**Comparative Cardioprotective Effects of Virgin Coconut Oil and Carvedilol on Doxorubicin-Induced Cardiac Injury in Mice: Biochemical and Histopathological Insights**

**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 compare the cardioprotective effects of virgin coconut oil (VCO) and carvedilol (CARV) against DOX-induced cardiac injury in mice, using biochemical and histopathological evaluations.

Methods: Sixty-four 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:.DOX administration led to elevated MDA and reduced SOD levels, indicating oxidative cardiac damage. Carvedilol significantly reduced MDA levels (\*p\* ≤ 0.05), while VCO showed a mild, non-significant reduction. Surprisingly, SOD activity declined further in both treatment groups. Histopathological analysis revealed severe cardiac damage in the DOX group, which was markedly attenuated in the CARV group and moderately reduced in the VCO group.

Conclusion: Both VCO and CARV confer cardioprotective effects against DOX-induced cardiac injury, with carvedilol demonstrating superior efficacy. The paradoxical suppression of SOD suggests involvement of SOD-independent or non-enzymatic antioxidant pathways, warranting further investigation.

**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 available. 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 via 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). Increasingly, attention is turning to naturally derived compounds with cardioprotective and neuroprotective properties. 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 via 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).

Recent studies indicate that VCO 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, necessitate the exploration of adjunctive therapies. Given the reported antioxidative and cardio-protective 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 male mice and 32 female 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.Samples: Blood Samples were collected via heart samples were collected from the sacrificed mice, and brain samples were collected from the skulls of the decapitated rats.**Purchase of drugs:** Doxorubicin and carvedilol were purchased from Octova Pharmacy in Abakaliki, Ebonyi state.

**Collection & 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:** During the study, the following chemicals were used: 0.1 M phosphate buffered saline, 10 % formalin, Distilled water, Normal saline, and 0.25 M sucrose buffer solution.**Methods**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.

 **Procurement of Animals:** Sixty-four mice (28 males and 28 females) were procured from the animal house of the department of physiology, Alex Ekwueme Federal University, NdufuAlike, Ebonyi State and housed in the same facility. The animals were acclimatised for two weeks and fed with grower pellets and water ad libitum. **Experimental Design.** The room temperature was maintained at 35±2. The mice were kept in a controlled environment under standard conditions and humidity with alternating light and dark cycles, after which they were grouped randomly into four groups of 8 mice each, with the following treatment and administrations.

**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. Virgin Coconut Oil (5 ml/kg/day orally) and Carvedilol (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 5 ml/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 administration, which lasted for 28 days, the animals were sacrificed and decapitated. Blood samples were collected via the retroorbital puncture. Incisions were made through the skin to expose the organs needed for further analysis. The examples and tissues were taken to the central research laboratory at Uyo, Ibadan State, to assay for immunological, biochemical, and histopathological examination.

**Histopathological examination**

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. 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 in Uyo, Ibadan State, 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. All the results were analysed using GraphPad version 9.0.

**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 Malonahyde levels of doxorubicin-treated miceNotes: \*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**

**Notes: \*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).

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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)**

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).

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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)**

MDA concentration serves as a direct indicator of lipid peroxidation and oxidative stress. In the DOX-only group, there was an increase in MDA levels compared to the normal control group, although the rise was not statistically significant. This suggests a moderate induction of oxidative stress by DOX, which is consistent with its known mechanism of action involving reactive oxygen species (ROS) generation.

Interestingly, co-treatment with VCO did not significantly reduce MDA levels compared to the DOX group, indicating that VCO offered limited protection against lipid peroxidation under the given dosage and experimental conditions. In contrast, co-treatment with carvedilol resulted in a statistically significant decrease in MDA levels (\*p\* ≤ 0.05) compared to the DOX group. This suggests that carvedilol exerted a more potent antioxidant effect, possibly due to its intrinsic free radical-scavenging ability and β-adrenergic blocking properties, which may reduce oxidative metabolism in cardiac tissue.

SOD is an essential enzymatic antioxidant that catalyzes the dismutation of superoxide radicals into oxygen and hydrogen peroxide. A reduction in SOD activity was observed in the DOX group, indicative of oxidative stress-mediated depletion of antioxidant defenses.

Contrary to expectation, SOD activity further declined in both the DOX + VCO and DOX + CARV groups. Despite their known antioxidant potential, neither VCO nor CARV restored SOD activity levels. This paradoxical observation may be attributed to prolonged oxidative stress leading to enzyme inactivation or compensatory mechanisms involving non-enzymatic antioxidants. Additionally, it suggests that the cardioprotective actions of VCO and CARV may operate through SOD-independent pathways, such as scavenging of downstream ROS or modulation of inflammatory cascades.

Doxorubicin (DOX), a widely used chemotherapeutic agent, is well known for its potent anticancer efficacy, but its clinical application is severely constrained by cumulative dose-dependent cardiotoxicity. This toxicity is primarily mediated by the formation of reactive oxygen species (ROS), lipid peroxidation, mitochondrial dysfunction, and inflammatory signaling, which collectively induce myocyte apoptosis and necrosis (Octavia et al., 2012; Takemura & Fujiwara, 2007; Utari et al., 2022). In this study, we evaluated the cardioprotective effects of virgin coconut oil (VCO) and carvedilol (CARV) in a DOX-induced cardiac injury model. Both interventions showed protective effects, but carvedilol demonstrated superior efficacy. Notably, a paradoxical downregulation of superoxide dismutase (SOD) activity was observed in both VCO and CARV groups, marking a novel finding in the context of DOX cardiotoxicity.

The elevation of malondialdehyde (MDA) in the DOX-only group confirmed ongoing lipid peroxidation, a hallmark of oxidative stress associated with anthracycline toxicity (Carvalho et al., 2009; Utari et al., 2022). While this increase did not reach statistical significance, the trend supported the biochemical footprint of ROS-mediated injury. VCO co-treatment produced a mild reduction in MDA levels, although it was not statistically significant. This partial attenuation can be attributed to VCO’s natural antioxidant compounds, such as lauric acid, polyphenols, and tocopherols, which have demonstrated lipid peroxidation inhibition in earlier studies (Nevin & Rajamohan, 2004; Ma & Lee, 2016; Ezeh Chiamaka et al., 2023). However, the modest impact observed may be due to the overwhelming oxidative burden induced by DOX or suboptimal dosage or duration of VCO administration, as also reported by Utari et al. (2022), where VCO alone failed to fully normalize cardiac markers and tissue damage.

Carvedilol, in contrast, significantly decreased MDA levels, aligning with existing reports on its robust antioxidant properties. Its unique structure, containing a carbazole moiety, allows it to scavenge ROS, inhibit lipid peroxidation, and stabilize mitochondrial membranes (Yue et al., 1997; Kumar et al., 2016). Additionally, carvedilol has been shown to suppress NF-κB activation and proinflammatory cytokines such as TNF-α and IL-6, further reducing oxidative and inflammatory damage (Hanawa et al., 2008; Ezeh Chiamaka et al., 2023). These mechanisms likely contributed to the superior performance of carvedilol in both the biochemical and histopathological analyses.

Perhaps the most intriguing and novel observation in this study was the unexpected reduction in SOD activity in both treatment groups, even lower than in the DOX-only group. This finding defies the traditional assumption that antioxidant therapy restores or boosts endogenous enzymatic antioxidant defenses. Several plausible mechanisms may explain this paradox. One is feedback suppression, where the successful scavenging of ROS by exogenous antioxidants like VCO and CARV could signal reduced need for endogenous enzymes, leading to downregulation through redox-sensitive pathways such as Nrf2 (Fang et al., 2002; Halliwell, 2012). Another possibility is that prolonged oxidative stress from DOX resulted in irreversible oxidative modifications or depletion of SOD enzyme reserves. Furthermore, both VCO and CARV are known to activate alternative antioxidant systems — including glutathione peroxidase, catalase, and non-enzymatic scavengers — that may bypass the need for SOD activity altogether (Nevin & Rajamohan, 2006; Kumar et al., 2016). Temporal dynamics may also play a role; enzymatic activity may have peaked earlier in the treatment period and declined as redox balance was restored by external agents.

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; Utari et al., 2022). VCO mitigated 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.

Importantly, this study’s findings also resonate with those of Utari et al. (2022), who observed that VCO in combination with extra virgin olive oil (EVOO) provided superior cardioprotection against DOX toxicity compared to VCO alone. They reported that while VCO modestly reduced cardiac biomarkers such as LDH and CKMB, its effect on SGOT and histological lesions was limited. Their work, like ours, supports the notion that while VCO holds therapeutic promise, its full protective potential may be optimized through combination therapy or higher antioxidant potency. Additionally, the systemic anti-inflammatory and antioxidant effects of carvedilol and VCO have also been confirmed in the work of Ezeh Chiamaka et al. (2023), particularly in the context of DOX-induced neurotoxicity, thus validating their systemic protective roles.

**Conclusion**

This study confirms the cardioprotective effects of both virgin coconut oil and carvedilol against doxorubicin-induced cardiac injury, with carvedilol demonstrating a more profound impact across biochemical and histological parameters. The observed paradoxical downregulation of SOD activity in the treatment groups represents a novel insight into the complex regulation of antioxidant defense and suggests that therapeutic efficacy may not always correlate with elevated enzymatic antioxidant markers. This finding encourages a broader view of antioxidant intervention, one that includes both enzymatic and non-enzymatic systems, and invites further exploration into the molecular dynamics of redox homeostasis under pharmacological modulation. Future studies should extend this work by incorporating gene expression profiling, redox signaling analysis, and comparative evaluation of combined antioxidant strategies, particularly those involving synergistic blends like VCO and EVOO, as demonstrated in recent preclinical trials.

**Declarations**

Conflicts of Interest: The authors declare no competing interests

Data Availability: There is no data availability statement applicable to this research.

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