively engaged.

The systemic protective effects of both agents are further corroborated by Ezeh Chiamaka et al. (2023), who demonstrated neuroprotective benefits of VCO and carvedilol in DOX-treated mice. Furthermore, our observations echo the findings of Utari et al. (2022), who reported that VCO, when combined with extra virgin olive oil (EVOO), exhibited enhanced cardioprotective effects compared to VCO alone. This suggests that combination antioxidant therapy may be necessary to fully counteract DOX-induced toxicity. The potential for synergistic interaction between natural and pharmacologic antioxidants warrants further exploration, including studies on dosing optimization, redox pathway profiling, and mitochondrial-specific outcomes.

**Conclusion**

The study identified virgin coconut oil (VCO) and carvedilol as offering potent histological protection against doxorubicin-induced cardiac injury. This protection clinically indicates that both VCO and carvedilol can help preserve the structural integrity of heart tissue, safeguarding cardiac health and function in the face of anthracycline-induced cardiotoxicity. The inability of virgin coconut oil and carvedilol to exhibit antioxidant properties highlights the complexity of redox regulation under oxidative stress. This shows that Cardioprotection and the underlying mechanism may not depend solely on restoring enzymatic antioxidants but rather involves SOD-independent pathways, non-enzymatic scavenging, mitochondrial preservation, and inflammatory modulation. Future studies should investigate the temporal dynamics of antioxidant responses, assess complementary pathways such as glutathione peroxidase and catalase, and explore the potential of combination antioxidant therapies for optimizing protection against anthracycline cardiotoxicity.

**Ethical Approval:**

The ethical committee approved the protocol of this study by the rules and guidelines in experimenting at the Department of physiology, Alex Ekwueme Federal University, Ndufu-Alike, Ebonyi State.

**Disclaimer (Artificial intelligence)**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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