



Differential Amelioration of Aminoglycoside-Induced Oxidative Stress ... Musah, I., Et. al. (2026)

Differential Amelioration of Aminoglycoside-Induced Oxidative Stress by Virgin Coconut Oil in the Vestibulocochlear Tissue and Serum of Wistar Rats

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Abstract

Aminoglycoside (AG)-induced ototoxicity is primarily driven by the generation of reactive oxygen species (ROS) within the inner ear, leading to irreversible hair cell damage and death. Virgin coconut oil (VCO) is a natural product with potent antioxidant properties, but its specific effect on ROS levels within the vestibulocochlear tissue was unexplored. This study investigated the differential effects of VCO on concentrations of total ROS and inflammatory cytokine in the vestibulocochlear tissue and serum of rats treated with gentamicin (GTM). Thirty male Wistar rats were divided into six groups (n=5): normal control, GTM-only (80 mg/kg i.p.), GTM + Vitamin E (20 IU/kg, p.o.), and three GTM + VCO groups (1, 5, and 10 ml/kg, p.o.). Treatments were for 30 days, following which animals were sacrificed and serum and vestibulocochlear tissue homogenates were collected and assessed for total ROS, interleukin-1 β (IL-1 β), and tumor necrosis factor-alpha (TNF- α) using enzyme-linked immunosorbent assay (ELISA) kits. GTM treatment significantly elevated total ROS concentrations in both the vestibulocochlear tissue (146.02 \pm 15.95 μ g/mL) and serum (107.50 \pm 1.29 μ g/mL) compared to controls (tissue: 125.19 \pm 2.68 μ g/mL; serum: 87.49 \pm 4.38 μ g/mL; $p < 0.05$). Co-administration with VCO at all doses (1, 5, and 10 ml/kg) significantly reduced tissue ROS levels below control values ($p < 0.05$), with the 5 ml/kg dose being the most effective (83.59 \pm 2.92 μ g/mL). VCO was found to exert dose-dependent antioxidant effect on total ROS and TNF- α . These findings provide a biochemical basis for VCO's otoprotective effects as a therapeutic adjuvant during AG therapy.

Keywords: Aminoglycoside, Gentamicin, Ototoxicity, Virgin Coconut Oil, Reactive Oxygen Species, Oxidative Stress, TNF- α , Antioxidant.

Introduction

Aminoglycoside antibiotics, particularly gentamicin, remain indispensable in clinical practice for the treatment of severe gram-negative infections and multidrug-resistant tuberculosis (MDR-TB), especially in resource-limited settings like rural Nigeria (Frymark *et al.*, 2010; Heysell *et al.*, 2018). However, their use is significantly hampered by often irreversible nephrotoxicity and ototoxicity, affecting both cochlear and vestibular function in a substantial proportion of patients (Modongo *et al.*, 2015; Rizk *et al.*, 2020; Selimoglu, 2007). The pathogenesis of aminoglycoside-induced ototoxicity is complex but is now understood to be critically dependent on their accumulation in the mitochondria and the subsequent generation of reactive oxygen species (ROS). Gentamicin enters hair cells via mechano-electrical transducer channels (Marcotti *et al.*, 2005) and accumulates within mitochondria, where it forms redox-active complexes with iron (e.g., Fe²⁺-gentamicin). These complexes catalyze the Fenton reaction, generating highly damaging ROS such as superoxide anions, hydrogen peroxide, and hydroxyl radicals (Clerici *et al.*, 2005; Fu *et al.*, 2021; Schacht *et al.*, 2012).



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This oxidative stress overwhelms the intrinsic antioxidant defenses of hair cells, leading to mitochondrial dysfunction, activation of apoptotic pathways (e.g., via caspase-3 and c-Jun N-terminal kinase [JNK]), and ultimately, cell death (Huth *et al.*, 2011; Wei *et al.*, 2005). In addition to direct oxidative damage, gentamicin can also trigger inflammatory responses, with some studies implicating cytokines like tumor necrosis factor-alpha (TNF- α) in the ototoxic cascade (Fu *et al.*, 2021; Hirose & Liberman, 2003). Given the central role of oxidative stress, the search for effective antioxidant otoprotectants has been a major research focus. Agents such as D-methionine, N-acetylcysteine, and various polyphenols have shown promise in preclinical models (Campbell *et al.*, 2016; Fetoni *et al.*, 2012; Sha & Schacht, 2000). Virgin coconut oil (VCO), an unrefined oil extracted from fresh coconut kernels, has emerged as a potent natural antioxidant. It is exceptionally rich in medium-chain fatty acids (especially lauric acid) and polyphenolic compounds, which have demonstrated the ability to scavenge free radicals, reduce lipid peroxidation, and enhance the activity of endogenous antioxidant enzymes like superoxide dismutase and catalase (Arunima & Rajamohan, 2014; Nevin & Rajamohan, 2006; Zekrumah *et al.*, 2023). While VCO has shown neuroprotective effects in other models (Alghamdi, 2018; Rahim *et al.*, 2017), its specific impact on ROS generation directly within the vestibulocochlear tissue, has not been investigated. The present study was designed to elucidate a possible biochemical basis for VCO effect on oxidative stress burden within the inner ear. Therefore, we measured the concentrations of total ROS, along with the pro-inflammatory cytokines IL-1 β and TNF- α , in both the vestibulocochlear tissue and serum of male Wistar rats following chronic gentamicin exposure, with and without VCO co-administration. This allowed us to assess the differential effects of VCO within the inner ear versus its systemic anti-inflammatory and antioxidant actions.

Materials and Methods

Ethical Approval

All experimental procedures were in accordance with the Ahmadu Bello University Committee on Animal Use and Care (Approval Number: ABUCAUC/2023/066) and conducted in accordance with international guidelines for the care and use of laboratory animals.

Animals and Experimental Design

Thirty (30) male Wistar rats (initial weight range: 79-141 g) with normal startle reflex were obtained from the animal house of the Department of Human Physiology, Ahmadu Bello University, Zaria. They were housed under standard conditions with *ad libitum* access to feed and water and allowed to acclimatize for two weeks before commencement of the experiment. Rats with good startle reflex were selected and randomly assigned to six groups (n=5 per group).

Table 1: Experimental Design

Groups	Treatment
Normal Control Group	Normal saline only group
Gentamicin Only group	Received gentamicin (80 mg/kg, i.p.) daily
GTM +VCO1	Received VCO (1 ml/kg, p.o.) and gentamicin (80 mg/kg, i.p.)
GTM +VCO5	Received VCO (5 ml/kg, p.o.) and gentamicin (80 mg/kg, i.p.)
GTM +VCO10	Received VCO (10 ml/kg, p.o.) and gentamicin (80 mg/kg, i.p.)
GTM + Vit E	Received Vit E (20IU/kg, p.o.) and gentamicin (80 mg/kg, i.p.)

All treatments were administered daily for 30 consecutive days. VCO was given by oral gavage at 10:00 am, followed by intraperitoneal gentamicin at 12:00 noon to control for circadian variations in toxicity (Singh *et al.*, 2005; Blunston *et al.*, 2015; Rahim *et al.*, 2017; Cao *et al.*, 2019).



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Preparation of Virgin Coconut Oil

VCO was extracted from mature coconut kernels using a cold-process fermentation method as previously described (Nevin & Rajamohan, 2004; Yusuf *et al.*, 2016). Briefly, coconut endosperm was blended into a viscous slurry and squeezed through a cheesecloth to obtain coconut milk. The milk was refrigerated for 48 hours, then allowed to thaw at room temperature. The separated oil was collected, vigorously stirred to remove residual water, and filtered to obtain the final VCO product used for administration.

Sample Collection and Preparation

At the end of the 30-day treatment period, all rats were anesthetized with an intraperitoneal injection of ketamine (75 mg/kg) and diazepam (5 mg/kg) (Molina *et al.*, 2015). Blood samples were collected via cardiac puncture into plain bottles, allowed to clot, and centrifuged at 3000 × g for 10 minutes to separate serum, for biochemical analysis. Following blood collection, the animals were decapitated, and the left temporal bone was dissected. The thin, bulbous area of the mastoid bone containing the cochlea and vestibular apparatus (the vestibulocochlear organ) was carefully harvested as described by Neal *et al.* (2018). The tissue was rinsed in ice-cold saline, blotted dry, weighed, and homogenized in a suitable buffer. The homogenate was centrifuged, and the supernatant was collected for analysis.

Biochemical Assays

Concentrations of total ROS, interleukin-1 β (IL-1 β), and tumor necrosis factor-alpha (TNF- α) in both serum and vestibulocochlear homogenates were quantified using commercial rat enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions. The kit specifications were as follows: i) Total ROS (Cat. No. CK-bio-20410): Standard curve range 20-800 $\mu\text{g/mL}$, sensitivity 1.0 $\mu\text{g/mL}$, ii) IL-1 β (Cat. No. CK-bio-15468): Standard curve range 5-300 pg/mL , sensitivity 1.0 pg/mL , and iii) TNF- α (Cat. No. CK-bio-15469): Standard curve range 10-320 pg/mL , sensitivity 1.0 pg/mL .

Data Analysis

Data were analyzed using SPSS software (version 23.0). All values were expressed as mean \pm standard error of the mean (SEM). Comparisons between multiple groups were performed using a one-way analysis of variance (ANOVA), followed by Tukey's *post-hoc* test for multiple comparisons. A value of $p < 0.05$ was considered statistically significant.

Presentation of Results

Effect of VCO on Vestibulocochlear Tissue ROS

The concentration of total ROS in the vestibulocochlear homogenate is shown in Figure 1. Chronic gentamicin administration in the GTM-only group resulted in a significant elevation of tissue ROS ($146.02 \pm 15.95 \mu\text{g/mL}$) compared to the normal control group ($125.19 \pm 2.68 \mu\text{g/mL}$, $p < 0.05$), confirming the induction of local oxidative stress. Remarkably, co-administration of VCO in all three treatment groups not only prevented this rise but reduced tissue ROS concentrations to levels significantly below those of the normal control group ($p < 0.05$ for all VCO groups vs. control). The mean ROS concentrations were $102.51 \pm 2.58 \mu\text{g/mL}$ for GTM+VCO1, $83.59 \pm 2.92 \mu\text{g/mL}$ for GTM+VCO5, and $101.94 \pm 5.97 \mu\text{g/mL}$ for GTM+VCO10. The reduction was most pronounced in the GTM+VCO5 group, which was also significantly lower than the GTM+VCO1 and GTM+VCO10 groups ($p < 0.05$). In contrast, the GTM+Vit E group showed a significantly elevated tissue ROS concentration ($151.17 \pm 4.67 \mu\text{g/mL}$). This was significantly higher than both the normal control group ($p < 0.001$) and the GTM-only group ($p < 0.05$), and was also significantly greater than all VCO-treated groups ($p < 0.001$).

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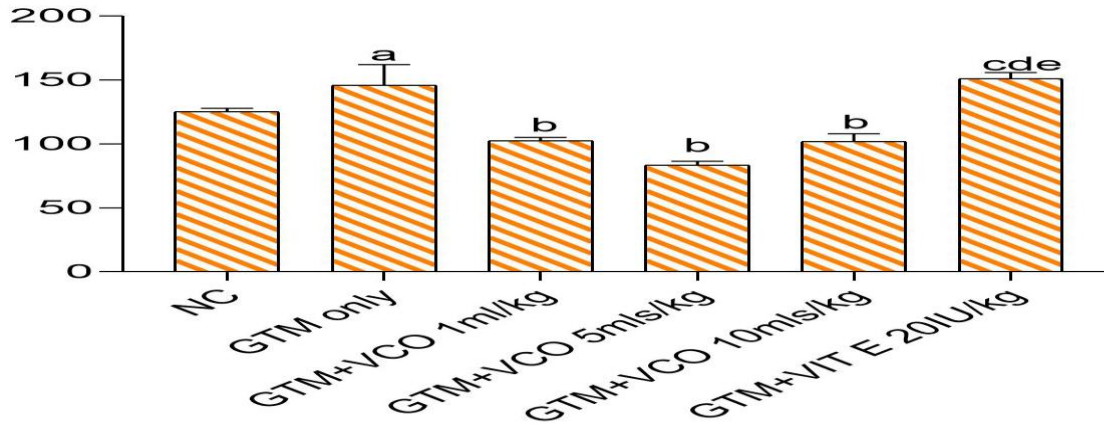


Figure 1: Results showing mean vestibulocochlear tissue ROS concentration ($\mu\text{g/mL}$) against the six experimental groups. Error bars represent SEM. Significant differences between groups are indicated by different letters ($p < 0.05$).

Effect of VCO on Serum ROS

The pattern of ROS modulation in the serum (Figure 2) was similar but not identical to that seen in the tissue. The GTM-only group had significantly elevated serum ROS ($107.50 \pm 1.29 \mu\text{g/mL}$) compared to the normal control ($87.49 \pm 4.38 \mu\text{g/mL}$, $p < 0.05$). The GTM+VCO5 ($86.87 \pm 0.73 \mu\text{g/mL}$) and GTM+VCO10 ($82.56 \pm 6.61 \mu\text{g/mL}$) groups both showed significantly reduced serum ROS concentrations compared to the GTM-only group ($p < 0.05$) and were comparable to the normal control. The GTM+VCO1 group had a mean serum ROS of $95.75 \pm 1.64 \mu\text{g/mL}$, which was not significantly different from the control or GTM-only groups ($p > 0.05$). The GTM+Vit E group also showed a significant reduction in serum ROS ($83.26 \pm 2.96 \mu\text{g/mL}$) compared to GTM-only ($p < 0.05$), contrasting with its effect in the tissue.

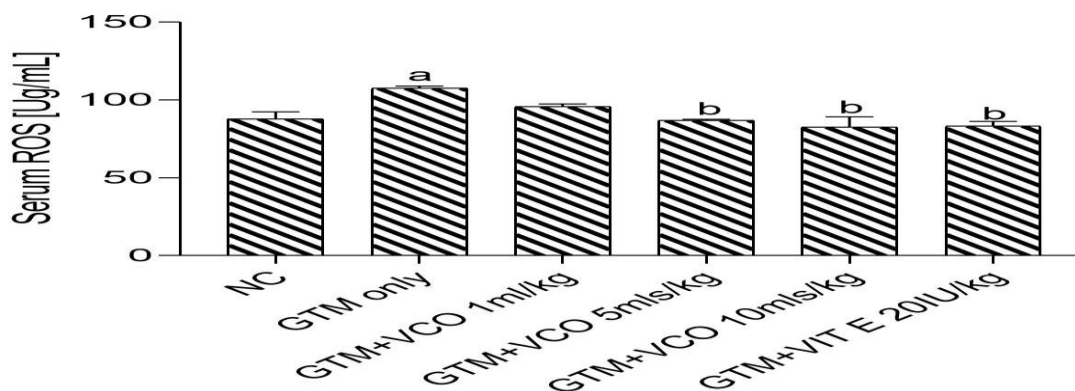


Figure 2: Results showing mean serum ROS concentration ($\mu\text{g/mL}$) against the six experimental groups on the X-axis. Error bars represent SEM. Significant differences between groups are indicated by different letters $p < 0.05$.

Effect of VCO on Inflammatory Cytokines

TNF- α Concentrations

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The effects on TNF- α are presented in Figure 3 (serum) and Figure 4 (tissue). In the serum, gentamicin induced a marked and significant inflammatory response. The GTM-only group had a mean TNF- α concentration of 258.27 ± 24.91 pg/ml, which was more than double that of the normal control (119.37 ± 10.15 pg/ml, $p < 0.001$). This systemic increase was significantly attenuated by VCO co-administration. The GTM+VCO5 (132.09 ± 12.60 pg/ml), GTM+VCO10 (96.78 ± 6.43 pg/ml), and GTM+Vit E (102.18 ± 9.36 pg/ml) groups all had serum TNF- α levels significantly lower than the GTM-only group ($p < 0.01$) and not significantly different from the normal control. In the vestibulocochlear tissue, however, the pattern was different. While the GTM-only group showed a trend towards elevated TNF- α (121.18 ± 7.95 pg/ml) compared to the control (100.88 ± 6.49 pg/ml), this difference did not reach statistical significance ($p = 0.08$). All VCO and Vitamin E-treated groups had tissue TNF- α levels comparable to the control group.

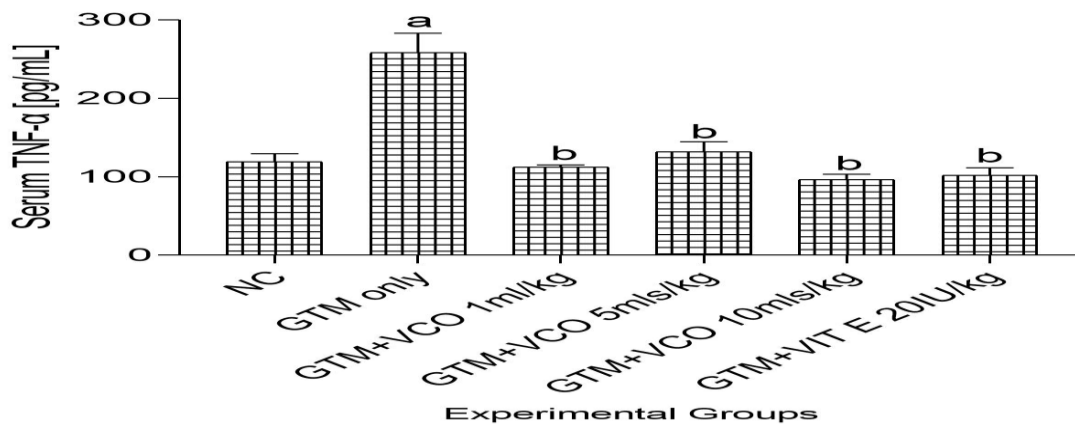


Figure 3: Results for serum TNF- α (pg/ml). Superscripts with different letters indicate statistical significance ($p < 0.05$).

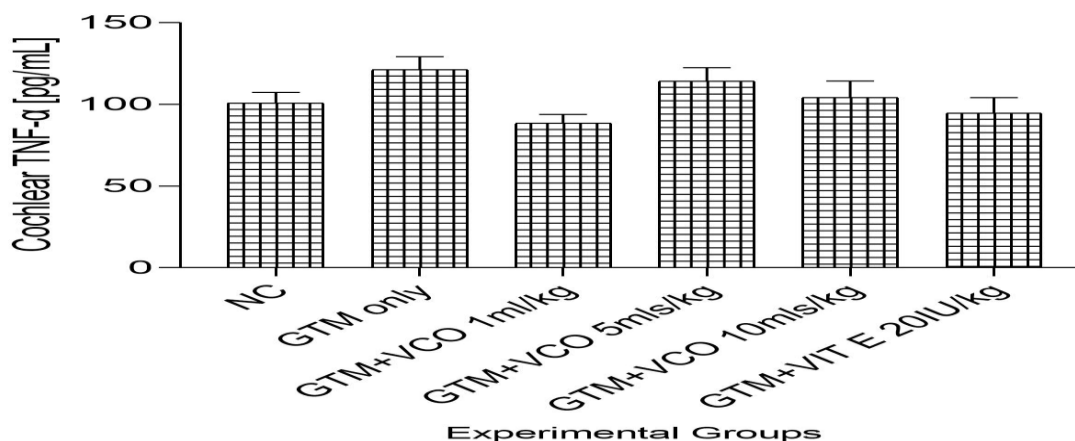


Figure 4: Results for Vestibulocochlear tissue TNF- α (pg/ml).

3.3.2 IL-1 β Concentrations



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There were no statistically significant differences in IL-1 β concentrations between any of the treatment groups, either in the serum or in the vestibulocochlear tissue ($p > 0.05$ for all comparisons). The data are summarized in Table 2.

Table 2. Serum and Vestibulocochlear Tissue IL-1 β Concentrations

Group	Tissue IL-1 β (pg/ml)	Serum IL-1 β (pg/ml)
Normal control group	2.76 \pm 0.10	3.42 \pm 0.48
Gentamicin Only group	2.98 \pm 0.14	2.69 \pm 0.24
GTM + VCO 1ml/Kg	2.74 \pm 0.09	2.79 \pm 0.11
GTM + VCO 5ml/Kg	2.74 \pm 0.11	2.88 \pm 0.22
GTM + VCO 10ml/Kg	3.18 \pm 0.13	2.69 \pm 0.11
GTM + Vit E 20IU/kg	2.95 \pm 0.27	2.96 \pm 0.17

Values are mean \pm SEM. No significant differences were found between any groups ($p > 0.05$)

Discussion of Findings

This study provides some biochemical evidence supporting the otoprotective role of virgin coconut oil against gentamicin-induced damage. Our findings demonstrate that VCO exerts differential antioxidant effects, significantly reducing ROS accumulation within the vestibulocochlear tissue the primary site of ototoxic injury, while also mitigating systemic oxidative stress and inflammation. The significant elevation of total ROS in both the vestibulocochlear tissue and serum of the GTM-only group is entirely consistent with the established mechanism of aminoglycoside ototoxicity. Gentamicin is known to generate ROS via iron-chelate complexes within mitochondria, overwhelming local antioxidant defenses and triggering apoptotic hair cell death (Clerici *et al.*, 2005; Fu *et al.*, 2021; Huth *et al.*, 2011; Schacht *et al.*, 2012). Our results confirm that a 30-day course of gentamicin at 80 mg/kg is sufficient to induce a state of chronic oxidative stress in the inner ear. This study demonstrated a significant reduction of vestibulocochlear tissue ROS by VCO. All three doses of VCO not only prevented the gentamicin-induced rise in ROS but actually lowered ROS concentrations significantly below levels of the control group. This suggests that VCO possesses a potent and direct antioxidant capacity within the cochlear and vestibular microenvironment. This aligns with the known properties of VCO, which is rich in polyphenolic compounds (e.g., gallic acid, ferulic acid) and medium-chain fatty acids that can act as direct free radical scavengers (Marina *et al.*, 2009; Nevin & Rajamohan, 2006; Zekrumah *et al.*, 2023). Furthermore, VCO has been shown in other organ systems to upregulate the expression of endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, thereby enhancing the tissue's intrinsic capacity to neutralize ROS (Arunima & Rajamohan, 2014; Famurewa *et al.*, 2020). The dose-response relationship, with the 5 ml/kg dose appearing most effective in tissue, may reflect a saturation of uptake or a ceiling effect for certain bioactive compounds within the inner ear. This robust local antioxidant effect provides a clear mechanistic basis for the preservation of auditory and vestibular function we previously observed in these same animals (Musah, 2024). The differential effect of VCO on ROS in inner ear versus serum is noteworthy. While the 1 ml/kg dose significantly reduced tissue ROS, it did not significantly lower serum ROS. This may indicate that the inner ear is more permeable to or accumulates VCO's active components, or that the ROS generated locally in the tissue is more accessible to scavenging by VCO active components or its metabolites. Alternatively, it could suggest that the primary antioxidant action of VCO in this model is a local one, with the reduction in serum ROS at higher doses (5 and 10 ml/kg) being a secondary, systemic effect. The pattern for TNF- α was also differential. Gentamicin caused a dramatic, two-fold increase in systemic (serum) TNF- α , which was effectively normalized by VCO at 5 and 10 ml/kg. This demonstrates a significant anti-



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inflammatory effect of VCO, consistent with reports of its ability to modulate inflammatory pathways, likely by inhibiting the activation of nuclear factor kappa-B (NF- κ B) (Intahphuak *et al.*, 2010). However, within the vestibulocochlear tissue itself, gentamicin did not induce a statistically significant rise in TNF- α , and VCO had no measurable effect. This finding suggests that while systemic inflammation may be a component of the broader response to gentamicin, the primary drivers of local ototoxicity are likely direct oxidative stress and perhaps other local inflammatory mediators (e.g., IL-6) or apoptotic signaling pathways (e.g., JNK), rather than a robust local TNF- α response (Eshraghi *et al.*, 2007; Fu *et al.*, 2021). The lack of any change in IL-1 β in either compartment further supports the notion that this particular cytokine is not a major player in this model of chronic gentamicin ototoxicity.

Conclusion

This study demonstrates that virgin coconut oil effectively and differentially ameliorates gentamicin-induced oxidative stress. Its most critical action is the dramatic reduction of ROS accumulation directly within the vestibulocochlear tissue, providing a possible biochemical rationale for its functional otoprotective effects. Additionally, VCO mitigates systemic inflammation by lowering serum TNF- α . These findings establish VCO as a promising, accessible adjuvant therapy to combat the debilitating ototoxic side effects of aminoglycoside, particularly gentamicin.

Areas of Limited Evidence / Future Directions

While this study measured total ROS, it did not identify the specific radical species involved or measure the activity of endogenous antioxidant enzymes (e.g., SOD, catalase, GPx) in the tissue. The lack of a significant local inflammatory response (TNF- α , IL-1 β) does not rule out the involvement of other inflammatory mediators or apoptotic pathways (e.g., JNK, caspase-3).

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