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Influence of kolaviron and vitamin E on ethylene glycol monoethyl ether-induced haematotoxicity and renal apoptosis in rats

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The present study investigated the protective effects of kolaviron, a biflavonoid from the seed of *Garcinia kola*, and vitamin E on ethylene glycol monoethyl ether (EGEE)-induced haematotoxicity and renal apoptosis in male rats. EGEE was administered at a dose of 200 mg kg^{-1} alone or simultaneously administered with kolaviron (100 and 200 mg kg^{-1}) and vitamin E (50 mg kg^{-1}) for 14 days. Results of haematological examination showed that white blood cells, platelets, neutrophils and mean corpuscular haemoglobin concentration were significantly lower, whereas lymphocytes were increased in EGEE-exposed rats compared with those in the control. Administration of EGEE caused a significant decrease in the superoxide dismutase and catalase activities as well as in the glutathione level but significantly increased glutathione S-transferase activity and levels of hydrogen peroxide and lipid peroxidation in kidneys of rats compared with those in the control. Also, EGEE-treated rats showed significant elevation in the serum urea and creatinine with marked increase in the frequency of terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling assay-positive apoptotic cells in the tubular epithelial cells in comparison with the control. Co-administration with kolaviron or vitamin E exhibited chemoprotective effects against EGEE-mediated haematotoxicity, augmented renal antioxidant status and prevented the induction of renal apoptosis. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—ethylene glycol monoethyl ether (EGEE); nephrotoxicity; oxidative stress; apoptosis; rat

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INTRODUCTION

Glycol ethers are widely used as solvents in a large number of industrial, household and cosmetic applications. Previously reported toxicity studies on ethylene glycol monoethyl ether (EGEE) in animal models indicated that in mice, the LC_{50} for 7 h was 1820 ppm; death was attributed to lung and kidney injuries. In rabbits, repeated daily doses (1 ml kg^{-1}) of EGEE given orally caused albuminuria and haematuria on the seventh day with death on the eight day due to kidney injury.[1] Severe adverse effects including disorders of the nervous system, bone marrow, haematopoietic systems, blood and kidneys, and reproductive toxicity have been reported following acute or chronic exposure to glycol ethers.[2–4] Sixty to eighty percent of ethylene glycol ethers and their acetates are metabolized via alkoxyacetaldehydes to alkoxyacetic acids. The minor pathway results in the production of ethylene glycol, glycolaldehyde, glycolic acid and glyoxylic acid to oxalic acid.[5,6]

In Nigeria, EGEE is used as a raw material in many industries where most operations such as mixing and cleaning are performed manually with 8-h minimum exposure period daily. The occupational painters and artisans that use products containing EGEE routinely carry out their work without gloves and respirators, thereby exposing such workers to dermal contact and absorption of EGEE. Several deaths were reported in Nigeria recently as a result of usage of propylene glycol contaminated with diethylene glycol in the production of 'My Pikin' teething paracetamol syrup by a local pharmaceutical company. The death of those children was majorly due to kidney failure.[7–9]

Cellular toxicity results when the rate of formation of reactive metabolites is more than the rate of their removal. The primary function of the renal system is the elimination of waste products, derived either from endogenous metabolism or from the metabolism of xenobiotics. Kidneys sensitivity to chemicals is due to its ability to concentrate the tubular fluid by removing water and salts, and in the process concentrates any toxic chemicals it contains. The biotransformation of chemicals to reactive, and thus potentially toxic, metabolites is a key feature of nephrotoxicity.[10]

Apoptosis is a special form of cell death, which can be triggered by a variety of signals and pathophysiological conditions, including oxidative stress. Oxidative changes and reactive oxygen species (ROS) have been associated with apoptosis in many cell types.[11] The mode of cell death depends on the severity of the oxidative damage.[12] To counteract the damaging effect of ROS, aerobic cells are provided with extensive antioxidant defence mechanisms.[13] Endogenous antioxidant enzymes as well as non-enzymatic antioxidant can limit the effects of ROS but quickly become overwhelmed by large quantities of ROS. Recently, intense

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interest has focused on the chemoprotective properties of a series of natural products. In particular, some natural products act as chemoprotective agents by preventing cell death via apoptosis.[14]

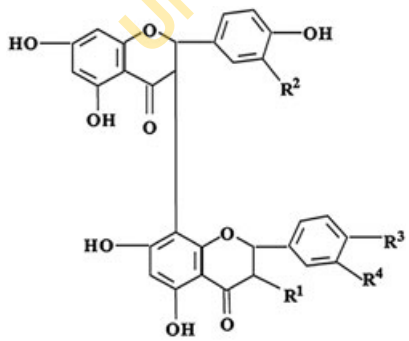
In West and Central Africa, *Garcinia kola* seeds are used in folk medicine and in many herbal preparations for the treatment of ailments such as laryngitis, liver disorders and bronchitis.[15] The biflavonoid isolated from the seed of *G. kola* is known as kolaviron (Figure 1). Several studies have demonstrated the protective effects of kolaviron against hepatotoxicity and oxidative stress induced by 2-acetylaminofluorene,[16] carbon tetrachloride[17] and aflatoxin B_1[18] in animal model. Furthermore, kolaviron has been shown to exhibit potent antioxidant and metal chelating activities *in vitro*[19] as well as inhibition of carcinogen-induced genotoxicity in human liver-derived HepG2 cells[20]. More pertinently, a previous study on the protective effect of kolaviron on potassium bromate-induced nephrotoxicity has been reported.[21] Vitamin E is a well-known natural antioxidant capable of protecting living organisms against the toxic effects of environmental chemicals. Vitamin E is a potent lipid-soluble antioxidant in the biological system with the ability to directly quench free radicals and function as a membrane stabilizer.[22] Vitamin E is usually supplemented in feed as DL-α-tocopheryl acetate, which is stable with respect to oxidation during feed processing and storage.[23]

In the present study, our objective was to investigate the role of oxidative stress and apoptosis in EGEE-mediated nephrotoxicity in rats. We also evaluated the possible protective effects of kolaviron and vitamin E against EGEE-induced haematotoxicity and renal apoptosis in rats.

MATERIALS AND METHODS

Chemicals

EGEE, epinephrine, glutathione (GSH), 5,5′-dithio-bis-2-nitrobenzoic acid, hydrogen peroxide and 1-chloro-2,4-dinitrobenzene were purchased from Sigma Chemical Company (St. Louis, MO, USA). All other reagents were of analytical grade and were obtained from the British Drug Houses Limited (Poole, Dorset, UK). Kits for serum urea and creatinine were purchased from Randox Laboratories Limited, UK.



	R^1	R^2	R^3	R^4
GB 1	OH	H	OH	H
GB 2	OH	H	OH	OH
Kolaflavanone	OH	H	OMe	OH

Figure 1. Chemical structure of kolaviron

Extraction of kolaviron

Kolaviron was isolated according to published procedure.[24] Briefly, the powdered seeds were extracted with light petroleum ether (bp 40–60 °C) in a soxhlet for 24 h. The defatted dried marc was repacked and extracted with acetone. The extract was concentrated and diluted twice its volume with water and extracted with ethyl acetate (6 × 300 ml). The concentrated ethyl acetate yielded a golden yellow solid termed kolaviron. Kolaviron was identified by direct comparison of the ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR and electron ionization mass spectral results with previously published data.[24]

Animal model

Thirty healthy adult male Wistar rats weighing approximately 190 ± 5 g obtained from the Department of Biochemistry, University of Ibadan, Ibadan, Nigeria, were used for this study. They were housed in plastic cages placed in a well-ventilated rat house, provided with rat pellets and water *ad libitum* and subjected to natural photoperiod of 12-h light : 12-h dark. All the animals received humane care according to the criteria outlined in the 'Guide for the Care and Use of Laboratory Animals' prepared by the National Academy of Science and published by the National Institute of Health. The experiment was performed according to the guidelines and approval of institutional animal ethics committee.

Experimental protocol

The rats were randomly assigned to five groups of six rats per group. Group I rats received corn oil alone at 2 ml kg^{-1} and served as control. While group II rats were treated with 200 mg kg^{-1} EGEE alone by gavage for 14 days, groups III and IV were pretreated with kolaviron at 100 (KV1) and 200 (KV2) mg kg^{-1} day^{-1} in corn oil, respectively, by gavage for the first 7 days followed by a daily administration of both kolaviron and EGEE simultaneously for the last 14 days of the experiment. Group V rats were pretreated with vitamin E at 50 mg kg^{-1}[25] in corn oil by gavage for the first 7 days followed by a daily administration of both vitamin E and EGEE simultaneously for the last 14 days of the experiment. The doses of kolaviron and EGEE, and the duration of experiment were selected on the basis of our previous publications.[26,27] Twenty-four hours after the last treatment, all the rats were sacrificed by cervical dislocation, and blood was collected by cardiac puncture for haematological analyses and serum biochemistry. The kidneys were quickly removed, weighed and placed on an ice bath. The body weights of rats were taken before exposure to various treatments and prior to sacrifice.

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Detection of apoptosis

Apoptosis in the biopsies of kidneys from each group was detected by terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining. The paraffin-embedded kidneys were sectioned and stained using the DeadEnd Colorimetric Apoptosis Detection System (Promega Corp., Madison, WI, USA) as directed by the manufacturer. Briefly, the tissue sections were deparaffinized, rehydrated and fixed in 4% paraformaldehyde solution in phosphate buffered saline (PBS). Proteinase K (20 μg ml^{-1}) treatment for 15 min was followed by a second fixation in 4% paraformaldehyde solution in PBS. The sections were incubated with equilibration buffer (200 mM potassium cacodylate, pH 6·6, 25 mM Tris–HCl, pH 6·6, 0·2 mM dithiothreitol, 0·25 mg ml^{-1} bovine serum albumin and 2·5 mM cobalt chloride) for 10 min. Subsequently, the sections were allowed to react with rTDT reaction mixture (98 μl equilibration buffer, 1 μl biotinylated nucleotide mix and 1 μl rTDT enzyme) for 1 h at 37 °C in a humidified chamber. The slides were immersed in 2× SCC for 15 min to stop the reaction, and the endogenous peroxidase was blocked by incubating the sections with 0·3% H_2O_2 in PBS for 5 min. After incubation with streptavidin–horseradish peroxidase solution for 30 min at room temperature, slides were stained with diaminobenzidine–H_2O_2 in the dark. Positive nuclei were stained dark brown and were visualized under a light microscope. Negative controls with TUNEL assay were performed according to the instructions provided by the manufacturer.

Biochemical assay

The remaining portions of the kidneys from each group were homogenized in 50 mM Tris–HCl buffer (pH 7·4) containing 1·15% potassium chloride, and the homogenate was centrifuged at 10 000 *g* for 15 min at 4 °C. The supernatant was collected for the estimation of catalase (CAT) activity by using hydrogen peroxide as substrate according to the method of Clairborne.[28] Superoxide dismutase (SOD) was assayed by using the method described by Misra and Fridovich.[29] Glutathione S-transferase (GST) was assayed by using the method of Habig *et al.*[30] Protein concentration was determined by using the method of Lowry *et al.*[31] Reduced glutathione was determined at 412 nm by using the method described by Jollow *et al.*[32] Hydrogen peroxide generation was assessed by using the method of Wolff.[33] Lipid peroxidation was quantified as malondialdehyde (MDA) according to the method described by Farombi *et al.*[16] and expressed as micromoles of MDA per gram tissue. The levels of serum urea and creatinine were estimated by Fawcett *et al.*[34] and Henry,[35] respectively. K_2 ethylenediaminetetraacetic acid-added whole blood samples were used for haematological analyses immediately after collection with the aid of Sysmex Automated Hematology (KX-21, Kobe, Japan) analyzer.

Statistical analysis

Statistical analyses were carried out using one-way analysis of variance to compare the experimental groups followed by the Bonferroni's test by using SPSS (student version 7·5, SPSS Inc., UK), and *p*-values less than 0·05 were considered statistically significant.

RESULTS

Influence of kolaviron and vitamin E on the EGEE-induced haematotoxicity

The mean values of haematological parameters in rats exposed to EGEE alone, EGEE plus kolaviron, and EGEE plus vitamin E are presented in Table 1. Rats administered with EGEE had significant reduction in white blood cells (WBC), platelets, neutrophils and mean corpuscular haemoglobin concentration (MCHC) but significantly increased lymphocyte values when compared with those in

Table 1. Effect of kolaviron and vitamin E on EGEE-induced haematotoxicity in rats following 14 consecutive days exposure

	Control	EGEE	EGEE + KV1	EGEE + KV2	EGEE + Vit E
PCV (%)	49·25 ± 1·71	50·25 ± 3·77	47·0 ± 1·73	50·33 ± 2·0	48·75 ± 3·5
RBC ($\times 10^3$/μl)	8·23 ± 0·46	7·80 ± 0·65	7·98 ± 0·33	8·07 ± 0·55	7·95 ± 0·51
WBC ($\times 10^3$/μl)	8·95 ± 0·51	6·33 ± 0·15*	8·85 ± 0·37†	9·20 ± 1·16†,‡	9·09 ± 1·16†,§
Platelets ($\times 10^3$/μl)	983·25 ± 45·5	688·0 ± 84*	930·33 ± 38·8†	957·33 ± 70·2†	892·67 ± 60·0†,§
Hb (g dl^{-1})	14·83 ± 0·46	13·07 ± 0·35	14·18 ± 0·45	14·8 ± 0·56	14·2 ± 0·8
Neutrophils (%)	27·47 ± 1·53	15·60 ± 1·73*	20·20 ± 2·0†	22·67 ± 2·89†	21·33 ± 3·61†
Lymphocytes (%)	72·5 ± 7·59	84·35 ± 9·22*	79·75 ± 2·36	77·0 ± 1·73	78·67 ± 3·06
MCV (fl)	59·75 ± 1·26	65·25 ± 7·93	61·25 ± 3·59	62·5 ± 3·79	61·5 ± 2·38
MCH (pg)	18·0 ± 0·82	18·25 ± 0·5	18·5 ± 1·29	18·5 ± 0·85	18·0 ± 0·01
MCHC (g dl^{-1})	30·25 ± 0·5	26·0 ± 2·16*	30·0 ± 0·82†	29·5 ± 1·0†	29·0 ± 0·08†

The data are expressed as mean ± SD for six rats per group.
EGEE, ethylene glycol monoethyl ether; KV1, kolaviron at 100 mg kg^{-1} day^{-1}; KV2, kolaviron at 200 mg kg^{-1} day^{-1}; PCV, packed cell volume; RBC, red blood cell; WBC, white blood cell; Hb, haemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration.
*$p < 0·05$ against control.
$^{\dagger}p < 0·05$ against EGEE group.
$^{\ddagger}p < 0·05$ against EGEE + KV1 group.
$^{\S}p < 0·05$ against EGEE + KV2 group.

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the control group. The packed cell volume, red blood cell, haemoglobin, mean corpuscular volume and mean corpuscular haemoglobin (MCH) remain unaffected following exposure to EGEE. Co-administration with kolaviron or vitamin E significantly increased the values of WBC, platelets, neutrophils and MCHC, and decreased lymphocyte values to near control.

Influence of EGEE, kolaviron and vitamin E on serum levels of urea and creatinine

The serum levels of markers of renal damage, urea and creatinine are shown in Figures 2 and 3. When compared with the control, there were significant elevations in serum creatinine and urea levels following acute exposure of rats to EGEE. Kolaviron or vitamin E treatment reversed the EGEE-mediated increase in serum creatinine and urea levels, and maintained their normalcy in EGEE-treated animals.

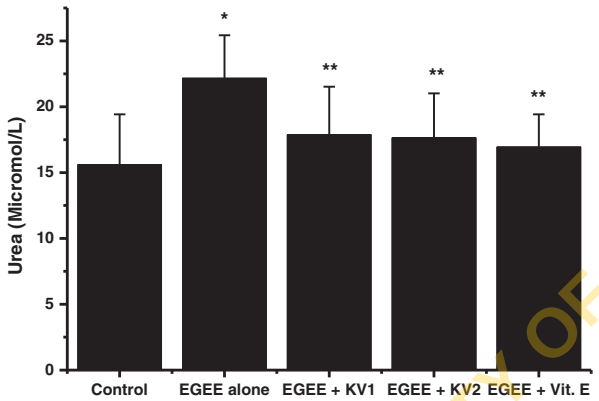

Figure 2. Effects of kolaviron and vitamin E on urea level in plasma of ethylene glycol monoethyl ether (EGEE)-exposed rats. Each bar represents mean ± SD of six animals. *Values differ significantly from those of control ($p < 0{\cdot}05$). **Values differ significantly from those of EGEE group ($p < 0{\cdot}05$)

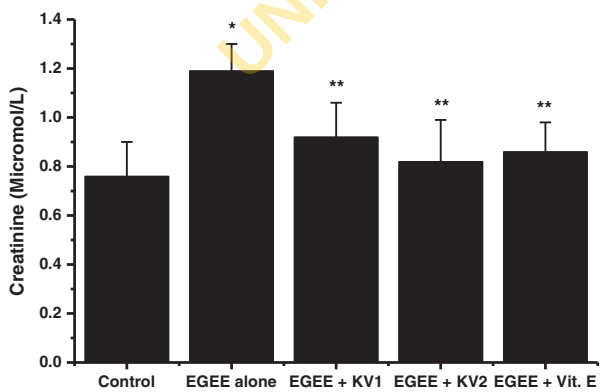

Figure 3. Effects of kolaviron and vitamin E on creatinine level in plasma of ethylene glycol monoethyl ether (EGEE)-exposed rats. Each bar represents mean ± SD of six animals. *Values differ significantly from those of control ($p < 0{\cdot}05$). **Values differ significantly from those of EGEE group ($p < 0{\cdot}05$)

Influence of kolaviron and vitamin E on the EGEE-induced renal oxidative stress

The biomarkers of oxidative stress in kidneys of rats following acute exposure to EGEE are presented in Figures 4–9. Rats administered with EGEE had a significant decrease in renal activities of SOD and CAT as well as in the GSH level but significantly increased GST activity and levels of H_2O_2 and MDA compared with those of the control group. Co-administration with kolaviron or vitamin E significantly increased SOD and CAT activities, and GSH level and completely reversed the EGEE-mediated increase in GST activity and levels of H_2O_2 and MDA to normalcy.

Influence of kolaviron and vitamin E on the EGEE-induced renal apoptosis

Following induction of oxidative stress by EGEE, apoptotic renal cells were identified and characterized by using the

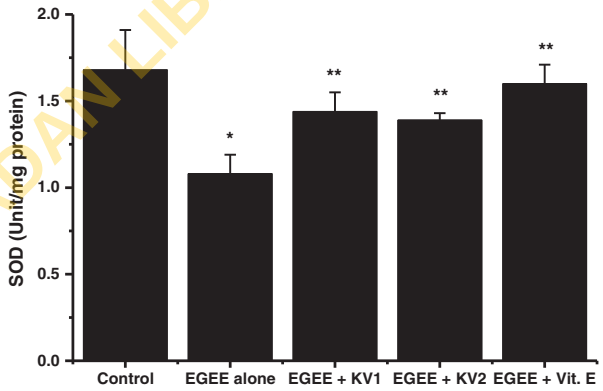

Figure 4. Effects of kolaviron and vitamin E on SOD activity in kidneys of ethylene glycol monoethyl ether (EGEE)-exposed rats. Each bar represents mean ± SD of six animals. *Values differ significantly from those of control ($p < 0{\cdot}05$). **Values differ significantly from those of EGEE group ($p < 0{\cdot}05$)

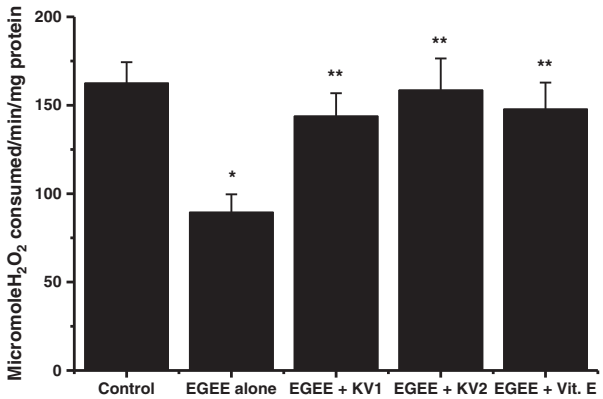

Figure 5. Effects of kolaviron and vitamin E on CAT activity in kidneys of ethylene glycol monoethyl ether (EGEE)-exposed rats. Each bar represents mean ± SD of six animals. *Values differ significantly from those of control ($p < 0{\cdot}05$). **Values differ significantly from those of EGEE group ($p < 0{\cdot}05$)

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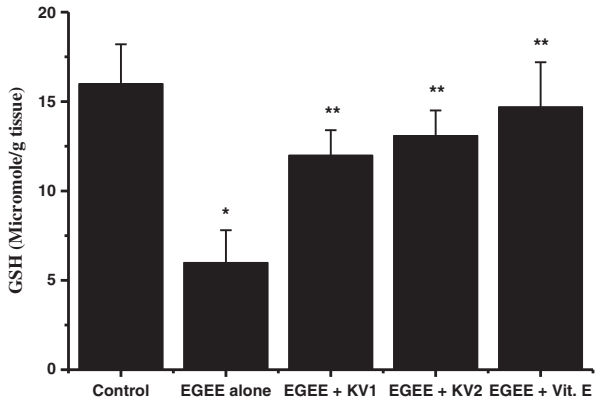

Figure 6. Effects of kolaviron and vitamin E on GSH level in kidneys of ethylene glycol monoethyl ether (EGEE)-exposed rats. Each bar represents mean ± SD of six animals. *Values differ significantly from those of control ($p < 0{\cdot}05$). **Values differ significantly from those of EGEE group ($p < 0{\cdot}05$)

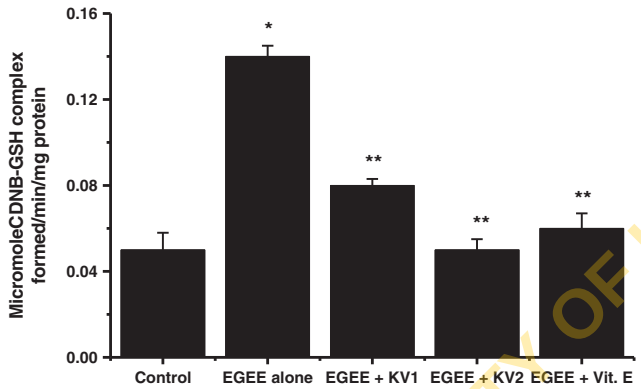

Figure 7. Effects of kolaviron and vitamin E on GST activity in kidneys of ethylene glycol monoethyl ether (EGEE)-exposed rats. Each bar represents mean ± SD of six animals. *Values differ significantly from those of control ($p < 0{\cdot}05$). **Values differ significantly from those of EGEE group ($p < 0{\cdot}05$)

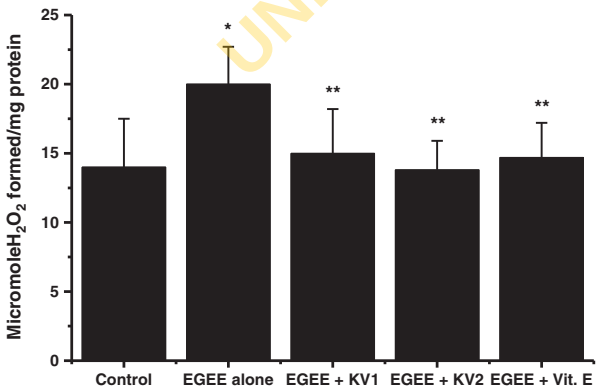

Figure 8. Effects of kolaviron and vitamin E on H_2O_2 level in kidneys of ethylene glycol monoethyl ether (EGEE)-exposed rats. Each bar represents mean ± SD of six animals. *Values differ significantly from those of control ($p < 0{\cdot}05$). **Values differ significantly from those of EGEE group ($p < 0{\cdot}05$)

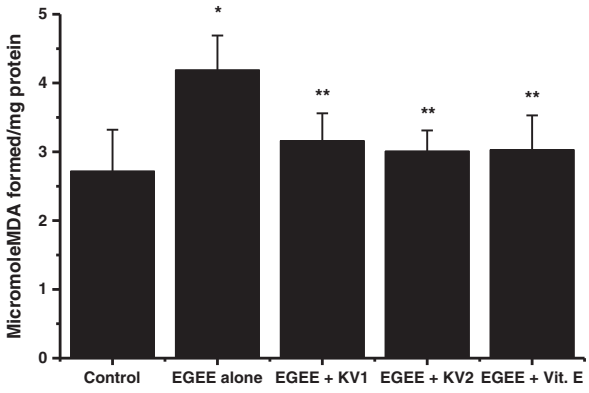

Figure 9. Effects of kolaviron and vitamin E on lipid peroxidation level in kidneys of ethylene glycol monoethyl ether (EGEE)-exposed rats. Each bar represents mean ± SD of six animals. *Values differ significantly from those of control ($p < 0{\cdot}05$). **Values differ significantly from those of EGEE group ($p < 0{\cdot}05$)

TUNEL assay. The influence of kolaviron and vitamin E on the EGEE-induced renal apoptosis is shown in Figure 10. There was a significant increase in the frequency of TUNEL-positive apoptotic cells in the tubular epithelial cells of rats treated with EGEE alone. The kidneys of rats co-treated with EGEE and KV1 showed significantly fewer TUNEL-positive cells as compared with those of the rats treated with EGEE alone. However, administration of KV2 or vitamin E significantly prevented the incidence of tubular epithelial cells apoptosis and maintained the frequency of viable cells in EGEE-treated rats.

DISCUSSION

The uncontrolled exposure to toxic industrial solvents, such as EGEE, is capable of inflicting biological damage leading to the pathology of many conditions including kidney damage, blood disorders and testicular dysfunction. In the present investigation, administration of EGEE caused significant alterations in some haematological parameters. The significant reduction in the number of WBC, platelets, neutrophils and MCHC in this experimental model indicates that exposure to EGEE could lead to bleeding, anaemia and reduced immunity. Our findings on EGEE treatment-related haematological toxicity are in agreement with earlier report on lithographers and female workers with potential exposure to glycol ethers.[36,37] The co-administration with kolaviron or vitamin E significantly improved haematological parameters by restoring to normalcy the number of WBC, platelets, neutrophils and MCHC in EGEE-treated animals, thus revealing their chemoprotective potentials against EGEE-induced haematotoxicity.

Renal functional indices showed that serum creatinine and urea were markedly elevated following EGEE administration. Elevation in the levels of serum creatinine and urea indicates renal dysfunction in EGEE-treated animals. Increase in serum urea may reflect a decrease in reabsorption at the renal epithelium, whereas increased serum creatinine

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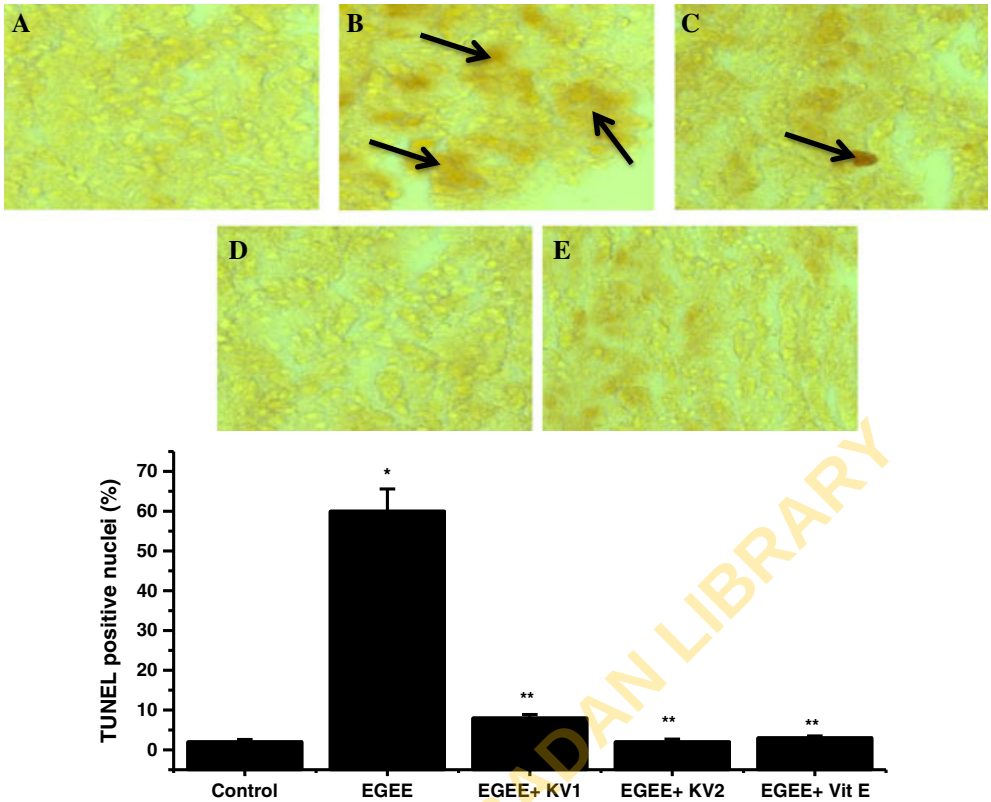

Figure 10. Inhibitory effects of kolaviron and vitamin E on induction of tubule cell apoptosis following kidney treatment. Control (A), EGEE alone (B), EGEE + KV1 (C), EGEE + KV2 (D), and EGEE + vitamin E (E). The arrows indicate terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL)-positive tubular cells

reflected impairment in the kidneys, particularly for glomerular filtration rate because of EGEE administration.[10] Interestingly, co-treatment of kolaviron or vitamin E significantly reversed the EGEE-mediated increase in the levels of urea and creatinine to normalcy. The reduction in the levels of biomarkers of renal damage indicates that kolaviron and vitamin E protect rat kidney against EGEE-induced renal dysfunction.

The existence of a mutually supportive relationship between metalloenzyme SOD, which accelerates the dismutation of endogenous cytotoxic superoxide radicals to H_2O_2, and CAT, which converts the deleterious peroxide radicals into water and oxygen, provides the first line of defence to the cells.[27,38] The decreased activities of renal SOD and CAT with concomitant elevation in H_2O_2 level observed in EGEE-treated animals may lead to increased steady-state levels of the deleterious superoxide radicals and H_2O_2. Hydroxyl radical could be formed by the interaction of superoxide radical with H_2O_2 through the Haber–Weiss reaction.[39] The overwhelming generation of free radicals in the renal milieu may contribute to the inactivation of these enzymes and may increase the oxidative stress in kidneys of animals treated with EGEE. However, amelioration was evident by marked increases in the SOD and CAT activities with decreased H_2O_2 level in kidneys of animals co-treated with kolaviron or vitamin E in comparison with those of EGEE-untreated animals. The ability of kolaviron to inhibit hydroxyl and superoxide anion radicals *in vitro* has been reported.[21] Kolaviron is highly bioavailable because of its ability to survive first-pass metabolism, which inactivates most flavonoids.[40] The present results may indicate that there was a quick scavenging of superoxide and hydroxyl radicals by kolaviron, possibly due to its high bioavailability, to keep their normal levels, thereby allowing the renal antioxidant system to efficiently decrease EGEE-mediated renal ROS generation.

Glutathione, a tripeptide containing cysteine with a reactive SH group, is a potent reductive non-enzymatic antioxidant, which maintains the intracellular redox status against pro-oxidative stress by scavenging free radicals. GST is involved in the biochemical conjugation of electrophilic oxidants with GSH to form more water-soluble compound products that are readily excreted from the system.[30,41,42] In the present study, EGEE treatment significantly increased GST activity and decreased GSH level. This observation suggests induction of the detoxification process mediated by this enzyme, which consequently depleted the GSH status in the kidneys of EGEE-treated rats. Administration with kolaviron or vitamin E effectively increased the GSH level and restored GST activity to normalcy in the kidneys of EGEE-treated animals.

ROS attack cellular components containing polyunsaturated fatty acid residues to produce peroxyl radicals, which can be rearranged via a cyclization reaction to endoperoxides, which eventually form *trans*-4-hydroxy-2-nonenal and MDA.[43–45] Increased ROS and oxidative changes have been

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associated with apoptosis in many cell types.[11,46] In the present study, TUNEL assay was performed to detect apoptotic cells in the kidneys of rats exposed to EGEE. The levels of MDA and TUNEL-positive cells were observed to increase significantly in the kidneys of animals exposed to EGEE. However, simultaneous administration with kolaviron or vitamin E significantly decreased the MDA levels and the number of TUNEL-positive cells in kidneys of EGEE-treated animals to near control. These findings confirm that both compounds have potent antioxidative properties.[21,47] The absence of any significant difference in the renal MDA level and TUNEL-positive cells in animals co-administered with kolaviron and vitamin E when compared with control animals indicates their efficient anti-lipid peroxidative and anti-apoptotic properties.

In mechanistic term, the presence of a C-4 carbonyl, and C-5 and C-7 hydroxyl groups of the A-ring of kolaviron and the presence of a hydroxyl group in the position three (3-OH) of the C-ring make kolaviron a potent inhibitor of lipid peroxidation.[48,49] Vitamin E has been reported to play a physicochemical role in the stabilization of biomembranes by virtue of lipid–lipid interactions between vitamins and unsaturated fatty acids.[50] Owing to the reactivity of the phenolic hydrogen on its C-6 hydroxyl group and the ability of the chromanol ring system to stabilize an unpaired electron, vitamin E can provide hydrogen for the reduction in peroxyl radicals before deleterious interaction with the cell membranes and other cell components.[42,47]

Taken together, the data presented in this study clearly demonstrate, for the first time, that both kolaviron and vitamin E elicited significant protection against EGEE-mediated haematotoxicity and renal injury. Moreover, they are efficient in protecting the kidney from oxidative damage and apoptosis induced by EGEE as evidenced by the restoration of antioxidant status and biomarkers of renal damage to normalcy. However, kolaviron appears to afford a better protective effect than vitamin E in its action against EGEE-induced toxicity in the present study. The antioxidant activities of kolaviron and vitamin E may account for their nephroprotective effects against renal cell apoptosis by reducing the generation of ROS. Kolaviron and vitamin E may be potential therapeutic tools for haematotoxicity and renal damage resulting from EGEE exposure.

CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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