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DMBA-Induced Kidney Dysfunction: Effects of Supplementary Dietary Vitamin K in Rats

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ABSTRACT

DMBA (7,12-Dimethyl-1,2-benzathracene) is a polycyclic aromatic hydrocarbon known to cause many toxic effects. Nephrotoxicity occurs following exposure of the kidneys to this potent mutagen and carcinogen (i.e., DMBA). This study investigated the prophylactic potentials of vitamin K-supplemented diet against DMBA-induced nephrotoxicity in experimental rats.
Twenty-eight (28) Wistar rats (mean weight of 135g) were randomly grouped into 4. The control (group 1) was fed with normal rat chow containing the recommended daily allowance (RDA) of vitamin K (0.0075%). Groups 2 and 3 received a single dose of DMBA (80 mg/kg body weight) intragastrically, while group 3 animals were maintained on a surplus vitamin K supplemented diet (0.075%). Group 4 animals were fed the surplus vitamin K supplemented diet alone, with no DMBA challenge. All exposure lasted for 16 weeks. Concentrations of kidney function parameters (BUN and creatinine), pro-inflammatory biomarkers (IL-2 and L-selectin), and electrolytes (K^+, Na^+, Mg^{2+}, and Ca^{2+}) were measured in the serum. Oxidative stress biomarkers (MDA and NO) were also monitored in addition to enzymatic and non-enzymatic antioxidant parameters. Histopathology of the kidney tissues was used to confirm possible alterations and protection. Our investigations revealed significant protection from DMBA-induced renal toxicity by surplus vitamin K inclusion in the diet.

Keywords: DMBA, Antioxidants, Nephrotoxicity, Polyaromatic hydrocarbons, Vitamin K.

Introduction

DMBA (7, 12-dimethylbenz[a]anthracene), a member of the polyaromatic hydrocarbons (PAHs), is an immune-suppressor and potent organ-specific pro-carcinogen and pre-mutagenic.[1] Recent data submits that DMBA provokes the generation of free radicals such as intracellular hydroxyl and superoxide anion radicals and other reactive oxygen species (ROS) that potentiate lipid peroxidation, DNA damage, and exhaustion of the cellular antioxidant capacities, as well as disruption of a variety of biochemical pathways.[1,2]
The kidneys are particularly vulnerable to DMBA-induced toxicities. They are metabolically active and receive a quarter of cardiac output (despite weighing below 1% of total body weight). They also filter water out from the filtrate and may thus concentrate and accumulate these toxic substances.[3,4] DMBA exposure has been shown to induce marked histological alternations in kidney, e.g., dilation of tubules and sloughing of the epithelium (signifying enhanced disintegration of tubules); with the epithelial cells of proximal convoluted tubules and Bowman's capsule being especially sensitive to DMBA-induced toxicity.[5,6]

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Moreover, DMBA-induced nephrotoxic changes are hallmarked by glomerular and tubular injuries attendant with lesions, polyps, and cancer tendencies.[5]
Given the doubtful efficacy and safety of conventional anti-nephrotoxic agents, it is imperative to search for safer and more reliable agents.[5] Experimental studies have outlined several beneficial effects of vitamin K, group of lipophilic vitamins. Besides, being a co-factor for gamma-glutamyl carboxylase (γ-GCX), other more promising protective roles for vitamin K have been observed. For instance, Li *et al.*[7] showed that vitamin K, via attenuation 12-lipoxygenase activation and thereby blocking the production of ROS, precludes oxidative cell death in pre-oligodendrocytes (p-OLs). Also, phylloquinone (vitamin K1) and menaquinone 4 (MK-4; vitamin K2) has been reported to shield p-OLs and immature nerve cells against glutathione depletion-induced oxidative injury and generation of ROS[7]. It has been shown to have cardio- and osteo-protective properties,[8] anti-tumour, and pro-apoptotic effects,[9,10] and anti-inflammatory activities,[11,12] as well as protection against chronic kidney disease.[13]This novel anti-oxidative and anti-inflammatory potentials make vitamin K a promising therapeutic agent against several diseases. There exist various experimental investigations into the protective effects of natural products and supplements on DMBA-induced toxicity.[1,5] However, to date, investigations into the impact of vitamin K supplementation on DMBA-induced renotoxicity remain scanty, hence the need for this research.

Materials and Methods

Experimental design
Twenty-eight healthy Wistar rats (mean weight of 135 g) were utilized for this study. These were housed and granted free access to feed and

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Biochemistry, Federal University of Agriculture, Abeokuta (ethical approval no: FUNAAB/CBS/BCH/180134).
The animals were grouped into four of seven animals each. Group 1 rats served as the control and were fed with a normal diet (containing the recommended daily allowance of vitamin K). Rats in the second and third groups were administered a single dose of DMBA (80 mg/kg body weight) intragastrically by gavage, according to Zingue *et al.*[15] While group 2 rats were on the normal diet, those in group 3 were maintained on surplus vitamin K diet (0.075 g/kg diet).[16] The last group were fed surplus vitamin K diet (0.075 g/kg diet) only, for the 16-week duration. The weight of the rats was recorded weekly all through the 16 weeks of study.

Sample collection
Animals were anesthetized under intraperitoneal injection of Ketamine/Xylazine (60 mg/kg and 6mg/kg respectively) at the end of the exposure. Blood samples were collected into plain bottles and serum was obtained after centrifugation of coagulated blood at 3500 rpm for 10 minutes. The kidneys were harvested and processed for biochemical, molecular, and histopathological analysis.

Biochemical analysis
Biochemical analyses were carried out in the kidney homogenates and serum.

Determination of antioxidants activities/concentrations
The activity of catalase (CAT) was determined according to the method described by Goth[17] as modified by Hadwan and Abed.[18] The activities of glutathione peroxidase (GPx) and glutathione-*S*-transferase (GST) were determined according to the method of Rotruck *et al.*[19] and Habig *et al.*[20]respectively. The superoxide dismutase (SOD) activity was measured following the method of Marklund and Marklund.[21]The concentrations of reduced glutathione (GSH) and vitamin C were determined following the methods previously described by Jollow *et al.*[22] and Omaye *et al.*[23] respectively.

Estimation of oxidative stress biomarkers
Lipid peroxidation was measured as malondialdehyde (MDA) concentrations, based on its reaction with thiobarbituric acid, as described by Beuge and Aust.[24] The concentration of nitric oxide (NO) was determined using Greiss reagent, as described by Rao.[25]

Indices for determining kidney function
The concentrations of creatinine, urea, sodium, potassium, magnesium, and calcium were determined, using commercially available kits obtained from Fortress Diagnostics Limited (Antrim, United Kingdom) following the manufacturer's instructions.

Estimation of serum interleukin 2 (IL-2) and selectin concentrations
The IL-2 and selectin concentrations in the serum were determined by the ELISA method, according to the manufacturer's instructions.

Histopathology study
Sections of the kidney tissues were fixed in 10% formalin solution, embedded in paraffin wax. Sections of tissues (5 µm thick) were mounted on slides, hematoxylin and eosin stains used for cellular, morphological identification, and evaluations were added. All sections were studied and photographed by a light photomicroscope, at the Department of Veterinary Pathology, Federal University of Agriculture, Abeokuta, Ogun State, Nigeria.

Statistical analysis
Values obtained were expressed as the mean ± standard error of the mean (n=7). The data obtained were analysed with one-way analysis of variance using a statistical software package, SPSS version 20. Comparison of significant groups was carried out using *post-hoc* Duncan's multiple range tests, with $p<0.05$ considered statistically significant.

Results and Discussion

Effects on body weight
By week 16, exposure to DMBA was observed to significantly ($p<0.05$) prevent body weight gain (by about 55.2%) in the DMBA group, compared to the normal diet group. Inclusion of surplus vitamin K diet, however, annulled this DMBA-induced weight loss (Figure 1). Rojas-Armas *et al.*[26] and Rajendran *et al.*[27] reported similar observations wherein DMBA administration led to significant body weight loss. Loss of appetite and subsequent reduced food and energy intake were suggested as possible explanations for the DMBA-inhibition of body weight gain. Similarly, Krishnamoorthy and Sankaran[28] reported significant weight losses in rats, which they ascribed to the reduced amount of fat tissues and skeletal muscle mass that was occasioned following exposure to DMBA.

Effects on the antioxidant capacity
Results revealed significant ($p<0.05$) decreases in the activities of enzymatic (SOD, GST, and GPx) and non-enzymatic (GSH and vitamin C) antioxidants, as well as increased activities of CAT, in both serum and kidneys of DMBA-administered rats when compared to the control group (Tables 1 and 2). DMBA and its metabolites have been reported to induce the production of free radicals such as intracellular hydroxyl and superoxide anion radicals and other ROS.[1,29] The ROS produced can move from the initial site of production to other sites or spread the injury to intact cells, propagating oxidative chain reactions, leading to several injurious effects.[30] To curtail this, the body uses antioxidants to react with these reactive species, and in the process, the cellular antioxidants may become depleted. Indeed, consistently decreased activities of antioxidant enzymes in experimental subjects have been reported following exposure to DMBA.[5,31] The results of this study corroborate initial reports in which the enzymatic and non-enzymatic antioxidant capacity were decreased in the serum and kidneys following DMBA administration. Besides, supplementation with surplus vitamin K to DMBA-administered rats significantly restored the antioxidants to near-normal levels, pointing to its antioxidant potentials against DMBA-induced ROS generation. The group fed surplus vitamin K diet alone had antioxidant activities/concentrations statistically in tune with the control group (Table 1).

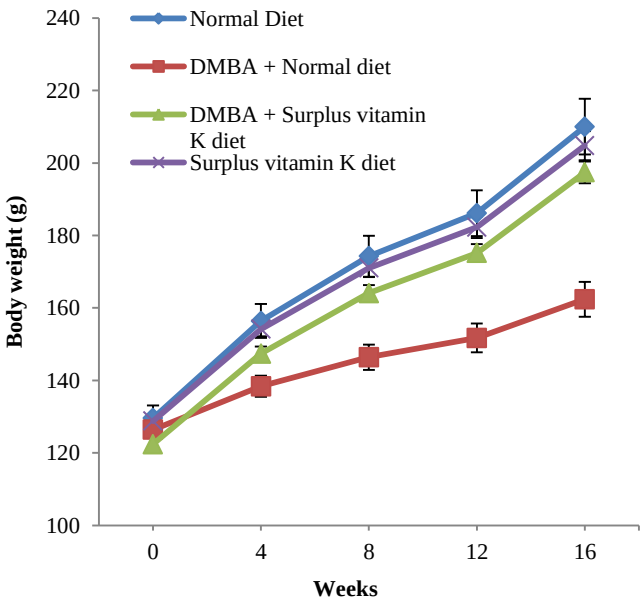

Figure 1: Effects of vitamin K supplemented diet on body weight (g) in the control and DMBA-exposed rats. Lines represent mean ± S.E.M (n = 10).

Effects on markers of oxidative stress/damage

Following the DMBA-induced production of reactive species and the resulting depletion of cellular antioxidants, oxidative stress ensues, wherein cellular components suffer oxidative attack by these unstable reactive species, leading to damage of DNA, lipids, and proteins.[32] Biomarkers of oxidative damage include NO and MDA. Concentrations of NO and MDA in both serum and kidney homogenates of the DMBA-administered control group (fed normal diet) were markedly increased compared with the control group (Table 3). The percentage increases were by 88.2 and 27.2 (in the serum) and 39.0 and 32.6 (in the kidney) respectively. These increments in the serum and kidney of rats exposed to DMBA, following the depletion of antioxidants, are unsurprising and have been similarly reported by Krishnamoorthy and Sankaran[28] and Kiran *et al.*[1]These authors also implicated DMBA-induced oxidative stress as the underplaying mechanism. However, supplementation with vitamin K significantly($p<0.05$) reduced the DMBA-induced elevations in oxidative damage markers (NO and MDA) as compared to DMBA + normal diet group [by 63.0 and 23.9% (in the serum), and 18.3 and 13.5% (in the kidneys) respectively]. More so, the group fed surplus vitamin K diet alone, on the other hand, had NO and MDA concentrations similar to control (Table 3). These protective effects displayed by vitamin K on the antioxidant system are attributable to and indicative of its antioxidant properties, which had begun to garner considerable scientific interest, since the last century. Vervoot *et al.*[33] showed the attenuating ability of vitamin k in microsomal lipid peroxidation while proposing the vitamin K cycle as a major mediator of its antioxidant property via direct scavenging of ROS. On the other hand, Ohyashiki *et al.*[34] concluded that the mechanism of inhibition of free radical generation by vitamin K is majorly through radical-chain reaction termination. The results of Li *et al.*[35] that vitamin k can halt oxidative death caused by GSH depletion, also lend credence to the antioxidant properties of vitamin K. Li *et al.*[7] similarly showed that vitamin K, by 12-lipoxygenase inactivation and resultant blockage of ROS production, precludes oxidative cell death in p-OLs. The scavenging ability of vitamin K removes the oxidative burden resulting in the sparing of cellular antioxidants, whose activities and concentrations can then be restored, accounting for the observed replenishment of cellular antioxidants, with a concomitant reduction in oxidative markers, following supplementation with vitamin K.

Effects on indices of kidney function

Given the damaging effects of DMBA-induced oxidative stress on cellular function and particular susceptibility of the kidney to DMBA-induced toxicity, this study also investigated the effects of DMBA administration and vitamin K (VK) supplementation on some biomarkers of kidney function. The concentrations of K^+ and Na^+ were significantly ($p < 0.05$) reduced, in both the serum and kidneys of DMBA-administered rats when compared to the control group (by 53.1 and 18.9 % in the serum and 75.8 and 44.8 % in the kidneys, respectively). No significant ($p < 0.05$) difference was observed across all treatment groups for Mg^{2+} concentration, while Ca^{2+} concentration was significantly ($p < 0.05$) increased in both serum and kidneys of the DMBA-administered control group when compared to the control group (by 17.9 and 58.0 % respectively) (Table 4). On the other hand, the concentrations of urea and creatinine in the serum of the DMBA only-administered group were markedly increased compared with the control group. The percentage increases were by 84.3 and 43.7 respectively. In the kidneys, however, percentage decreases of 32.4 and 48.0 in the concentrations of urea and creatinine respectively, were observed in the DMBA-administered control group compared to the control group (Table 5). Liberally filtered by the glomerulus, these biomarkers are then excreted via the urine with negligible metabolism by the kidney. Thus, altered levels in the blood, in most cases, may indicate the onset of kidney failure.[36] Accompanying DMBA-induced oxidative damages are modifications of cellular constituents (either by the reactive species themselves or products of oxidative damage like MDA), resulting in loss of function, which culminates in impaired cellular function and eventual organ failure.[1,5]Once the kidney is damaged or its function impaired, metabolites that should be normally filtered out from the blood into the urine are not (leading to decreased concentrations of these metabolites in the kidneys), but instead, enter back into circulation (accumulating in the blood).[37] These proposed events may, thus, account for the observed increase of K^+, Na^+, urea, and creatinine in the blood, with a concomitant decrease in the kidneys. Interestingly, co-treatment of DMBA-administered rats with the surplus vitamin K diet restored the decreased concentrations of K^+ and Na^+ as well as the increased Ca^{2+} concentrations to normal levels (Table 4), while the urea and creatinine concentrations were normalized in both the serum and kidneys. These findings that supplementation with vitamin K significantly ameliorated the DMBA-induced alteration in indices of renal function may be suggestive of not just its antioxidant properties, but also its reno-protective potentials, which has been previously suggested by Wuyts and Dhondt.[38]

Effects on serum concentrations of interleukin-2 and selectin

The effects of DMBA and vitamin K supplementation on serum concentrations of IL-2 are illustrated in Figure 2. The IL-2 concentration was significantly ($p < 0.05$) reduced in the DMBA-administered control group (by 49.0%) when compared with the control group (Figure 2).

Table 1: Effects of DMBA Administration and Vitamin K Supplement on the Specific Activities on Enzymatic Antioxidants in the Serum and Kidney of Experimental rats

SERUM				
Groups	**CAT (kU/g protein)**	**SOD (U/mg protein)**	**GST (U/mg protein)**	**GPx (U/mg protein)**
Normal Diet	0.05 ± 0.01^a	0.23 ± 0.01^b	4.65 ± 0.19^c	3.15 ± 0.16^c
DMBA + Normal diet	0.15 ± 0.03^b	0.13 ± 0.01^a	1.90 ± 0.16^a	1.41 ± 0.01a
DMBA + surplus VK diet	0.04 ± 0.02^a	0.22 ± 0.01^b	3.34 ± 0.04^b	1.79 ± 0.06^b
Surplus VK diet	0.05 ± 0.01^a	0.23 ± 0.02^b	4.31 ± 0.13^c	3.50 ± 0.02^c
KIDNEY				
Normal Diet	0.25 ± 0.03^a	2.89 ± 0.12^c	4.83 ± 0.19^c	46.51 ± 1.41^c
DMBA + Normal diet	1.41 ± 0.04^c	0.90 ± 0.05^a	1.96 ± 0.05^a	34.65 ± 0.72^a
DMBA + surplus VK diet	0.31 ± 0.04^b	1.84 ± 0.09^b	3.87 ± 0.04^b	40.01 ± 0.68^b
Surplus VK diet	0.25 ± 0.04^a	3.04 ± 0.09^c	3.94 ± 0.21^b	47.05 ± 1.17^c

Data are expressed as mean ± SEM (n = 10). Values having different superscript letters within the same column are significantly different ($p < 0.05$).
CAT = catalase, SOD = superoxide dismutase (SOD), GST = glutathione-S-transferase, GPx = glutathione peroxidase.

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Table 2: Effects of DMBA Administration and Vitamin K (VK) Supplementation on the Concentrations of reduced Glutathione (GSH) and Vitamin C in the Serum and Kidney of Experimental rats

	Serum		Kidney	
Groups	**GSH (µmol/L)**	**Vit C (mg/dl)**	**GSH (µmol /g tissue)**	**Vit C (mg/g tissue)**
Normal Diet	87.63 ± 3.97^{c}	1.38 ± 0.01^{c}	0.63 ± 0.03^{c}	27.44 ± 0.39^{c}
DMBA + Normal diet	66.15 ± 0.42^{a}	0.38 ± 0.02^{a}	0.17 ± 0.01^{a}	12.48 ± 0.69^{a}
DMBA + surplus VK diet	75.05 ± 4.39^{b}	1.11 ± 0.04^{b}	0.21 ± 0.01^{b}	23.84 ± 0.47^{b}
Surplus VK diet	89.08 ± 2.42^{c}	1.45 ± 0.07^{c}	0.62 ± 0.01^{c}	25.12 ± 1.27^{b}

Data are expressed as mean ± SEM (n = 10). Values having different superscript letters within the same column are significantly different ($p < 0.05$).

Table 3: Effects of DMBA Administration and Vitamin K (VK) Supplementation on the Concentrations of Nitric Oxide (NO) and Malondialdehyde (MDA) in the Serum and Kidneys of Experimental rats

	Serum		Kidney	
Groups	**NO(mmol/L)**	**MDA (µmol/L)**	**NO (mol/g tissue)**	**MDA (nmol/g tissue)**
Normal Diet	3.23 ± 0.24^{b}	27.31 ± 1.73^{a}	48.7 ± 0.59^{a}	24.36 ± 0.79^{a}
DMBA + Normal diet	6.08 ± 0.15^{c}	34.74 ± 1.15^{b}	67.7 ± 0.26^{b}	32.31 ± 0.63^{c}
DMBA + surplus VK diet	2.25 ± 0.24^{a}	28.03 ± 0.72^{a}	55.3 ± 1.71^{a}	27.95 ± 0.90^{b}
Surplus VK diet	3.40 ± 0.25^{b}	28.51 ± 2.31^{a}	49.0 ± 0.35^{a}	23.62 ± 0.71^{a}

Data are expressed as mean ± SEM (n = 10). Values having different superscript letters within the same column are significantly different ($p < 0.05$).

Table 4: Effects of DMBA Administration and Vitamin K (VK) Supplementation on the Concentrations of some Electrolytes in the Serum and Kidneys of Experimental rats

Groups	K^{+}	Na^{+}	Mg^{2+}	Ca^{2+}
SERUM	**(µmol/L)**	**(mg/dl)**	**(µmol/L)**	**(mg/dl)**
Normal Diet	1.92 ± 0.08^{b}	2.06 ± 0.06^{b}	0.60 ± 0.01^{a}	1.45 ± 0.04^{a}
DMBA + Normal diet	0.90 ± 0.03^{a}	1.74 ± 0.01^{a}	0.66 ± 0.02^{a}	1.71 ± 0.09^{b}
DMBA + surplus VK diet	1.97 ± 0.07^{c}	2.01 ± 0.06^{b}	0.60 ± 0.01^{a}	1.36 ± 0.01^{a}
Surplus VK diet	2.00 ± 0.03^{c}	2.48 ± 0.05^{c}	0.64 ± 0.02^{a}	1.33 ± 0.02^{a}
	K^{+}	Na^{+}	Mg^{2+}	Ca^{2+}
KIDNEY	**(µmol/g tissue)**	**(mg/g tissue)**	**(µmol/g tissue)**	**(mg/g tissue)**
Normal Diet	15.47 ± 0.42^{c}	6.29 ± 0.24^{b}	6.55 ± 0.08^{a}	13.74 ± 0.44^{a}
DMBA + Normal diet	3.74 ± 0.41^{a}	3.47 ± 0.10^{a}	6.88 ± 0.33^{a}	21.71 ± 0.28^{c}
DMBA + surplus VK diet	16.66 ± 0.26^{c}	6.93 ± 0.32^{b}	6.98 ± 0.11^{a}	17.90 ± 0.43^{b}
Surplus VK diet	5.01 ± 0.56^{b}	3.95 ± 0.22^{a}	7.03 ± 0.17^{a}	13.86 ± 0.53^{a}

Data are expressed as mean ± SEM (n = 10). Values having different superscript letters within the same column are significantly different ($p < 0.05$).

Table 5: Effects of DMBA Administration and Vitamin K (VK) Supplementation on the Concentrations of Urea (UR) and Creatinine (CR) in the Serum and Kidneys of Experimental rats

	Serum		Kidney	
Groups	**Urea (µmol/L)**	**CR (mg/dl)**	**UR (µmol/g protein)**	**CR (mg/g tissue)**
Normal Diet	7.77 ± 0.24^{a}	96.79 ± 1.7^{c}	50.65 ± 0.48^{c}	16.57 ± 0.37^{c}
DMBA + Normal diet	14.32 ± 0.45^{c}	139.05 ± 0.85^{d}	34.19 ± 0.7^{a}	8.61 ± 0.48^{a}
DMBA + surplus VK diet	10.40 ± 0.48^{b}	80.11 ± 1.09^{a}	40.94 ± 1.63^{b}	13.01 ± 0.90^{b}
Surplus VK diet	6.12 ± 0.40^{a}	82.21 ± 3.85^{b}	49.86 ± 1.85^{c}	16.54 ± 1.68^{c}

Data are expressed as mean ± SEM (n = 10). Values having different superscript letters within the same column are significantly different ($p < 0.05$).

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On the other hand, exposure to DMBA caused a significant ($p < 0.05$) increase, of 78.2 %, in the concentration of selectin, when compared with the control group (Figure 3). Selectins (cluster of differentiation 62 or CD62) are a family of cell adhesion molecules (or CAMs), that played an important role in inflammation and progression of cancer.[39,40] Moreover, Yusuf *et al.*[41] and Katz *et al.*[42] have reported elevated concentrations of selectins, following DMBA administration. On the other hand, interleukin-2 (IL-2) is a cytokine signalling molecule, with pleiotropic effects on the immune system, helping the body fight off infections.[43, 44] However, in conditions of oxidative stress, circulating IL-2 has been observed to be reduced.[45,46] Consistent with these previous reports, the serum concentrations of IL-2 were significantly increased in DMBA-administered rats compared to the controls, with the DMBA-induced oxidative stress possibly playing a part, whereas supplementation with vitamin K ameliorated these changes, increasing the IL-2 concentration (by 56.0%) and decreasing the concentration of selectins (30.8%). We attribute these beneficial effects to its anti-inflammatory properties,[11,12] thereby attenuating the progression of pro-inflammatory responses elicited by DMBA in the exposed rats.

Histopathology of Kidneys of rats administered DMBA and vitamin K

The histological alterations in all the treatment groups were presented in Figure 4A-D. Normal physiology with no visible lesions in kidney histology was observed in the control (normal diet) group (Figure 4A). On the other hand, kidney tissue histological examination of DMBA-administered rats revealed severe diffuse tubular degeneration and necrosis in Figure 4B (DMBA group fed normal diet). DMBA-administered rats fed with the surplus vitamin K diet showed mild to moderate diffuse tubular degeneration (Figure 4C).Normal physiology with no visible lesions in kidney histology was observed in rats given surplus vitamin K diet alone (Figure 4D).Thus, the oxidative cellular/tissue damage occasioned by DMBA-administration, evidenced by the results of body weight, antioxidant status, and oxidative stress markers were supported by the histological examinations of the kidneys of the different experimental groups.

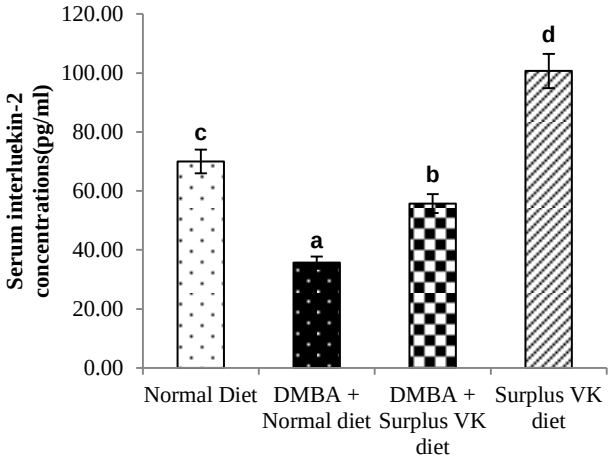

Figure 2: Effects of vitamin K on serum interleukin-2 concentrations in rats with DMBA-induced toxicity. Bars are mean ± sem (n = 10). Bars having different superscript letters are significantly different.

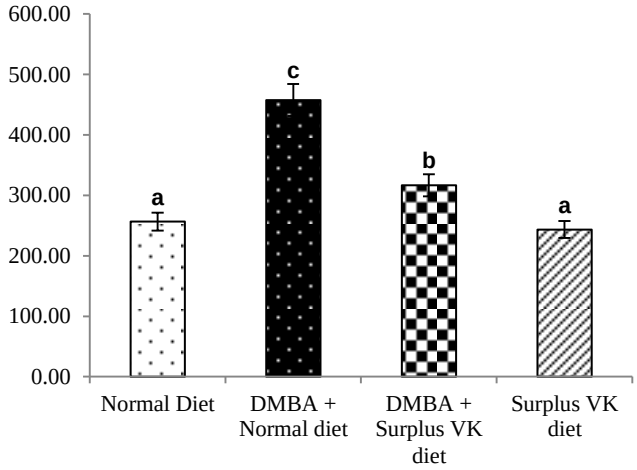

Figure 3: Effects of vitamin K on serum selectin concentrations in rats with DMBA-induced toxicity. Bars are mean ± sem (n = 10). Bars having different superscript letters are significantly different.

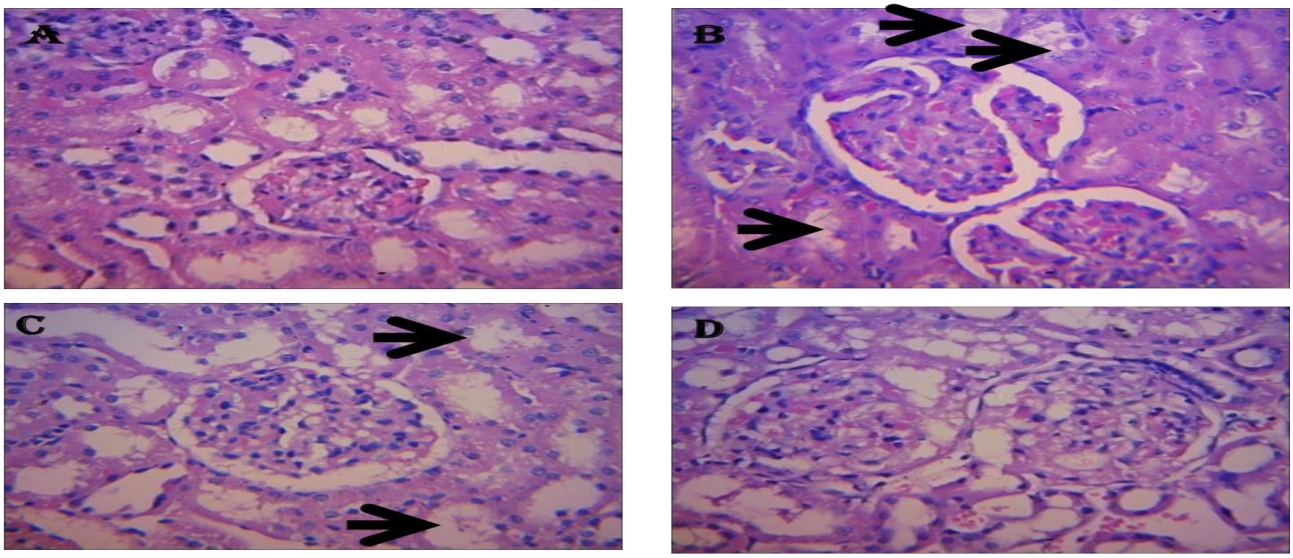

Figure 4: Representative photomicrographs of kidney sections from the control and the DMBA treated rats (H&E X400).Group A served as the control group and was fed a normal diet, Group B received DMBA + normal diet; Group C received DMBA + surplus vitamin K. Group D received surplus vitamin K diet alone.

Conclusion

Results from this present study, reveal that administration of DMBA can induce kidney dysfunction through mechanisms involving increased production of free radicals, which overwhelms the cellular antioxidants capacities, leading to ensuing oxidative stress. These changes are accompanied by suppressed production of IL-2 and increased secretion of selectins. Nevertheless, supplementation with vitamin K was observed to attenuate these DMBA-induced kidney dysfunctions, via mechanisms that involve its antioxidant properties.

Conflicts of interests

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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