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ANTI-INFLAMMATORY AND NEPHROPROTECTIVE INFLUENCE OF VIRGIN COCONUT OIL ON GENTAMICIN-INDUCED NEPHROTOXICITY IN NON-DIABETIC AND STREPTOZOTOCIN-INDUCED DIABETIC RATS

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ABSTRACT

Gentamicin is an effective antibiotic against severe infections, but a major downside is its nephrotoxic effects. Virgin coconut oil has potential antidiabetic effects, but there has been no study on its potential role in gentamicin-induced nephrotoxicity in streptozotocin -induced diabetic rats. Thus, the aim of the current study is to explore the anti-inflammatory and nephroprotective effects of virgin coconut oil on non-diabetic and streptozotocin-induced diabetic rats. A total of 48 adult male Sprague-Dawley rats were randomly divided into eight groups (n=6), including non-diabetic groups (groups 1-4) and streptozotocin-induced diabetic groups (groups 5-8). Groups 1 and 5 received a normal diet, groups 2 and 6 were fed a normal diet + gentamicin at 100 mg/kg/day for the last 10 days of the study period, groups 3 and 7 were treated with 10 ml/kg/day of virgin coconut oil for four weeks, and groups 4 and 8 were given gentamicin for the last 10 days of the study period plus virgin coconut oil for four weeks at the same doses mentioned. Gentamicin adminstaration caused oxidative stress, and led to antioxidant defense depression which was confirmed by elevated kidney Malondialdehyde (MDA) (4.53, 5.62) and reduced renal antioxidant enzymes including renal superoxide dismutase (59.82, 45.58), catalase (53.11, 37.3) and glutathione peroxidase (51.41.36.34) in non-diabetic (ND) and diabetic (D) rats, respectively. It also resulted in a significant increase of serum urea (31.72, 50.78), creatinine (2.88, 4.16), cystatin-C (13.75, 17.69), and inflammatory biomarkers interleukin-6 (IL-6) (84.01, 102.73) and tumor necrosis factor-α (TNF-α) (667.05, 853.05) in ND and D rats, respectively. Virgin coconut oil showed protective effects and significantly improved renal function parameters, including serum urea (17.35, 38.9), creatinine (1.69, 2.96) and cystatin-C (14.26, 15.94) for ND and D groups, respectively. Pre- and co-administration of virgin coconut oil exerted a remarkable protective effect against oxidative stress induced by gentamicin in normal and diabetic rats. Pro-inflammatory biomarkers were also improved in groups treated with virgin coconut oil. The results are promising in terms of the use of virgin coconut oil as a dietary agent in attenuating the progression of chronic renal disease, especially in the context of diabetes.

Key words: anti-inflammatory, nephroprotective, virgin coconut oil, gentamicin, streptozotocin, flavonoid, phenol, oxidative stress

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INTRODUCTION

Antibiotics, especially aminoglycosides, have been significantly associated with the development of nephrotoxicity. Gentamicin is one of the most efficacious antibiotics against serious infections, including Gram-negative infections. However, its application is limited due to its toxic effects on the kidneys [1]. The exact cause of gentamicin's kidney toxicity is yet to be discovered. However, the nephropathy is correlated with gentamicin accumulation in the tubular epithelial cells. Oxidative stress is the primary mechanism in the progress of gentamicin nephrotoxicity [2].

Diabetes mellitus is a metabolic condition that occurs due to defects in insulin action or secretion, which lead to hyperglycemia. Hyperglycemia is defined as one of the primary causes of kidney dysfunction in diabetic patients [3]. Thus, several studies have focused on antioxidants or functional foods with promising anti-oxidative, anti-inflammatory and nephro-protective effects.

Traditional medicines have a significant impact on fighting several diseases. Virgin coconut oil has 7 times more polyphenols than standard coconut oil. The antioxidant impact of virgin coconut oil is attributed to its high level of polyphenols, phenolic substances and fatty acids with medium-chain, and it has no cholesterol [4]. Virgin coconut oil has revealed significant antidiabetic and antioxidant properties. However, its impact on gentamicin-induced nephrotoxicity in diabetic rats has not been clarified. Thus, the aim of the current research was to define the anti-inflammatory and nephroprotective effects of virgin coconut oil on gentamicin-induced nephrotoxicity in non-diabetic and streptozotocin-induced diabetic rats.

MATERIALS AND METHODS

Drugs and Chemicals

Gentamicin and streptozotocin were bought from Sigma (St. Louis, MA., USA). The kits used for biochemical analysis were obtained from Randox Laboratory Ltd., UK. All other reagents used were obtained commercially and were analytical grade.

Laboratory Animals and Research Scheme

The study was done with 48 adult male Sprague-Dawley rats weighing 200 ± 10 g, which were acclimatized for a week. Diets were formulated according to the recommendations of the American Institute of Nutrition -1993 (AIN-93) and amended by Reeves *et al.* [5].

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Experimental Design

The animal protocol was in accordance with NIH Publication No. 85-23 (received 1985). Following one week of acclimatization, the rats were randomly divided into eight groups (n=6), including non-diabetic groups (groups 1-4) and streptozotocin-induced diabetic groups (groups 5-8). The rats were treated for 4 weeks as shown in Table 1.

Induction of Diabetes

Streptozotocin was administered intraperitoneally (i.p.) at 50 mg/kg to induce diabetes. Blood glucose was measured to ensure diabetic status. Non-diabetic groups were injected with citrate buffer i.p. [8]. At the end of the experimental period, all animals were sacrificed. the kidneys were quickly extracted and cleaned in ice-cold saline, labeled and stored at 80°C until analysis. Cardiac blood samples were collected and centrifuged, and the obtained serum was stored at 22 °C until analysis of biochemical parameters.

Estimation of Flavonoid and Phenol contents of Virgin Coconut Oil

The total flavonoid and phenol contents of virgin coconut oil were assessed by aluminum chloride spectrophotometric and the Folin–Ciocalteu methods, respectively [9,10]. The flavonoid was reported as milligrams of quercetin equivalent (QE) per 100 gram of virgin coconut oil. The phenol content was measured in milligrams of gallic acid equivalent (GAE) per 100 grams of virgin coconut oil.

Biochemical Analysis

Blood biochemicals were assayed using commercial kits. Serum glucose, BUN and serum creatinine were estimated using commercial kits. Serum insulin was determined using a commercial ELISA kit. Serum-cystatin C was estimated using an Elisa kit (Sunlong Biotech, Hangzhou, China).

Kidney Oxidative Stress Biomarkers

Previously reported methods were used to analyze superoxide dismutase (SOD) [11], catalase (CAT) activity [12], glutathione peroxidase (GPx) [13], and reduced glutathione (GSH) content [14]. Lipid peroxidation was estimated by measuring TBARS expressed in terms of MDA content using the method of Ohkawa *et al.* [15].

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Renal Cytokines

Renal nitric oxide (NO) was analyzed according to Green *et al.* [16]. Kidney levels of TNF-α and IL-6 levels along with serum NF-κB were assessed by an ELISA kit according to the manufacturer's specifications (R & D Systems Inc.; U.S.A.).

Statistical Analysis

Data were expressed as the Mean ± SE. Analysis of variance (ANOVA) in SPSS version 26 was used to compare the groups [17]. The mean differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

Effects of Virigin Coconut Oil on Glucose and Insulin

Hyperglycemia is a major phenomenon in diabetes mellitus because of the destruction of beta cells of the pancreas or insulin resistance. The results show a significant increase in blood glucose level (292.5 ± 4.5) and a significant decline in serum insulin in diabetic group (1.33 ± 0.09) compared to the non-diabetic control(94.09 ±2.19 and 2.94± 0.11 for glucose and insulin, respectively). Virgin coconut oil administration resulted in a significant decline in serum glucose and improvement in serum insulin level in diabetic rats. Gentamicin caused a significant increase in glucose with a significant decrease in insulin in diabetic rats, while pretreatment with virgin coconut oil improved these parameters, as shown in Figure 1.

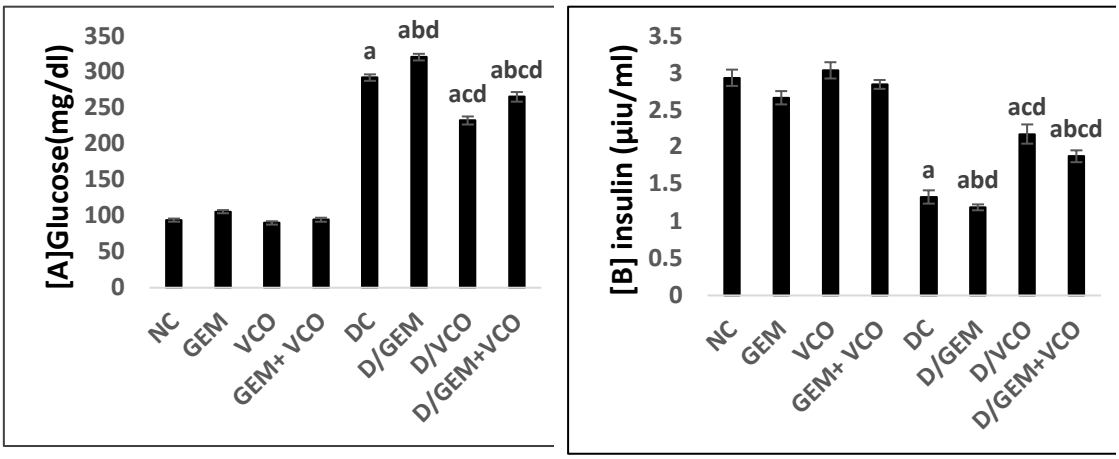

Figure 1: Effect of virgin coconut oil (VCO) and gentamicin (GEM) on (A) glucose and (B) insulin

Values are expressed as mean ± SEM (n = 6). [a] denotes significance of different groups vs. control group (P<0.05), [b]denotes significance of group treated with gentamicin alone vs. gentamicin + other groups (P<0.05), [c]denotes significance of group treated with virgin coconut oil alone vs. virgin coconut oil + other groups (P<0.05), [d] denotes significance of group treated with streptozotocin alone vs. streptozotocin + other groups (P<0.05)

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The results in the current study are in accordance with those of Alatawi and Alshubaily [18]. Coconut products alleviate hyperglycemic, hyperlipidemic and nephropathy indices in the context of streptozotocin treatment [19]. Coconut oil supplementation may have an effect on glycemic control through phenolic compounds mediating anti-inflammatory effects, which is in accordance with other recent research showing that coconut oil decreases blood sugar and improves glucose homeostasis [8].

The beneficial effect of coconut oil on improving serum insulin might have attributed to the high content of fatty acid. Lauric acid and polyphenols in virgin coconut oil can mimic insulin's effects and increase sensitivity to insulin [3]. These results are in accordance with some previous studies where virgin coconut oil improved fasting blood glucose levels, oral glucose tolerance and serum insulin in diabetic treated groups, compared to untreated diabetic rats. Virgin coconut oil's hypoglycemic effect is due to its high antioxidant content [20].

Effect of Virgin Coconut Oil on Renal Function Indices

Serum urea, creatinine and cystatin-C are used to assess kidney function. Creatinine is considered the most reliable parameter for assessing renal function in both experimental and clinical practices and indicates the structural damage of the kidneys [21]. The current findings show that 100 mg of gentamicin/kg body weight i.p. for 10 days induced nephrotoxicity, which is denoted by increases in serum creatinine, urea and cystatin-C levels (Figure 2). Pre- and co-administration of virgin coconut oil exerted a remarkable protective effect on renal function and improved gentamicin-induced renal toxicity. This was evidenced by a significant decline in renal function parameters in diabetic and non-diabetic rats.

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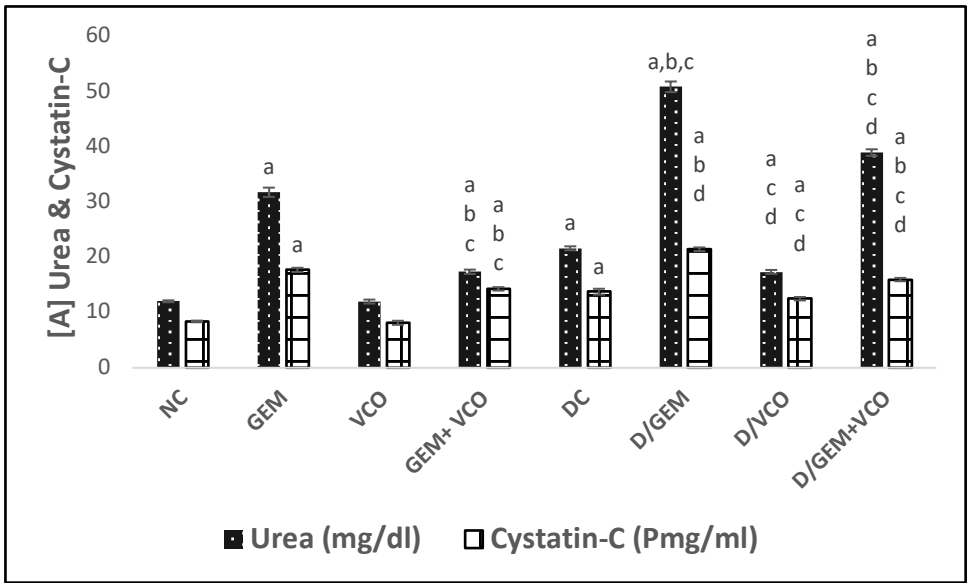

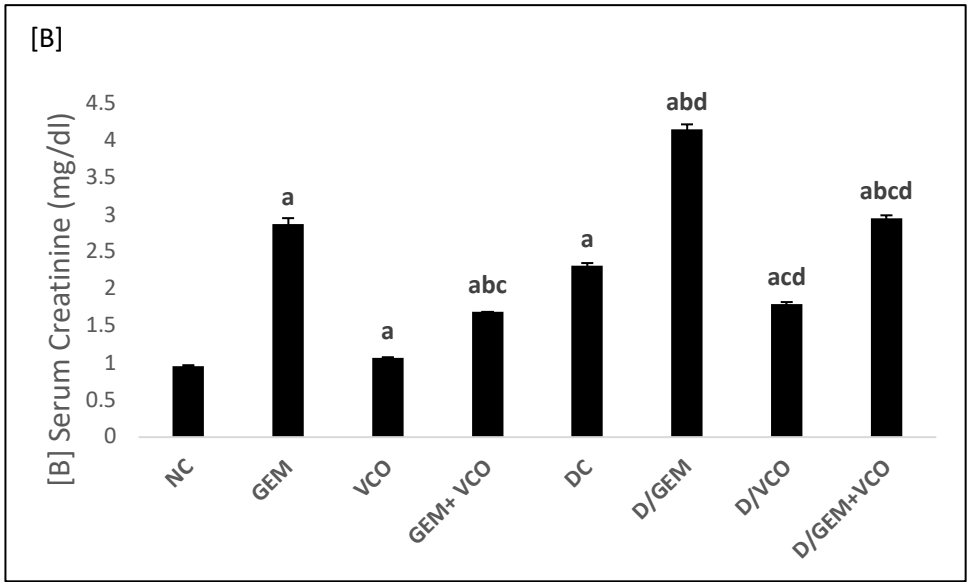

Figure 2: Effect of virgin coconut oil (VCO) and gentamicin (GEM) on (A) BUN and cystatin (B) serum creatinine

Values are expressed as mean ± SEM (n = 6). [a] denotes significance of different groups vs. control group (P<0.05), [b] denotes significance of group treated with gentamicin alone vs. gentamicin + other groups (P<0.05), [c] denotes significance of group treated with virgin coconut oil alone vs. virgin coconut oil + other groups (P<0.05), [d] denotes significance of group treated with streptozotocin alone vs. streptozotocin + other groups (P<0.05)

Accumulation of high levels of renal parameters in the blood results in the loss of renal function and integrity. The results of the current study agree with earlier research demonstrating increased serum renal markers as a consequence of

gentamicin nephrotoxicity [22]. A similar observation has shown a significant increase in renal-function biomarkers after gentamicin treatment [23]. The results of this study showed that virgin coconut oil inhibited the gentamicin-induced renal damage, which was revealed by noticeable drop in serum renal markers. Furthermore, the current results demonstrate that virgin coconut oil reduced nephrotoxicity induced by diabetes, and these findings agree with previous studies demonstrating that virgin coconut oil restores diabetic and antibiotic-induced nephrotoxicity [24]. The effect of virgin coconut oil on improving renal function can be attributed to its high antioxidant content, which works against the impairment of glomerular filtration rate that is caused by Reactive Oxygen Species (ROS) [25].

Virgin Coconut Oil Reduced Gentamicin-Induced Oxidative Stress in Renal Tissue

The body has an endogenous antioxidant defense mechanism against ROS. The antioxidant system comprises SOD, CAT and GPx. These enzymes are considered the first-line guards against the detrimental effects of ROS. However, the effect of endogenous antioxidant system will be imperfect if the production of ROS is extreme. Accordingly, it is essential to defend cells against the harmful effect of ROS via exogenous dietary antioxidants.

Redox homeostasis scavenges ROS and protects cells from oxidative collapse. However, excessive ROS generation and the resulting oxidative stress deteriorate redox homeostasis. Impaired redox homeostasis is the key mediator of gentamicin nephrotoxicity [26].

The findings show that the administration of gentamicin induced renal oxidative stress. This was confirmed by low renal levels of CAT, SOD, GPX and renal GSH in diabetic and non-diabetic rats, although intensity of the oxidative stress was higher in diabetic rats. These results agree with earlier studies, which attributed the nephrotoxic action of gentamicin to its stimulation of oxidative stress [27]. Evaluation of renal MDA levels showed a significant increase upon gentamicin administration, but feeding virgin coconut oil prior to gentamicin led to a significant decline of renal MDA in both diabetic and non-diabetic rats (Figures 3 and 4).

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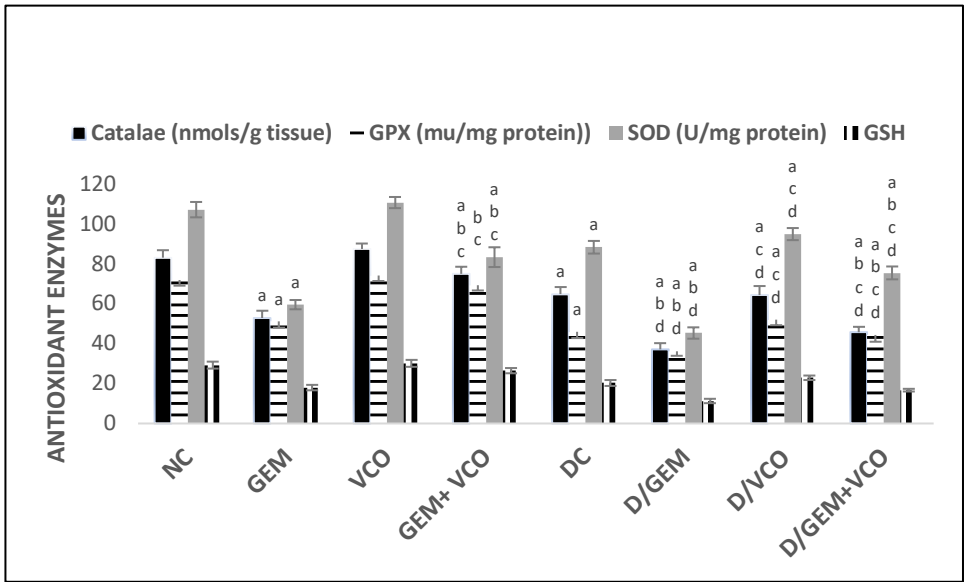

Figure 3: Effect of virgin coconut oil and gentamicin on antioxidant enzymes

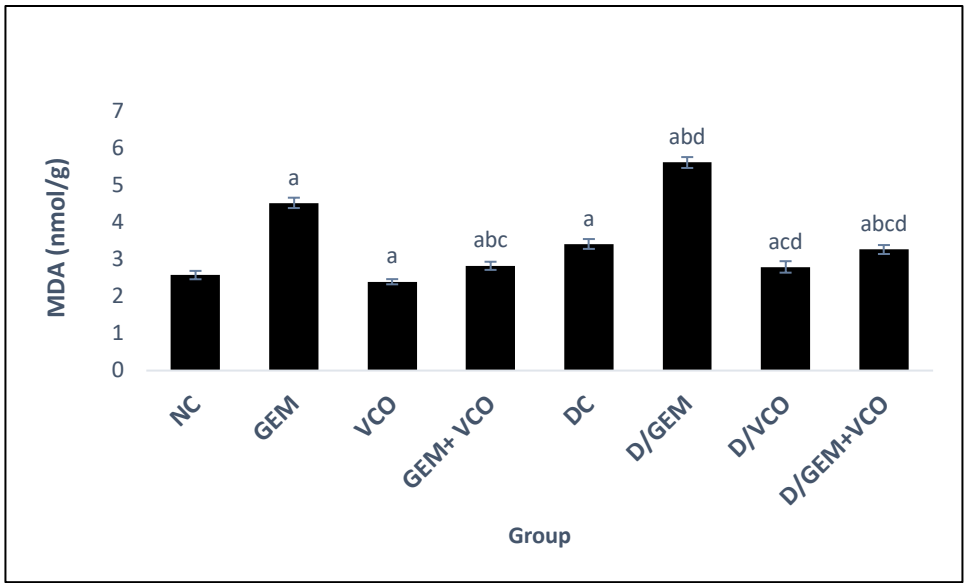

Figure 4: Effect of virgin coconut oil (VCO_ and gentamicin (GEM) on MDA

Values are expressed as mean ± SEM (n = 6). [a] denotes significance of different groups vs. control group (P<0.05), [b]denotes significance of group treated with gentamicin alone vs. gentamicin + other groups (P<0.05), [c]denotes significance of group treated with virgin coconut oil alone vs. virgin coconut oil + other groups (P<0.05), [d] denotes significance of group treated with streptozotocin alone vs. streptozotocin + other groups (P<0.05)

Gentamicin induced ROS effects by overwhelming the activity of kidney's CAT, SOD and GPx, which led to the depression of antioxidant defense. The current

results show that oxidative imbalance and depressed antioxidant defense occurred via the prominent increase in renal MDA levels. Furthermore, MDA serves as a bioactive oxidative stress indicator and a stimulator of inflammation [28].

Gentamicin enhanced ROS production and weakened the antioxidant defense. Interestingly, renal SOD, CAT, GPx and GSH levels were significantly improved in rats pre-and co-treated with virgin coconut oil compared to the gentamicin control (Figure 3). As a result, lipid peroxidation was prevented, as evidenced by a noticeable decline in kidney MDA levels (Figure 4).

Virgin coconut oil is promising as a functional food due its antioxidant abilities. The antioxidant potential of virgin coconut oil has been proven by recent in vitro and in vivo research [29]. The improvement in the antioxidant defense system could be explained by the powerful natural antioxidant content of virgin coconut oil. As per current results, VCO decreased the oxidative stress caused by gentamicin in both diabetic and non-diabetic rats. The renal activities of SOD, GPX, CAT and GSH were considerably enhanced in diabetic and non-diabetic rats treated with virgin coconut oil and were comparable to those of the gentamicin-control rats. However, the renal MDA level was significantly decreased in the virgin coconut oil-supplemented groups in comparison to the gentamicin-intoxicated diabetic and non-diabetic groups.

Virgin coconut oil is a vital dietary oil, and previous studies suggest that its powerful phenolic components contribute to its antioxidant property. There is considerable evidence that diabetes mellitus induces oxidative stress, which eventually affect various organs in the body. Coconut oil was reported to ameliorate oxidative stress by improving the antioxidant defense [29].

In agreement with the current study, some in vivo and in vitro studies demonstrated that virgin coconut oil supplementation increased the activity of CAT, SOD, GR and GPx and reduced MDA levels in the heart and kidneys of mice [30]. Virgin coconut oil has been shown to reduce MDA levels and boost endogenous antioxidants (GSH, CAT, and SOD) in diabetic mice [19].

A recent study has shown that virgin coconut oil has antioxidant activity that is able to suppress the neurotoxic oxidative effects of arsenic. Virgin coconut oil significantly increased SOD, CAT, and GPx activities compared to the controls. Therefore, virgin coconut oil's phenolics maintain SOD, CAT and GPx by inhibiting or neutralizing ROS generation [31]. Famurewa *et al.* [6] reported that virgin

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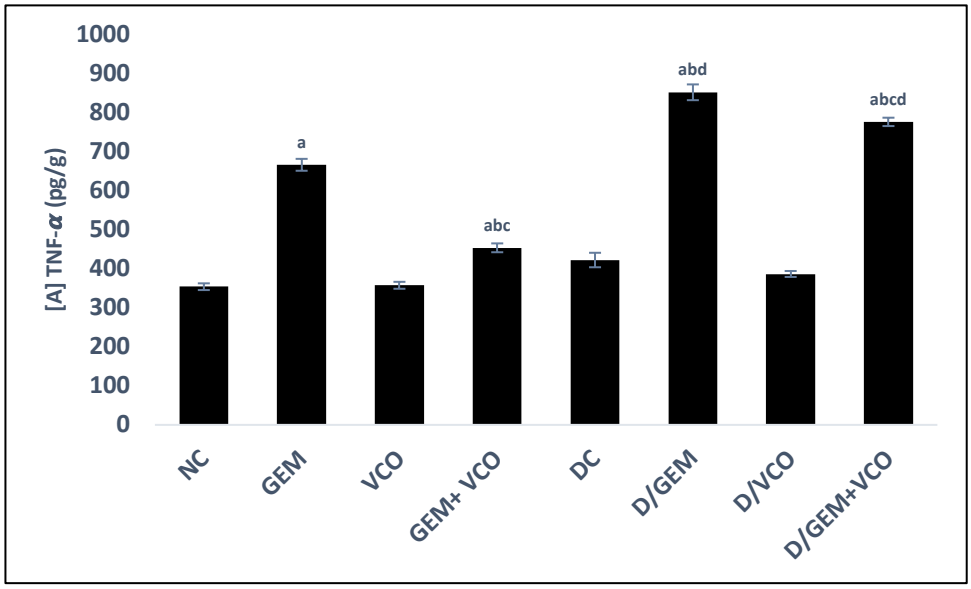
coconut oil inhibited diclofenac-induced nephrotoxicity as it enhanced SOD, CAT and GPx activities in the renal tissue with a reduction in MDA levels.

Effect of Virgin Coconut Oil on Pro-inflammatory Markers

Elevated ROS disturb redox balance, which in turn induces inflammation and cell apoptosis in many medical disorders. Oxidative stress activates the expression of nuclear factor-kappa B (NF-κB), which is a transcription factor that controls the expression of cytokines and iNOS. Activation of NF-κB facilitates its translocation to the cell nucleus, where it stimulates inflammatory gene expression [32]. In the current research, the inflammation of kidneys upon gentamicin administration was demonstrated by oxidative stress and the remarkable elevation of proinflammatory cytokines (IL-6 and TNF-α) and NO compared to gentamicin-intoxicated groups and other groups (Figure 5).



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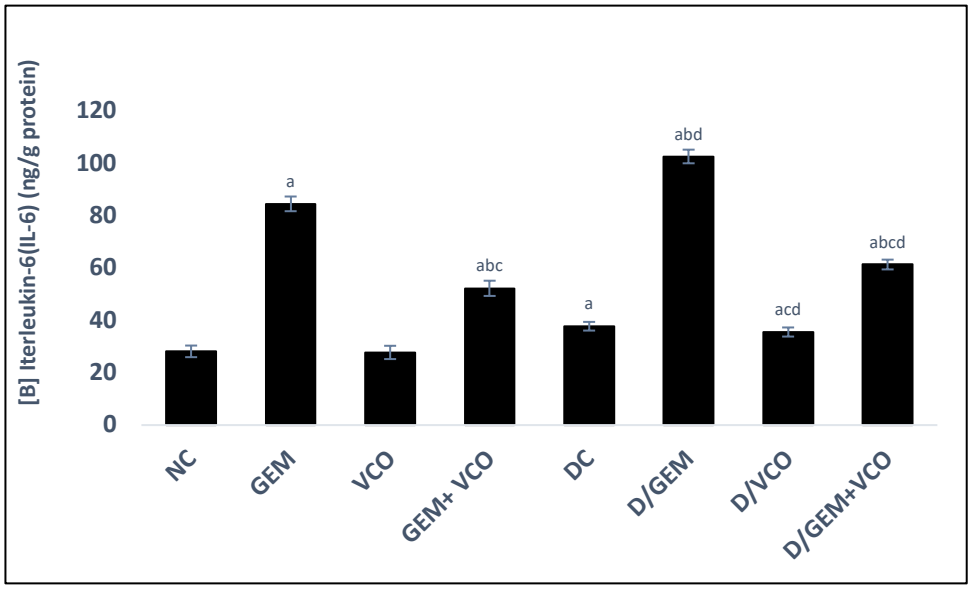

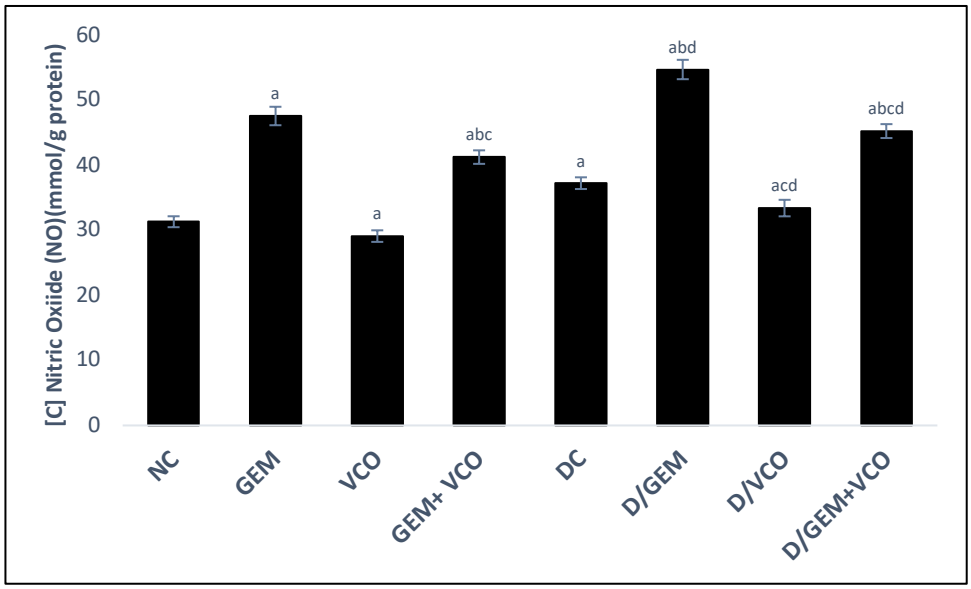

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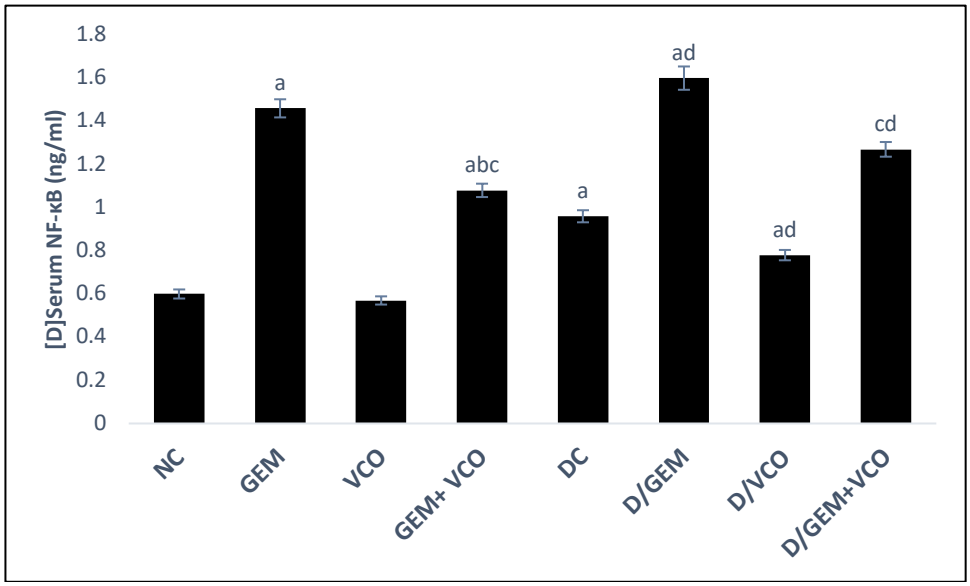

Figure 5: Effect of virgin coconut oil (VCO) and gentamicin (GEM) on (A) Renal TNF-*α*; (B) Renal IL-6; (C) Renal NO, and (D) Serum NF-κB

Values are expressed as mean ± SEM (n = 6). [a] denotes significance of different groups vs. control group (P<0.05), [b]denotes significance of group treated with gentamicin alone vs. gentamicin + other groups (P<0.05), [c]denotes significance of group treated with virgin coconut oil alone vs. virgin coconut oil + other groups (P<0.05), [d] denotes significance of group treated with streptozotocin alone vs. streptozotocin + other groups (P<0.05)

The current findings suggest that the renal inflammation might be attributed to gentamicin-induced oxidative stress and generation of free radicals, which caused activation and nuclear translocation of NF-κB. This is in accordance with other studies [26]. The marked increases in IL-6, TNF-α, and NO levels in gentamicin-intoxicated groups indicated their protein expression, which can lead to inflammatory renal damage. A similar observation was reported by Wu *et al.* [32].

High NO levels react with superoxide radicals to generate peroxynitrite, which is known to aggravate renal failure, and its inhibition could ameliorate gentamicin nephrotoxicity [27]. It has been reported that gentamicin stimulates inflammation and enhances the migration of monocytes and macrophages to the site of tissue injury [33]. Natural and synthetic antioxidants and free radicals provide nephroprotection in gentamicin-induced renal toxicity. The consumption of flavonoid-rich foods is beneficial to limit oxidative damage [34].

Recent research has demonstrated that gentamicin significantly increased renal cytokines and NO, but virgin coconut oil significantly modulated the levels of biochemical indices and downregulated the expressions of NO, iNOS, NF-κB,

caspase-3, and cytokines [35]. The anti-inflammatory effect of virgin coconut oil may be due to its capability to reverse the oxidative stress induced by gentamicin, as indicated by increases in antioxidant enzymes, including renal SOD, CAT, GPx and GSH, as well as reduced kidney MDA in the current study. Furthermore, virgin coconut oil's polyphenols demonstrate a beneficial health effect and work as modulators of inflammatory cascades to avoid pathogenesis [36]. The current health benefits of virgin coconut oil are in line with the earlier reports of antioxidant and anti-inflammatory effects of virgin coconut oil against cyclophosphamide, arthritis, insulin resistance, cardiovascular risk and hepatic steatosis [37].

CONCLUSION

In conclusion, the current results give indication that, while streptozotocin-induced diabetes exacerbates renal damage induced by gentamicin, virgin coconut oil may have the ability to lessen their effects. It might combat gentamicin-induced nephrotoxicity by blocking its mechanisms related to oxidative stress and inflammation. The results of the current research are promising in terms of the use of virgin coconut oil as a dietary agent in attenuating the progression of chronic renal disease, especially in the context of diabetes, but further studies are required to confirm the current findings.

Practical Applications

Virgin coconut oil may serve as a potential combinatorial agent against nephrotoxic side effects, especially in diabetic patients undergoing gentamicin treatment. There is potential for virgin coconut oil supplementation to be considered as a part of adjuvant strategies against side effects of gentamicin-renal toxicity.
It is worth noting that coconut oil is one of the most important edible oils in Africa and sub-Saharan Africa. Thus, it can be a promising functional food for the treatment of hyperglycemia, renal failure and inflammation in many African countries.

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N/A

Authors' contributions

Eman Aly Fadlalla and Ayman Seddik contributed equally to the conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing, review and editing. The authors approved the final manuscript.

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Disclosure Statement
No conflicts of interest exist.

Ethical considerations
The authors have declared that the guidelines of laboratory animal care were followed (National Institute of health guide for care and use of laboratory animal) {NIH Publication No. 85-23; received 1985}. All experiments were and have been in accordance with the appropriate ethics committee, Ain Shams University, Egypt.

Competing interests
Authors have declared that no competing interests exist.

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Table 1: Experimental design

Groups	Symbol	Treatment
(G1)	Normal Control (NC)	Rats received a normal diet
(G2)	Gentamicin (GM)	Rats were fed a normal diet + gentamicin (GM) (100 mg/kg/day) for the last 10 days
(G3)	Virgin coconut oil (VCO)	Rats were treated with 10 ml/kg/day of virgin coconut oil (VCO)
(G4)	(GM)+ (VCO)	Rats were given Gentamicin (GM) (100 mg/kg/day for the last 10 days) plus virgin coconut oil (VCO) at 10 ml/kg/day.
(G5)	Diabetic control (DC)	Diabetic rats received a normal diet
(G6)	Diabetic GM (D/GM)	Diabetic rats were treated + gentamicin (GM) (100 mg/kg/day)
(G7)	Diabetic VCO(D/VCO)	Diabetic rats were fed a normal diet + with 10 ml/kg/day of virgin coconut oil (VCO)
(G8)	Diabetic GM+VCO(D/GM/VCO)	Diabetic rats were given Gentamicin (GM) (100 mg/kg/day for the last 10 days) plus virgin coconut oil (VCO) at 10 ml/kg/day dose.

Rats were pretreated with 10 ml/kg body weight of virgin coconut oil for 4 weeks [6]. Rats received gentamicin (100 mg/kg bw, i.p.) for the last 10 days [7]

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Table 2: The flavonoids and phenolic contents of VCO

Sample	*Total phenolic content mg GAE / 100 g VCO*	*Total flavonoid mg QE / 100 g of VCO*
VCO	*95.70 ± 4.69*	*324.5 ± 5.78*

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