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In vivo respiratory toxicology of cooking oil fumes: Evidence, mechanisms and prevention

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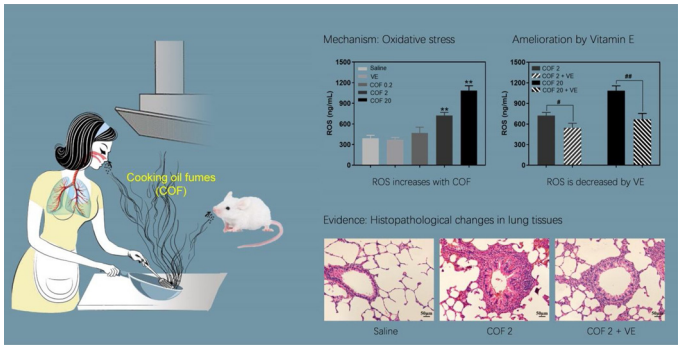
GRAPHICAL ABSTRACT



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ABSTRACT

Background: As cooking is an essential part of people's daily life, cooking oil fumes (COF) has been recognized as one of the major indoor air pollutant. Mounting epidemiological evidence has indicated that COF exposure is significantly associated with an increased risk of various health effects including lung cancer, but toxicological studies are very limited.

Objectives: We conduct a systematic study to provide toxicological evidence of COF exposure on the lungs, to examine the underlying toxicological mechanism, and to suggest intervention measures to mitigate this toxicity.

Methods: A total 96 female rats were randomly divided into control groups, COF exposure groups (0.2, 2, 20 mg/kg) and vitamin E protection groups, receiving appropriate treatment for 30 days. First we measured airway hyperresponsiveness (AHR) followed by a lung histological analysis to investigate the toxicological effects of COF. We next analyzed the biomarkers of oxidative stress, inflammation, and apoptosis to examine the underlying toxicological mechanism, and finally we investigated the protective effects of vitamin E against the toxicity of COF.

Results: AHR measurement indicated that the airway resistance increased with the COF dose and the lung histological assay showed narrowing of the airway lumen, which provided evidence of the toxicological effects of COF. The biomarkers of oxidative stress (ROS and MDA), pro-inflammation (TNF-α and IL-1β), and apoptosis

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(NF-κB and Caspase-3) were all significantly increased with COF dose. We observed that above toxicological effects and biomarker levels induced by COF were significantly ameliorated after administration of VE.
Conclusion: The toxicity of cooking oil fumes on the lungs is clear from the evidence and mechanism, and can be ameliorated by vitamin E. We suggested that oxidative stress may be primarily responsible for the observed cooking oil fumes-induced toxicity.

1. Introduction

Indoor air pollution, has become a global public health problem nowadays. Cooking is an essential part of people's daily life and now being promoted as one of the key strategies to solve the dietary problem so as to improve health and increase life span (Mills et al., 2017). Cooking has also been, however, identified as a major source of indoor air pollution (Abdullahi et al., 2013; Kim et al., 2011; Singh et al., 2017). Cooking induced pollution is mainly influenced by ventilation, cooking fuel and cooking oil. In recent decades, with the development of the global economy, great progress has been made to reduce the pollution caused by the cooking process by improving the ventilation and changing the cooking fuel from the solid fuels (biomass or coal) to clean fuels such as gas and electricity (Bonjour et al., 2013; Zhao et al., 2018). Yu et al. (2020) found that the use of ventilation and the cessation of solid fuel use reduced the risks of all-cause and cardiopulmonary mortality by more than 60 % within five years.

Cooking oil fumes (COF) has now become the major pollutant induced by cooking. Cooking requires a large amount of oil, with an average consumption of 44 g of oil per adult per day. In recent years, to both disinfect and enhance the flavor of food, cooking at high temperature has become popular, and this produces more oil fumes (Ho et al., 2019). COF contains a complex mixture of toxic pollutants including metals, benzene, particulate matters (PM), volatile organic compounds, polycyclic aromatic hydrocarbons (PAHs), quinones and carbonyl compositions. Therefore, exposure to COF can have multiple health effects including cardiopulmonary diseases (Abdullahi et al., 2013; Wong et al., 2013), diabetes (Wang et al., 2013), brain damage (Naseri et al., 2019), sleep disorders (Wei et al., 2017), female reproductive problems (Zhang et al., 2020), and even diseases in the next generation due to maternal exposure during pregnancy (Fang et al., 2020).

In addition, COF may have a probably carcinogenic effect on humans (Group 2A carcinogen), according to the classification of the International Agency for Research on Cancer (IARC) (Wang et al., 2019). A number of recent epidemiological studies have reported that exposure to COF was significantly associated with an increased risk of lung cancer in Chinese women who are non-smokers (Jia et al., 2018; Li et al., 2008; Yu et al., 2006). In China, women spend much more time in the kitchen and are more likely to be exposed to COF. Pan et al. (2008) reported that female workers had a greater oxidative stress response to oxidative stress induced by COF in contrast with male workers in restaurant, further providing additional evidence of the relationship between lung cancer in Chinese women and COF. Since lung cancer is the most common cause of cancer death and is on the rise worldwide, especially among women who spend more time cooking in low- and middle-income countries including China (Sun et al., 2007), the toxicology of COF on human lung warrants urgent investigation.

Toxicological studies of how exposure to COF affects the human lung are very limited. During the past decade, both *in vivo* and *in vitro* studies have examined different toxicological effects including oxidative stress (Cao et al., 2013; Ke et al., 2016), inflammation (Hou et al., 2017), and apoptosis (Che et al., 2014; Dou et al., 2018). However, the findings are inconclusive. Toxicological evidence concerning exposure to COF is scarce and the underlying toxicological mechanism is still unclear. On the other hand, intervention measures to effectively reduce this toxicity are lacking. Vitamin E (VE), a low-molecular natural antioxidant, has been demonstrated to be effective in treatment of chronic diseases associated with oxidative stress such as cardiovascular disease (Lorenzon Dos Santos et al., 2020). Whether VE can be used to reduce the COF's toxicity has been another focus of the present work.

To fill these knowledge gaps, we conducted a systematic study to examine the toxicological effects of COF on the rat lung. We first measured the airway resistance and then performed a lung histological assay to investigate the toxicological effects of COF. We next analyzed the biomarkers of oxidative stress, inflammation, and apoptosis to examine the underlying toxicological mechanism, and finally we investigated the protective effects of VE against the toxicity of COF.

2. Experiments

2.1. Cooking oil fumes

In September 2018, we selected six family kitchens in Changsha where we collected the COF condensation from the collection cup of the exhaust hood. The condensation was sterilized with dry heat (160℃, 2 h) in oven and then kept in a refrigerator prior to use. When using, different concentrations of COF were dissolved in Tween-80 (Amresco, Solon, OH, USA), an effective biocompatible surfactant, and diluted with sterile saline. Finally, the suspension was fully mixed and sterilized with ultrasonic shaking for 15 min. The main toxic components of the COF condensation, 16 PAHs and 17 metals, were analyzed by gas chromatography − mass spectrometry (GC − MS) with a DB-5MS capillary column (model 7890/5975, Agilent, USA) and inductively coupled plasma mass spectrometry (ICP-MS) (ELAN DRC II, PerkinElmer, USA) respectively, and the results were shown in Table 1.

2.2. Animals and experimental protocol

The experimental protocol was approved by the ethics committee of Central South University. Female Wistar rats were provided by the Hubei Province Experimental Animal Center and housed in standard environmental conditions (12-h light–dark cycle, 50–70 % humidity and 20–25 ˚C) with adequate food and water.

A total of 96 female Wistar rats (6–8 weeks, 180 − 220 g) were divided randomly into eight groups (n = 12): (1) 0.9 % saline group (Saline), (2) 0.05 % tween-80 group (Tween) and (3) 100 mg kg^{-1} bw group (VE) are the control groups; (4) 0.2 mg kg^{-1} bw group (COF 0.2), (5) 2 mg kg^{-1} bw group (COF 2), and (6) 20 mg kg^{-1} bw group (COF 20) are groups treated with different COF doses; (7) 2 mg kg^{-1} bw and 100 mg kg^{-1} bw group (COF 2 + VE) and (8) 20 mg kg^{-1} bw and 100 mg kg^{-1} bw group (COF 20 + VE) are the groups treated with both COF and VE. The doses of COF and VE were respectively estimated according to daily exposure and ingestion of the general population.

The rats received the COF suspensions or 0.9 % saline, or 0.05 % tween-80 once every 3 days, *via* intratracheal instillation, for a total of 10 instillations (30 days). The instillation volume was 0.1 ml/100 g bw. VE was given by intragastric administration 4 h after the intratracheal instillation.

Five rats from each group were used for measuring airway hyperresponsiveness (AHR) and cell counting analysis. The remaining 7 rats in each group were used to lung histological assay and biomarker analysis. The detailed experimental protocol is shown in Fig. 1.

Table 1
PAHs and metals in COF condensation.

Major components	Concentration (ng/mL)
PAHs	
Pyr	2208
Flua	1336
Phe	1308
Ant	259
Flu	223
Acy	133
Nap	125
BaA	95
BaP	93
Chr	89
BghiP	84
BbF	72
BkF	63
Ace	54
Icdp	41
DahA	23
Metals	
Ti	22670
Ca	19235
Ni	10908
Na	9939
K	6148
Fe	6069
Zn	3426
Al	3298
Mg	3158
Cu	286
Mn	152
Pb	133
Cr	86
Cd	43
As	32
V	5
Co	4

2.3. Measurement of airway hyperresponsiveness

We first examine AHR, which is associated with an increased risk of developing respiratory symptoms or diseases, such as asthma. To measure AHR, airway resistance with Methacholine (MCH) (Sigma-Aldrich, St. Louis, MO, USA) was recorded using the AniRes2005 Lung Function System (Bestlab ver2.0; Beijing, China). The rat was first anesthetized with 10 % pentobarbital sodium and respiration maintained by tracheal intubation with a small animal ventilator (exhalation rate and the expiration/inhalation time ratio were preset to 70/min and 1.5, respectively). MCH was injected *via* a catheter at 5 min intervals at doses of 0.025, 0.05, 0.1 and 0.2 mg kg^{-1} bw. The expiratory resistance (Re), inspiratory resistance (Ri), and dynamic lung compliance (Cldyn) were recorded in real-time (Deng et al., 2020).

2.4. Cell counting of bronchoalveolar lavage fluid

To examine whether acute lung injury is induced by COF, we determined the cell counts in bronchoalveolar lavage fluid (BALF). After measuring AHR, a medical syringe was connected to the tracheal intubation to inject saline into the lungs of the rat to extract BALF. The collected BALF was then centrifuged at 4 °C and 1000 rpm for 10 min, and then we used the Blood Cell Analysis System (MTN-21; Matenu Technology, Changchun, China) to count the total cells, neutrophils, lymphocytes, and eosinophils in the cell sediment (You et al., 2014).

2.5. Lung histological assay

To observe any pathological changes in the lung caused by COF, we carried out a lung histological analysis. The rats were killed by cervical dislocation and then the lung tissues were removed and rinsed in phosphate-buffered saline (PBS). The left lung was used for preparation of histopathology slices. Samples were kept in 4% neutral paraformaldehyde buffer for 24 h at room temperature and then cut into pieces. The pieces were stained with hematoxylin and eosin (H&E),

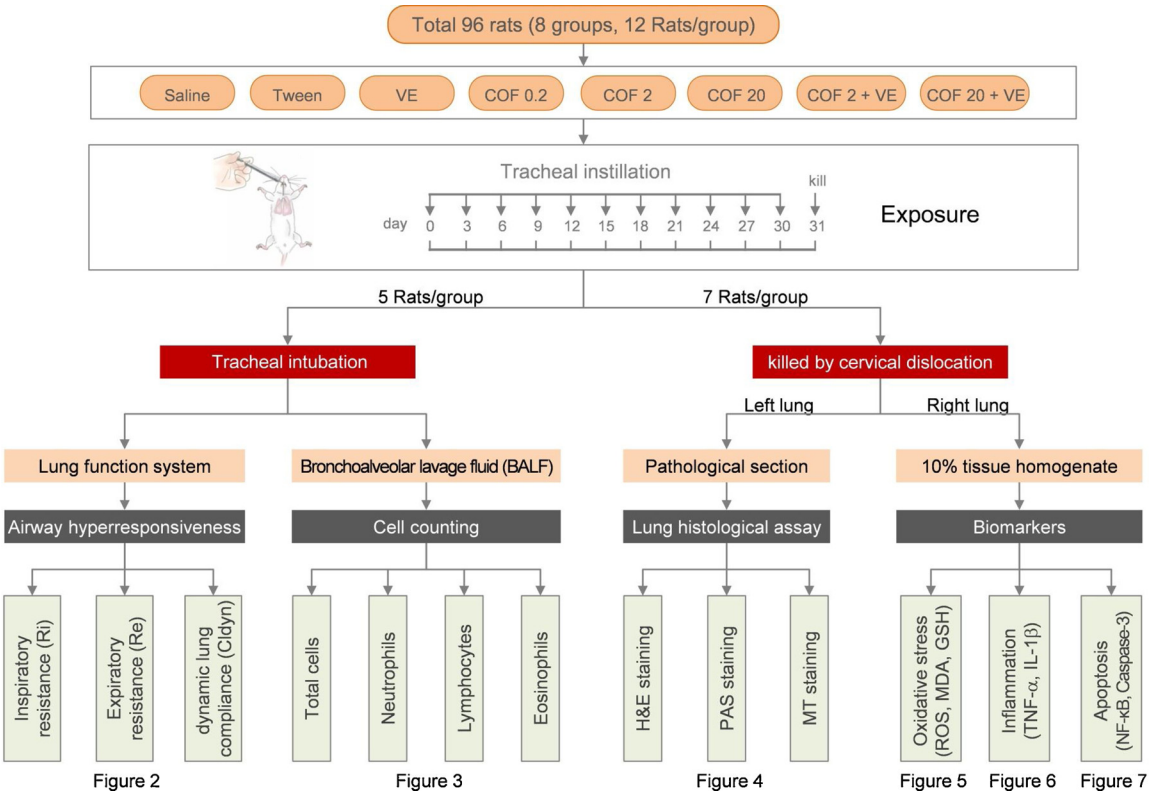


Fig. 1. Experimental protocol for the toxicology of cooking oil fume (COF).

Masson's trichrome (MT), and periodic acid-Schiff (PAS), which were observed using the Olympus Microscope (BX53, Tokyo, Japan) (Deng et al., 2020). A Smith score was used to quantitatively evaluate lung injury and the extent of the pathological lesions was graded between 0 and 4, including pulmonary edema, alveolar and interstitial inflammation, alveolar and interstitial hemorrhage, and atelectasis (Xu et al., 2019).

2.6. Biomarkers analyses

The right lung tissue was used for analysis of various biomarkers. We placed the lung tissue in a glass homogenizer and added PBS buffer to produce a 10 % tissue homogenate. The tissue homogenate was then centrifuged at 4 ˚C and 10,000 rpm for 10 min, and the supernatant was collected and stored at −80 ˚C for subsequent testing. We used ELISA kits (Biolegend, CA, USA) to detect the pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α) and Interleukin-1β (IL-1β), and the apoposis factors, Caspase-3 and Nuclear factor-κappa B (NF-κB) in the lung homogenates (Deng et al., 2020). The levels of oxidative stress biomarkers, including ROS, malondialdehyde (MDA), and glutathione (GSH), were measured using DCF fluorescence, thiobarbituric acid, and glutathione peroxidase (GSH-Px) assay kits, respectively (Li et al., 2013).

2.7. Statistical analyses

All data were presented as Mean ± SEM. SPSS ver18 (SPSS, Chicago, IL, USA) and GraphPad Prism ver7.0 (Origin Lab, Berkeley, CA, USA) were used for statistical analysis and mapping. One-way ANOVA combined with an independent sample *t*-test was used to compare the significance of differences between groups. A $p < 0.05$ was considered to be a significant difference.

3. Results

The airway damage caused by COF is illustrated by the AHR

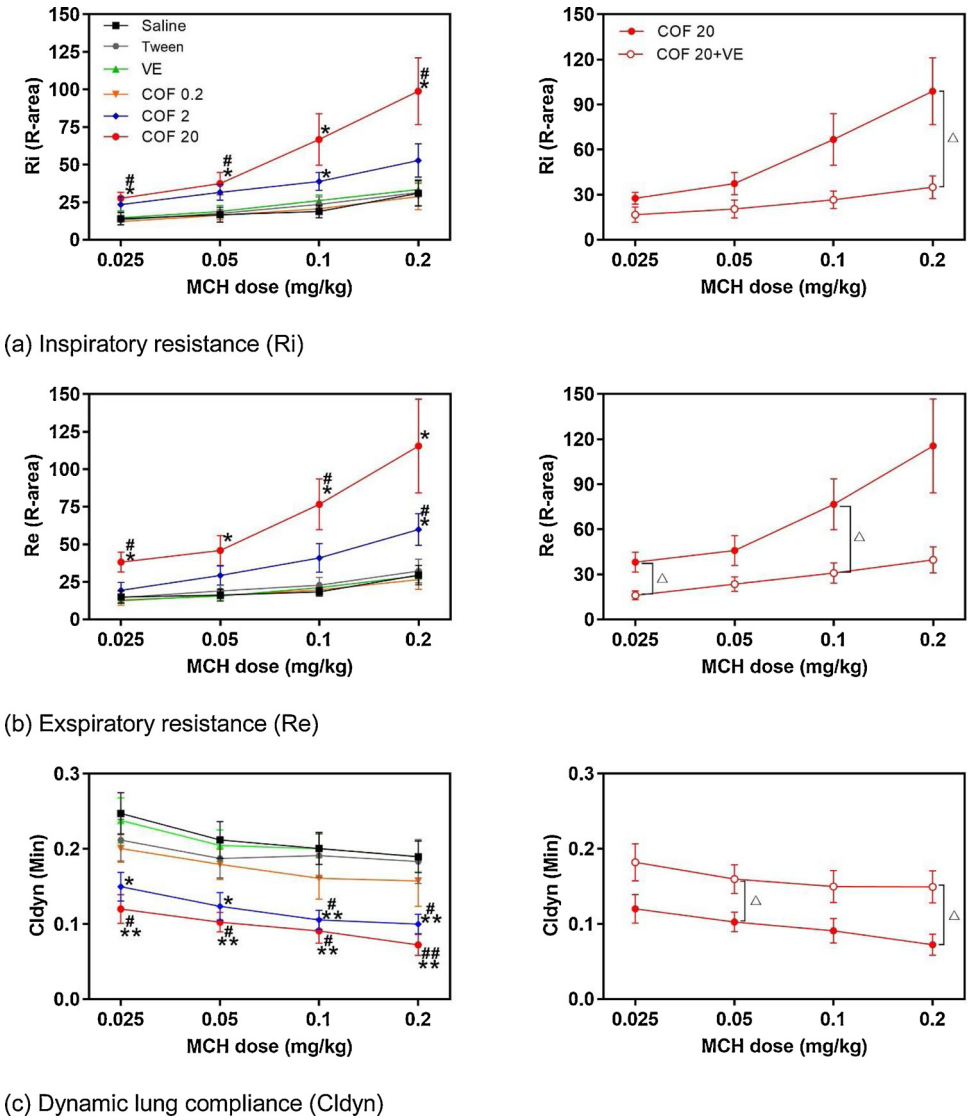


Fig. 2. Effects of exposure to COF on airway hyperresponsiveness (AHR) and amelioration by VE in rats: (a) Ri, (b) Re, and (c) Cldyn. Figures on the left are for different COF doses: the saline control, tween control, VE control, COF exposure groups (0.2, 2, 20 mg kg^{-1} bw); Figures on the right are comparisons between the COF 20 and COF 20 + VE groups.
* $p < 0.05$ and ** $p < 0.01$ (compared with saline control group);
# $p < 0.05$ and ## $p < 0.01$ (compared with tween control group);
Δ $p < 0.05$ (COF + VE groups compared with the COF exposure groups with the same concentration).

measurements as shown in Fig. 2. We observed that the changes of Ri, Re and Cldyn in the saline, tween, and VE control groups were almost the same, but the airway resistance, both *Ri* and *Re*, increased with COF dose, particularly at high MCH. Accordingly, the lung compliance, Cldyn, decreases with COF, which indicates that COF caused serious damage to both large and small airways and supports the authenticity of pulmonary dysfunction. However, the administration of VE significantly attenuates the damage, as shown by the fact that *Ri* and *Re* were decreased while Cldyn increased in the groups receiving VE treatment.

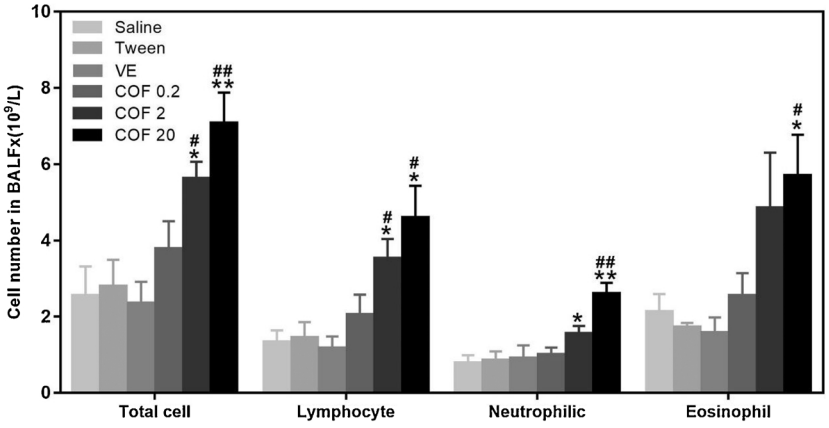
Lung injury was reflected by the increase in the number of inflammatory cells. Fig. 3 shows that the total number of cell, lymphocytes, neutrophils and eosinophils in three control groups are low, but are markedly increased in COF exposure groups, particularly at high doses (20 mg/kg). Our results also showed that the airway inflammation caused by COF was ameliorated by VE.

We further observed lung histological changes due to exposure to COF. Fig. 4 shows that as the COF concentration in 2 mg/kg and 20 mg/kg, the treatment of COF seemed to contribute significantly to the deterioration of lung histological changes compared with the saline or tween group. The Smith score for quantifying lung injury was also confirmed our findings. Moreover, pathological changes in lung tissue deteriorated with COF concentration increasing, such as increased inflammatory cell infiltration, goblet cell hyperplasia, mucus overproduction, and increased fibrosis as seen in the slices stained by H &E, PAS and MT methods. The administration of VE was shown to attenuate these deterioration effects.

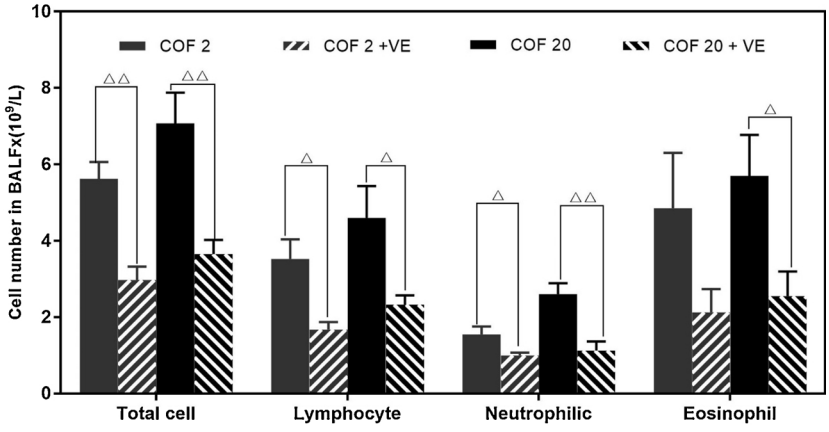
The toxicology of COF was demonstrated by the biomarker analysis. We observed that the levels of oxidative stress as indicated by ROS and MDA were significantly increased and accordingly the antioxidant capacity as indicated by GSH was decreased with the COF dose (2 mg/kg and 20 mg/kg) (Fig. 5). Compared with the saline or tween control group, exposure to COF significantly increased the levels of pro-inflammatory cytokines as indicated by TNF-α and IL-1β. The level of TNF-α was increased in 2 mg/kg and 20 mg/kg COF exposure groups, and IL-1β level was significantly increased in 20 mg/kg COF groups, which confirms the establishment of inflammation in COF-induced rat lung tissues (Fig. 6). In addition, the levels of apoptosis cytokines as shown by NF-κB and Caspase-3 were significantly increased in 2 mg/kg and 20 mg/kg COF exposure groups in the lung tissues, and NF-κB and Caspase-3 increased markedly with the increase of COF concentration (Fig. 7). The ameliorating effects of VE were also observed in almost all biomarkers except Caspase-3.

4. Discussion

This study is the first, according to the authors' best knowledge, to systematically investigate the toxicological effect of COF on the lungs.

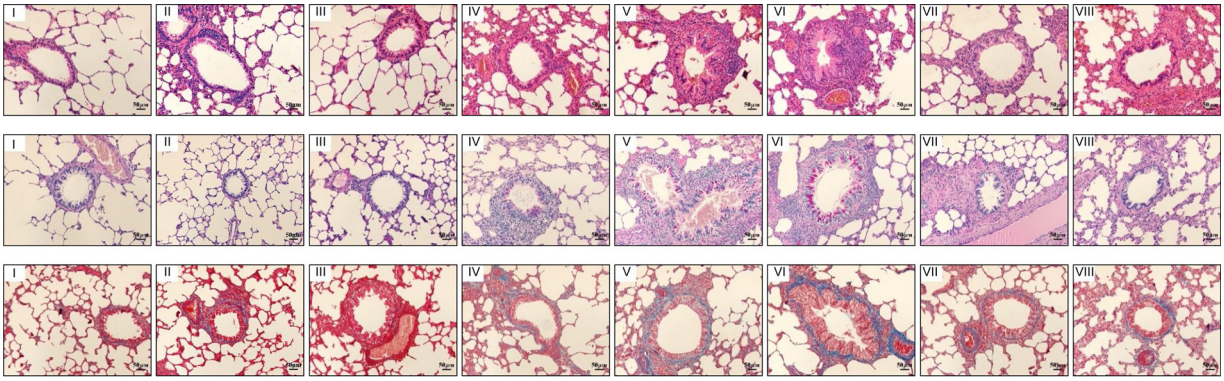


(a) Effects of COF on the inflammatory cell recruitment.

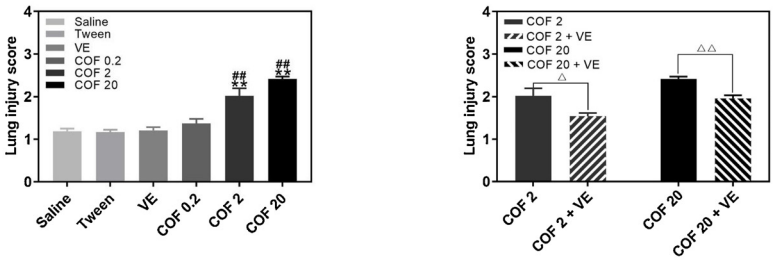


(b) Effects of VE on the COF-induced inflammatory cell recruitment.

Fig. 3. Effects of exposure to COF on inflammatory cell recruitment (the total cells, neutrophils, lymphocytes and eosinophils) in the bronchoalveolar lavage fluid (BALF) and amelioration by VE in rats: (a) The effects at different COF doses: the saline control, tween control, VE control, COF exposure groups (0.2, 2, 20 mg kg^{-1} bw); (b) The effects of VE on the COF-induced inflammatory cell recruitment.
* $p < 0.05$ and ** $p < 0.01$ (compared with saline control group);
# $p < 0.05$ and ## $p < 0.01$ (compared with tween control group);
Δ $p < 0.05$ and ΔΔ $p < 0.01$ (COF + VE groups compared with the COF exposure groups with the same concentration).



(a) Histopathological changes in lung tissues



(b) Lung injury score

Fig. 4. Effects of exposure to COF on histopathological changes in lung tissues and quantification of lung injury: (a) H&E stained sections, PAS stained sections and MT stained sections are shown from top to bottom. H&E stained sections revealed eosinophil proliferative inflammation and airway obstruction in lung tissue; PAS stained sections showed the secretion of secretory goblet cell proliferation in the airway; MT stained sections showed peribronchial collagen deposition and lung fibrosis. I: Saline control; II: Tween control; III: VE control; IV: COF 0.2; V: COF 2; VI: COF 20; VII: COF 2 + VE; VIII: COF 20 + VE. (b) Quantification of lung injury by Smith score. Figures on the left are for different COF doses: the saline control, tween control, VE control, COF exposure groups (0.2, 2, 20 mg kg-1 bw); Figures on the right are comparisons between the COF 20 and COF 20 + VE groups.
** $p < 0.01$ (compared with saline control group);
$p < 0.01$ (compared with tween control group);
Δ $p < 0.05$ and ΔΔ $p < 0.01$ (COF + VE groups compared with COF exposed groups with same concentration).

The airway resistance, cell counts in BALF, and the histological assays of lung tissue all provided evidence of the toxicological effects of COF. The biomarkers of oxidative stress (ROS, MDA and GSH), inflammation (TNF-α and IL-1β), and apoptosis (Caspase-3 and NF-κB) indicated the underlying toxicological mechanism. We found the toxicity of COF can be prevented by administration of the anti-oxidant, VE.

The long-term toxicological risk of COF exposure on lung cancer has received considerable attention in recent years. Mounting epidemiologic evidence suggests that household or occupational exposure to COF is likely to be another important cause of lung cancer (Wang et al., 2019, 2009). However, studies of short-term toxicological effect of COF on respiratory diseases are scarce. We found that COF caused acute airway injury by increasing the respiratory resistance and decreasing the lung compliance. This is consistent with several limited observations: Ke et al. (2016) reported higher prevalence rates of dyspnea or respiratory symptoms in kitchen workers and recently Chen et al. (2018) found that exposure to COF may aggravate the development of chronic bronchitis in women. Numerous studies have observed that household air pollution from cooking fuels is associated with the development or exacerbation of respiratory diseases, including asthma, decline in lung function, acute lower respiratory tract infection or pneumonia (Gordon et al., 2014; Kurmi et al., 2012; Wong et al., 2013).

We provided multiple evidence of the acute lung injury caused by COF exposure. Firstly, the airway damage was illustrated by the airway resistance and lung compliance (Fig. 2), which are two widely used indicators for evaluating the respiratory physiology of the animals (Qiao et al., 2009). Short-term exposure to COF may weaken the elasticity of lung tissue and airway lumen stenosis by increasing the airway secretion, which ultimately affected the normal lung function. Secondly, the lung injury was reflected by the increase of inflammatory cells (Fig. 3). Wang et al. (2010) found that the number of alveolar macrophages in the BALF was dramatically increased without a significant elevation in neutrophil and lymphocyte counts in trans-trans 2,4-decadienal (t,t-2,4-DDE) treated animals. Thirdly, we illustrated the pathological deterioration of the lung tissue caused by COF (Fig. 4), not only in the airway structure but also the characteristics of airway lesions.

Our finding of a dose-response relationship indicates that higher dose of COF causes worse health effects, which is consistent with several similar studies. Yu et al. (2006) found that the risk of lung cancer increases with cooking dish-years (2.56 per 10 dish-years) and Wang et al. (2019) observed that a higher risk of lung cancer was associated with longer daily cooking duration. Another study found that the odds ratios of cough, wheeze and symptoms in the previous 30 days increase by 1.15, 1.16 and 1.16, respectively, for every 10 h spent in the kitchen (Juntarawijit and Juntarawijit, 2017).

The health effects of COF on the respiratory system may be due to the deposition of COF particles in the lungs. Cooking fumes produced by oil and food at a high temperature contain a large amount of fine PM, particularly ultrafine particles (UFP) (Wang et al., 2018). The fine PM and UFP can be inhaled and deposited in the deep regions of the lung (Deng et al., 2019, 2018; Wang et al., 2018). Numerous epidemiological studies have observed the adverse health effects of exposure to fine PM and UFP on respiratory diseases (Chu et al., 2019; Islam et al., 2020; Li et al., 2020; Zhou et al., 2020).

To investigate the possible mechanisms underlying the aforementioned pathological changes caused by COF, we measured the biomarkers in lung tissue. Our study disclosed the toxicological effect of COF on the lung by examining the biomarkers of oxidative stress (ROS, MDA and GSH), pro-inflammation (TNF-α and IL-1β), and apoptosis

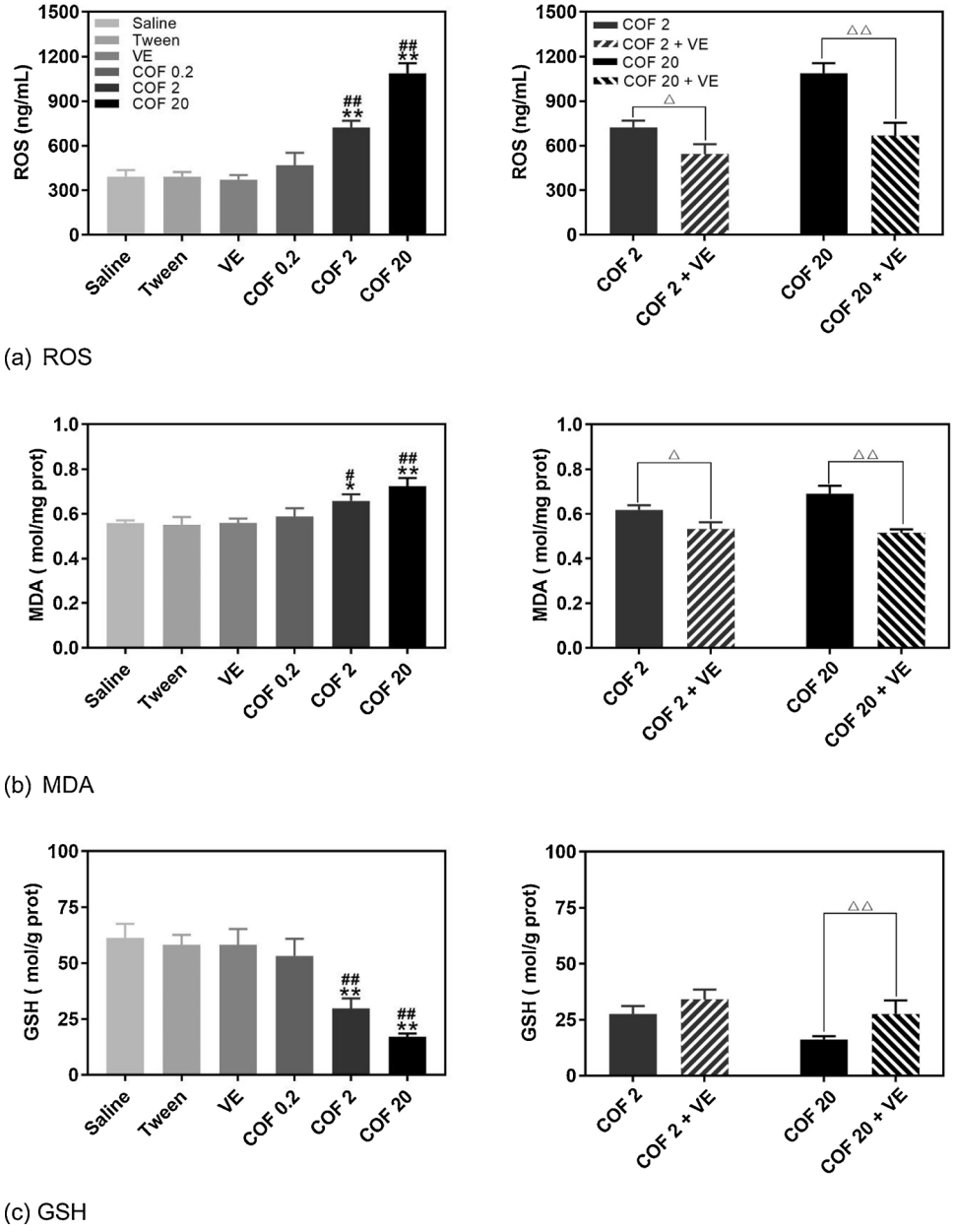
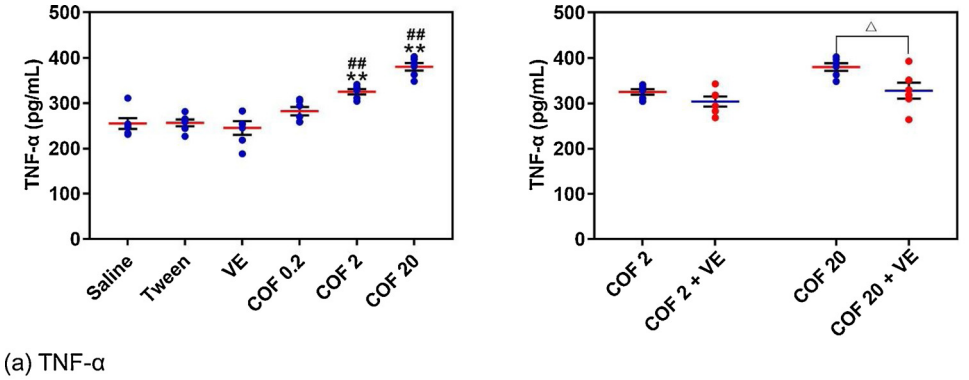


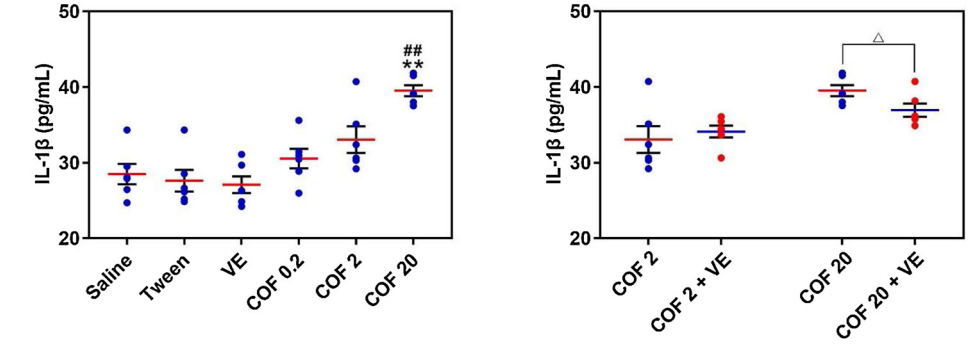
Fig. 5. Effects of exposure to COF on oxidative stress cytokine and the amelioration by VE in rats: (a) ROS, (b) MDA, and (c) GSH. Figures on the left are for different COF doses: the saline control, tween control, VE control, COF exposure groups (0.2, 2, 20 mg kg^{-1} bw); Figures on the right are comparisons between the COF 20 and COF 20 + VE groups.
* $p < 0.05$ and ** $p < 0.01$ (compared with saline control group);
# $p < 0.05$ and ## $p < 0.01$ (compared with tween control group);
Δ $p < 0.05$ and ΔΔ $p < 0.01$ (COF + VE groups compared with the COF exposure groups with the same concentration).

(NF-κB and Caspase-3). Several human biomonitoring studies have found that exposure to COF may cause oxidative DNA damage and lipid peroxidation in terms of urinary concentrations of 1-Pyrenol and 8-hydroxydeoxyguanosine (8-OHdG) (Cao et al., 2013; Ke et al., 2016). *In vitro* studies have shown that exposure to COF induced oxidative stress that ultimately leads to cell injury and/or death of epithelial and alveolar A549 cells in the lung (Dou et al., 2018; Tung et al., 2001), which is consistent with our findings (Fig. 5). According to our results (Figs. 5–7), we suggest a mechanism to explain the toxicological effects of COF on the lungs as shown in Fig. 8. Oxidative stress is assumed to be the crucial mediator of the toxicological effect. It not only reduces GSH activity allowing the antioxidant defence system to be overwhelmed, but it can also lead to apoptosis by activating Caspase-3. On the other hand, oxidative stress can also cause damage to the DNA by activating NF-κB, which mediates the process of inflammation.

Our study suggests that VE has a protective effect against the toxicity of COF. Use of VE as a therapeutic agent has garnered renewed interest and many countries have formulated dietary intake recommendations for VE (Galli et al., 2017). Given the key role of oxidative stress and inflammation in lung injury, the anti-oxidant and anti-inflammatory effects of VE are reasonable. It has been demonstrated that VE has the potential to revent or treat diseases, including cancers (Lee et al., 2005). Some studies have also observed the association between VE intake and pulmonary health (Allen et al., 2009). Especially, fruits and vegetables are rich in VE and can provide a protective effect on the human lung. Epidemiologic studies have indicated that a low fruit and vegetable diet may be associated with the development of asthma and allergic disorders (Nurmatov et al., 2011). We assume that

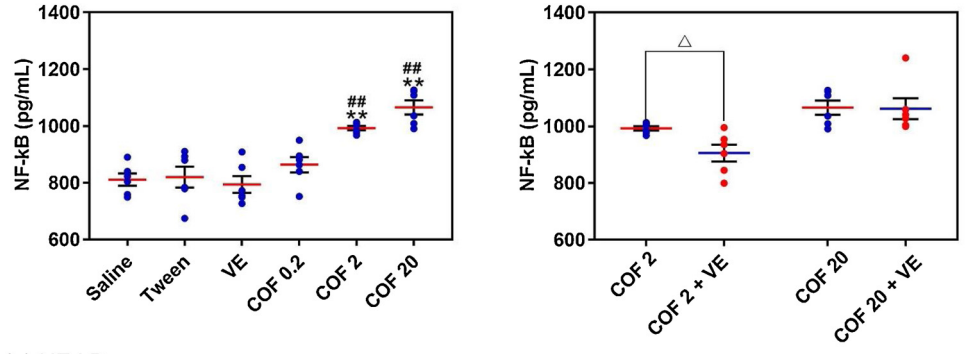


(a) TNF-α

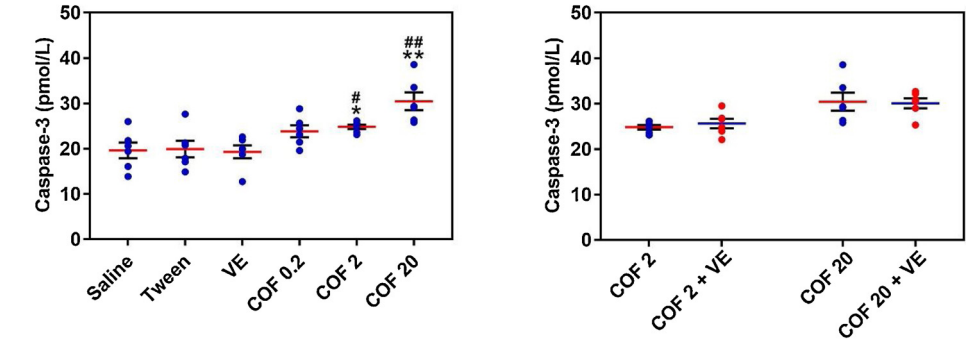


(b) IL-1β

Fig. 6. Effects of exposure to COF on inflammation cytokines and the amelioration by VE in rats: (a) TNF-α, and (b) IL-1β. Figures on the left are for different COF doses: the saline control, tween control, VE control, COF exposure groups (0.2, 2, 20 mg kg-1 bw); Figures on the right are comparisons between the COF 20 and COF 20 + VE groups.
** $p < 0.01$ (compared with saline control group);
$p < 0.01$ (compared with tween control group);
Δ $p < 0.05$ (COF + VE groups compared with the COF exposure groups with the same concentration).



(a) NF-kB



(b) Caspase-3

Fig. 7. Effects of exposure to COF on apoptosis cytokines and the amelioration by VE in rats: (a) NF-kB, and (b) Caspase-3. Figures on the left are for different COF doses: the saline control, tween control, VE control, COF exposure groups (0.2, 2, 20 mg kg-1 bw); Figures on the right are comparisons between the COF 20 and COF 20 + VE groups.
* $p < 0.05$ and ** $p < 0.01$ (compared with saline control group);
# $p < 0.05$ and ## $p < 0.01$ (compared with tween control group);
Δ $p < 0.05$ (COF + VE groups compared with the COF exposure groups with the same concentration).

the ameliorative effect of VE on COF-induced lung injury in rats is related to its ability to scavenge ROS. VE can react with active free radicals or scavenge oxygen free radicals directly, convert lipid peroxides into hydroxyl lipids, avoid cell membrane and intracellular nucleic acid from being attacked by external free radicals, and reduce the degree of lipid peroxidation and reduce the damage of DNA (Mishra et al., 2019). In addition, it has the ability to protect and improve antioxidant enzyme systems, such as GSH, superoxide dismutase (Stone et al., 2018).

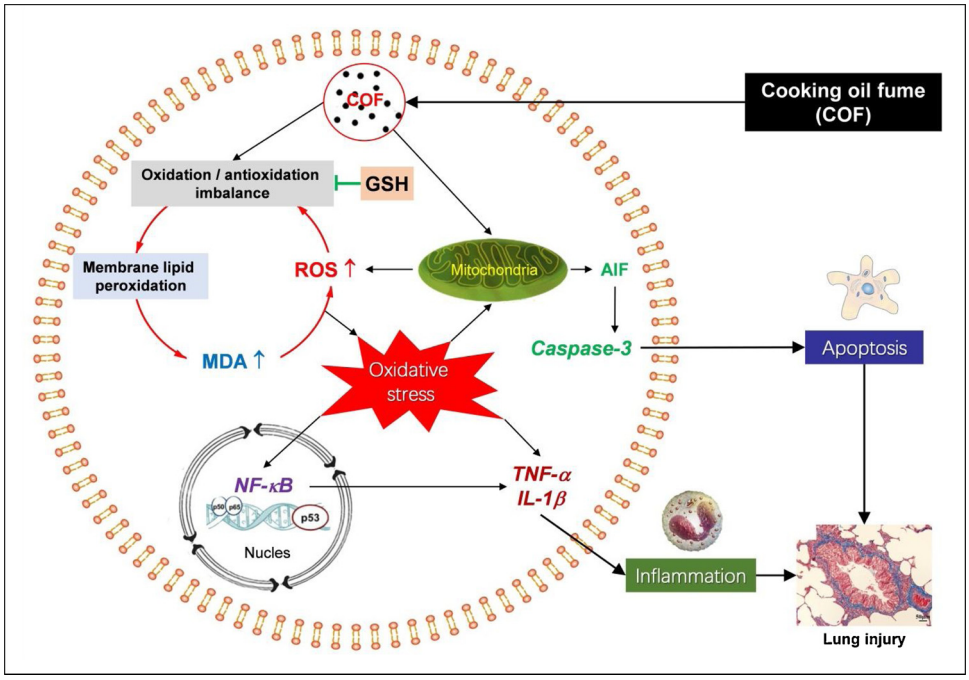


Fig. 8. Suggested mechanism for the toxicology effect of COF on the lung.

However, the protective effect of VE on Caspase-3 has not been shown yet in our study, we speculate that this may be related to multiple apoptosis pathways.

Finally, we should acknowledge the main limitations of the present work. Firstly, since the composition of COF varies greatly, depending upon various factors such as type of cooking oil, cooking temperature, cooking style, cooking pan, food being cooked and chemical additives (Ho et al., 2019; Peng et al., 2017), COF contains a complex mixture of toxic chemical compounds including PAHs, metals, heterocyclic amine, aldehydes and other harmful gasses. We are the first to show the main components in COF condensation (Table 1). However, we analyzed the PAHs and metals only. As a comparison, we summarized the main compounds in COF particulates in the recent literatures (Table S1 shown in Supplemental Materials). It is expected that the concentrations in the condensation is much higher than those in particulates. It is generally established that PAHs, aldehydes and metals are the most abundant and toxic components of COF, regardless which edible oil or cooking method is used, and higher oil temperature and oil volume produce more toxic substance. Among the PAHs compounds, Benzo(a) pyrene was classified as group 1 carcinogens (IARC 2012) and has been proved to be closely related to lung cancer (Lin et al., 2015) and other cancers (Lee et al., 2010). Tt-2,4-DDE, the most abundant aldehyde identified in COF, attracted widespread attention due to its high toxicity and mainly contributed to the genotoxicity of COF (Peng et al., 2017). Hence, a deeper understanding of these major toxic substances of COF-induced lung injury may require further research. Secondly, we did not investigate the relationship between VE dose and its protective effect. However, it would be reasonable to assume that, since the higher the dose of COF, the greater the resulting toxic effect, more VE will be needed to protect against the toxicity of greater exposure to COF. In addition, future studiey is warranted to elucidate the role of VE in the attenuation of lung disease.

5. Conclusions

We systematically examine the toxicological effects of COF on the rat lungs. Our findings show the toxicological evidence by the airway resistance and lung histological assay, suggest an underlying toxicological mechanism based on the analysis of the biomarkers of oxidative stress, inflammation, and apoptosis, and illustrate the protective effects of VE against the toxicity of COF. The *in vivo* toxicological study implies human health effect of exposure to COF. We suggest that oxidative stress may be primarily responsible for the observed COF-induced toxicity, and VE can effectively ameliorate the toxicity.

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Declaration of Competing Interest

The authors declared that they have no conflicts of interest to this work.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the

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