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ORIGINAL RESEARCH

# Folic Acid Supplementation Reversed Lung Inflammatory Response, Oxidative Damage and Histopathological Alterations in an LPS-Induced Rat Model of Lung Injury

Mohammad Hossein Eshaghi ghalibaf[1,2], Elahe Kamelnia[3], Sepide Behrouz[1,2], Rasul Saberi[1,2], Zahra Kioumarsi[1,2], Mohammad Hossien Boskabady[1,2]

[1]Applied Biomedical Research Center, Basic Sciences Research Institute, Mashhad University ofMedical Sciences, Mashhad, Iran; [2]Department of Physiology, School of Medicine, MashhadUniversity of Medical Sciences, Mashhad, Iran; [3]Department of Biology, Faculty of sciences, Mashhad Branch, Department of Biology, Faculty of sciences, Mashhad Branch, Islamic Azad University, Mashhad, Iran

Correspondence: Mohammad Hossien Boskabady, Department of Physiology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, Tel +985138828565, Email boskabadymh@mums.ac.ir

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**Aim:** Lipopolysaccharide (LPS) induced systemic inflammation is a well-known experimental model for studying damage to various organs, and the lungs are known to be one of the targets of the detrimental effects of inflammatory processes. Activation of specific signaling pathways such as LPS /Toll-like receptor (TLR)/Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kβ) induces an inflammatory response and impairs the function of the respiratory system. Folic acid (FA) is a water-soluble vitamin that plays a special role in biological processes such as cell division. Limited studies have evaluated the lung protective effects of folic acid. Therefore, we conducted this preclinical study to demonstrate the lung protective effect of FA and its possible mechanisms in LPS-induced lung injury.

**Material and Methods:** Rats were divided into five groups (n =10 in each group): a normal control group, LPS challenged group treated with saline, and three group challenged with LPS and treated with FA (5.10, and 20 mg/kg). Rats were treated with FA for three weeks, and in the third week, LPS was injected daily after FA administration. Lung inflammatory response and oxidative stress biomarkers as well as histopathological status was assessed in the end of study. Data were analyzed using Prism version 8 using one-way ANOVA with Tukey's post hoc tests.

**Results:** FA supplementation resulted in markedly decreased lipid peroxidation level and increased superoxide dismutase (SOD), catalase (CAT) and thiol activity both in the lung and broncho-alveolar lavage fluid (BALF) ($P<0.05$ to $P<0.001$). Treatment with FA also reduced lung inflammatory response by reversing increased total and differential white blood cells (WBC) counts ($P<0.05$ to $P<0.001$). Also, FA administration improved lung histopathological change ($P< 0.01$).

**Conclusion:** The dose-dependent improvement effect FA supplementation on LPS-induced oxidant/antioxidant balance, inflammatory response and histopathological alterations of lung was shown for the first time. The potential therapeutic intervention of FA in LPS-induced lung damage was highlighted.

**Keywords:** folic acid, LPS, lung, oxidative, inflammation

## Introduction

Systemic inflammation is an exaggerated defense response of the body immune system to a noxious stressor such as chemical and physical injury or infection.[1,2] The lung has been identified as the most vulnerable organ in inflammatory conditions such as sepsis.[3] Uncontrolled production of pro-inflammatory mediators plays a key role in the development of inflammation-associated lung injury.[4] LPS is a component with pro-inflammatory properties found in Gram-negative bacterial outer membrane and is most used endotoxin to elicit an inflammatory state in experimental studies.[5] LPS is most used endotoxin



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to establish acute lung injury (ALI) models in experimental study in which causing inflammatory and oxidative damage due to toll like receptor 4 (TLR4)/NF-kβ signaling pathway activation in lung tissue.[4,6] Recent studies have shown immunomodulatory effect of nutritional therapy on inflammatory disease and water-soluble vitamins have emerged as one of the most widely utilized therapeutic options among healthcare practitioners.[7] Folic acid (FA), or vitamin B9, is an essential nutrient that that plays both structural roles in macromolecules and functional roles in key biological processes, such as deoxyribonucleic acid (DNA) synthesis during rapid cell growth and division.[8] The results of a clinical evaluation showed that FA intake can improve indicators related to respiratory system function in patients with chronic obstructive pulmonary disease (COPD).[9] In addition, FA supplementation showed anti -inflammatory and antioxidant activity in several clinical and preclinical studies.[10,11] Recently, we evaluated the protective effect of FA in LPS-challenged animal and we reported memory improving, antioxidant and anti-inflammatory property of FA.[12] Although several recent studies have confirmed the anti-inflammatory and antioxidant properties of folic acid, there is a clear lack of studies on the effect of this agent on LPS-induced lung damage. Therefore, in the present study, we use experimental model of LPS-induced lung injury to assess the lung protective effect of FA.

# Materials and Method

This preclinical work was conducted using 8- to 10-week-old male Wistar rats (Mashhad University Laboratory Animals Center) which maintained under standard status (at 22–24°C), with free access to food and water. All experiments were approved by the Animal Ethics Committee of the Mashhad University of Medical Sciences (Ethical No. IR.MUMS. REC.1402.051). In addition, all experimental procedures of this work were performed in compliance with the National Institutes of Health Guidance for the Care and Use of Laboratory Animals.

## Experimental Procedure and Treatment Protocols

Experiments were randomly allocated into the five following groups (n=10 in each group):

### Control Group (1)

In this group, rats received vehicle (l mL/kg-physiological saline 0.9%) instead of LPS by intraperitoneal (i.p.) injection and were given drinking water without FA supplementation.

### LPS Group (2)

In this group, LPS (1 mg/kg) administrated in the last week of study protocol (Third week) by intraperitoneal injection without FA supplementation.

### Treatment Groups (3–5)

In these groups, animals were orally treated with FA (5, 10, and 20 mg/kg) for three weeks and in third week challenged with LPS before FA administration. Figure 1 shows the protocol of animal exposure to LPS, treatments and a table of the study groups. LPS and FA dosage were chosen based on our previous studies.[12]

## Biochemical Assessment

In the last day of the study period, after deep anesthesia induction by ketamine and xylazine combination (100 mg/kg and 15 mg/kg, respectively, i.p.) rats were sacrificed. Right lung was removed and 5 mL of BALF collected according to our previous work. BALF and a homogenate of lung tissue with PBS were centrifuged at 2500 rpm for 15 min and stored at −70°C until measurement of oxidative stress indicators. We followed our previous protocols to determine the content of malondialdehyde (MDA), activities of superoxide dismutase (SOD), catalase (CAT), and thiol group levels in BALF and lung supernatant.[13] In order to measure the lipid peroxidation, TBA +HCL+ supernatant combination was used to determine the MDA level and finally, the absorbance of this mixture was read at 535 nm. For measuring total thiol content, the absorbance of supernatant + ethylene diamine tetra acetic acid disodium salt (Na2EDTA) combination was read at 412 nm and then 2, 2′-dinitro-5, 5′-dithiodibenzoic acid (DTNB) reagent was added to this mixture and the absorbance was read again (A2). Also, SOD activity in lung tissue and BALF was defined based on the amount of enzyme inhibiting 50% of pyrogallol auto-oxidation and a colorimetric reaction method was used for enzyme activity measuring at 570 nm. The rate of the decrease in the H2O2 was considered as a CAT activity marker in the lung homogenate.

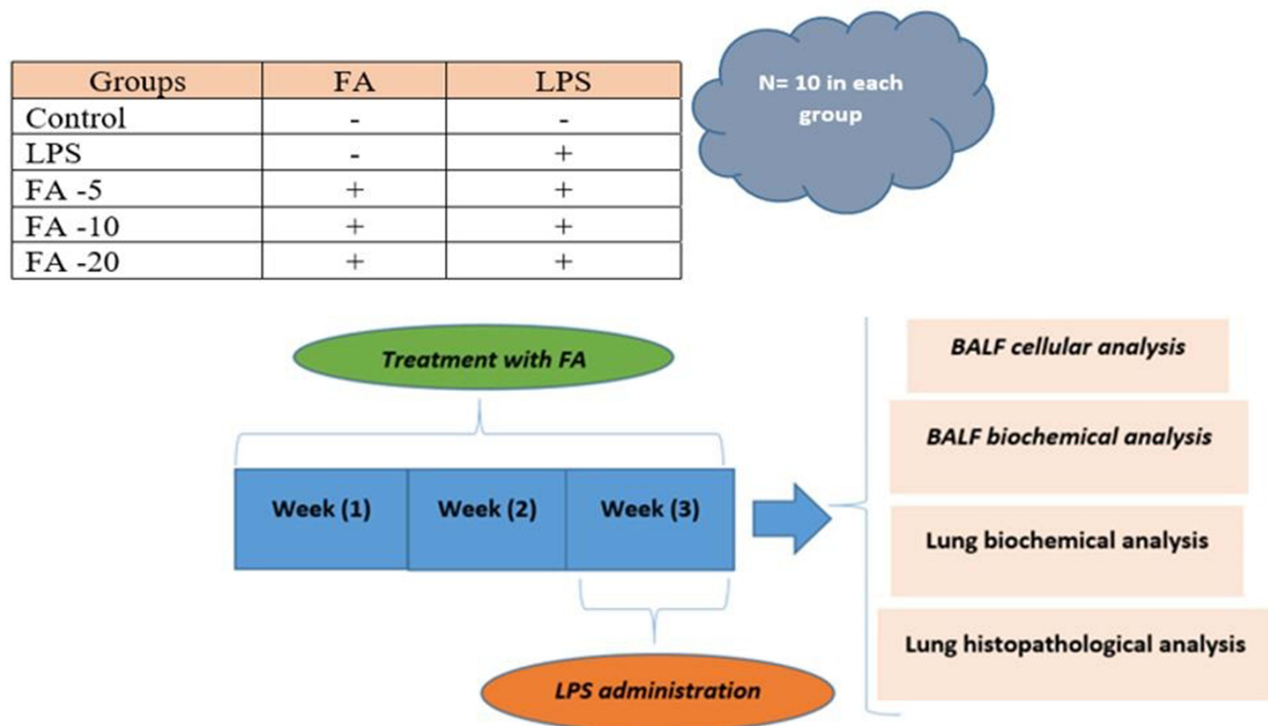


**Figure 1** Study design and experimental protocol.

## BALF Cellular Analysis

For analyzing the cytological status of BALF, we used conventional method based on our previous works. Briefly, the number of BALF total WBC was counted under a microscope using a hemocytometer. In addition, for differential cell count analysis, we used Wright-Giemsa staining. For differential counting, the stained slide was evaluated under a microscope, and the proportion of each cell type was determined as a percentage and calculated based on the total count of each sample.[13]

## Histopathological Evaluation

After animal scarification, left lung was removed and histopathological indexes including inflammation and hemorrhage assessed under a light microscope. Briefly, we used formalin for tissue fixation (72 h) and alcohol, for dehydration process. Then, tissue cleared in xylene, embedded in paraffin and sectioned into thin Section using a microtome. Deparaffinization was performed by Hematoxylin and eosin combination and lung tissue slices were scored from 0 to 4 according our previous works for inflammation and hemorrhage. Histopathological analysis (0 = normal, 1 = Minimal injury 2 = Mild damage 3 = Moderate injury 4 = sever damage) was performed by pathologist in blind order.

## Statistical Analysis

Data expression performed by using means ± standard error of the mean (SEM) and one-way ANOVA with Tukey's post hoc tests used for group comparisons using Prism version 8. $P < 0.05$ was considered as statistically significance.

# Results

## BALF Cellular Analysis

In LPS challenged group, cytological evaluation revealed a remarkable total WBC and differential counts increase compared to the control group ($P<0.001$). FA supplementation (10 and 20 mg/kg) markedly diminished total WBC, eosinophil and monocyte counts compared to the LPS group ($P<0.01$ to $P<0.001$). Also, treatment with FA (5, 10, 20 mg/

kg) markedly reversed the leucocyte count compared to the LPS group (P<0.01 to P<0.001). FA (20 mg/kg) markedly reduced the count of neutrophil compared to LPS group (P<0.001). Comparative assessment between three doses of FA showed that the effect of FA (20 mg/kg) on cytological indicators (Total WBC, lymphocyte, monocyte, eosinophil) was higher than its low dose (P<0.05 to P<0.001). FA (20 mg/kg) also showed a more suppressive effect on neutrophil rise compared to its two other doses (P<0.05 to P<0.01), (Figures 2 and 3).

## BALF Oxidative Indicator Analysis

In LPS challenged group, lipid oxidation indicator (MDA) level in the BALF was markedly higher and antioxidant markers such as SOD, CAT and thiol were markedly lower than the control rats (all cases, P<0.001). Treatment with FA (10 and 20 mg/kg), reversed MDA level in the BALF (P<0.05 to P<0.001) and the improving effect of FA (20mg/kg) on MDA level was higher than its low dose (5mg/kg) (P<0.05). FA supplementation also increased CAT (FA 10 and 20 mg/kg) and SOD (FA 5, 10 and 20 mg/kg) activity in the BALF compared to the LPS group (P<0.01 to P <0.001). Improving effect of high dose of FA (20 mg/kg) on CAT activity was markedly higher than the low dose (5 mg/kg) of FA (P<0.01). In addition, the improvement effect of FA 5 and FA10 mg/kg on SOD activity was markedly lower than high dose (20 mg/kg) of FA (P<0.001). In LPS challenged rats, thiol level in the BALF markedly decreased compared to the control animals (P<0.001). FA therapy (10 and 20 mg/kg) markedly increased thiol level compared to the LPS challenged rats (P<0.05 to P<0.001). Improvement effect of low dose of FA (5mg/kg) on thiol level was markedly lower than its high dose (20 mg/kg), (P<0.001), (Figure 4).

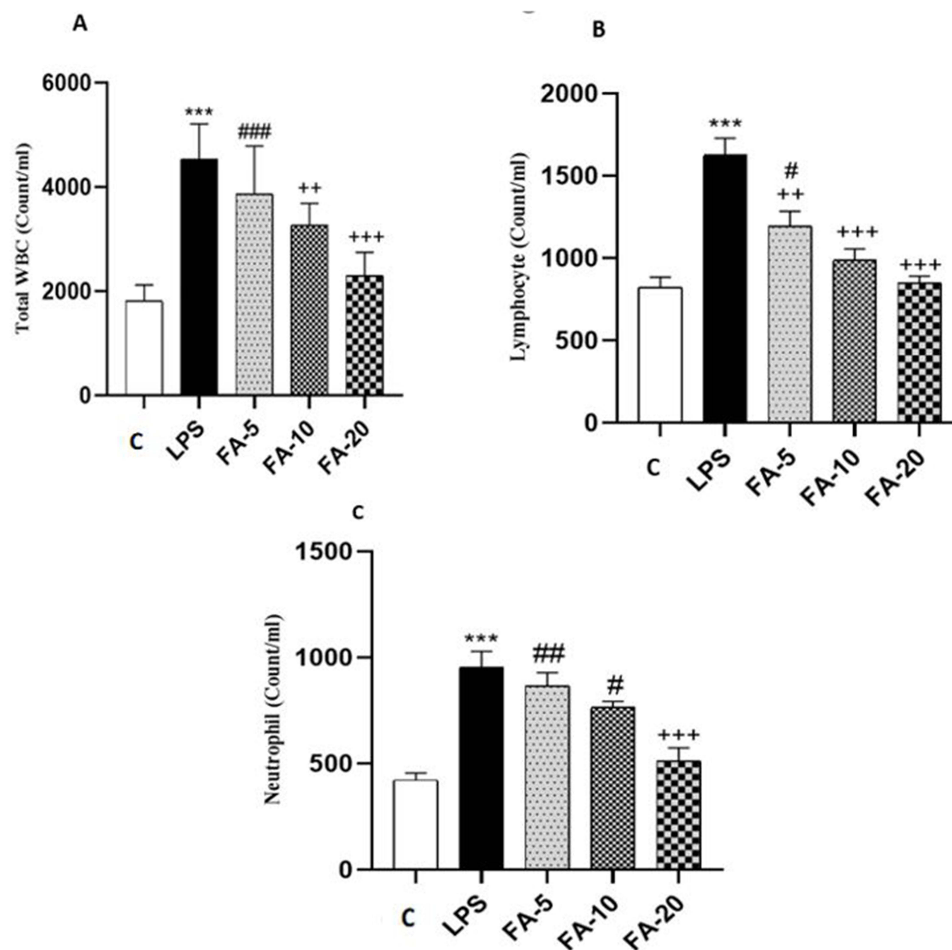


**Figure 2** Total WBC (**A**) lymphocyte (**B**) and neutrophil (**C**) in the bronchoalveolar lavage fluid. LPS vs control group; ***p <.001. Treatment groups vs LPS challenged group; ++p <.01 and +++p <.001. High dose of FA vs other treated groups; #p <.05, ##p <.01, and ###p <.001. The results were expressed as mean ± SEM. One-way ANOVA followed by Tukey's multiple comparison test was applied for comparisons among different groups (n = 10 in each group).

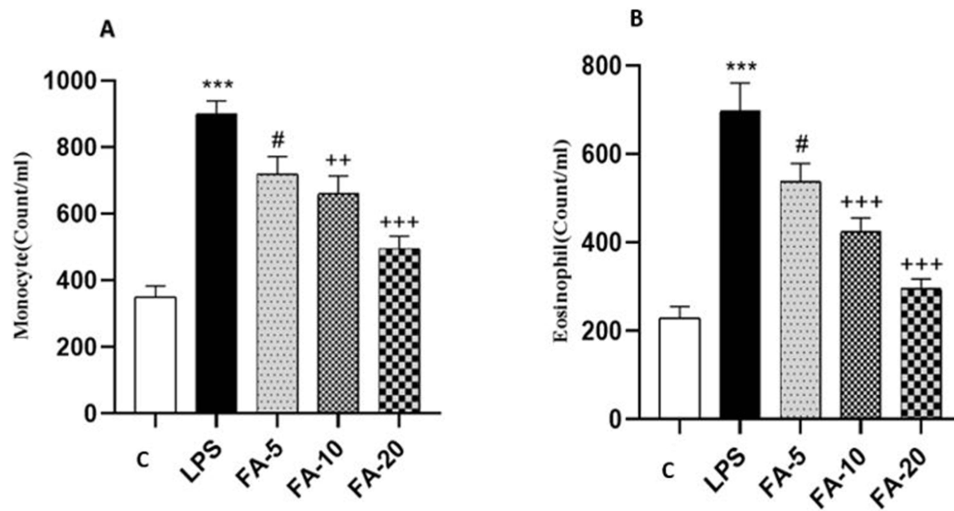


**Figure 3** Monocyte (**A**) and eosinophil (**B**) in the bronchoalveolar lavage fluid. LPS versus control group; ***p <.001. Treatment groups versus LPS challenged group; ++p <.01 and +++p <.001. High dose of FA versus other treated groups; # p <.05. In each group, 10 rats were examined and the results were expressed as mean ± SEM. One-way ANOVA followed by Tukey's multiple comparison test was applied for comparisons among different groups.

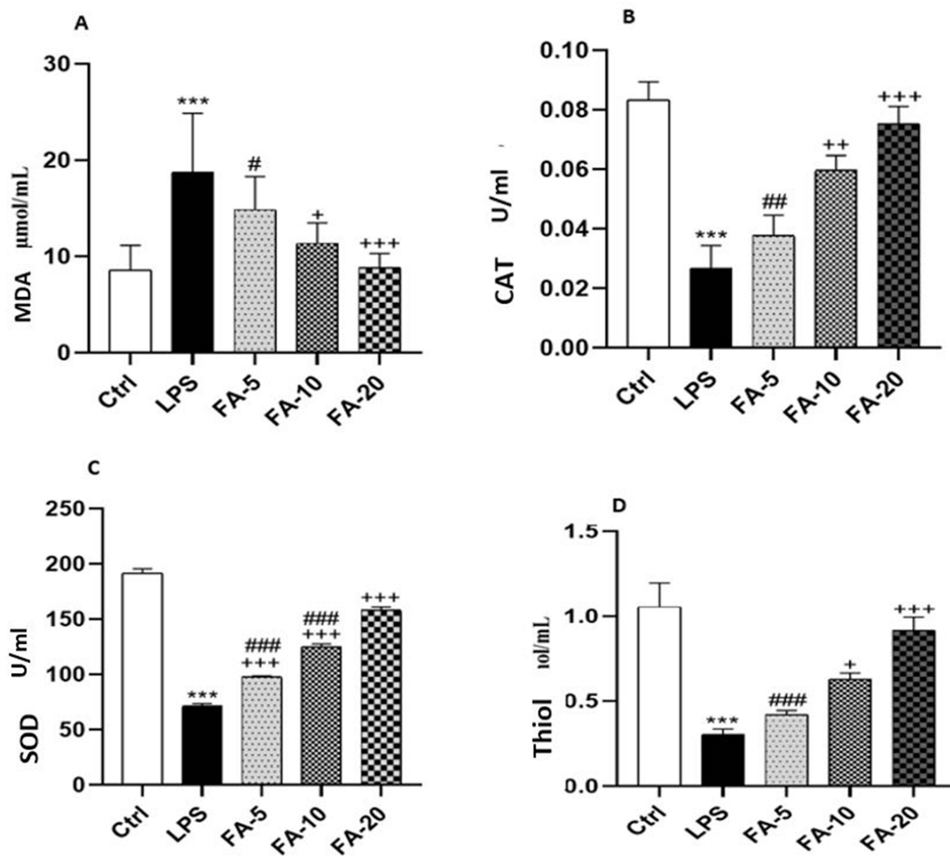


**Figure 4** BALF oxidative stress markers. MDA (**A**), CAT (**B**), SOD (**C**) and thiol (**D**). LPS versus control group; ***p <.001. Treatment groups versus LPS challenged group; +p < 0.05, ++p <0.01 and +++p <.001. High dose of FA versus other treated groups; #p <.05, ## p<0.01 and ### p<0.001. In each group, 10 rats were examined and the results were expressed as mean ± SEM. One-way ANOVA followed by Tukey's multiple comparison test was applied for comparisons among different groups.


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## Lung Tissue Oxidative Indicator Analysis

LPS administration markedly increased MDA level and suppressed the activity of SOD, CAT and total thiol compared to the control group (P<0.01 to P<0.001). Treatment with FA (20 mg/kg) markedly reduced MDA level compared to the LPS challenged group (P<0.05). FA (5, 10, 20 mg/kg) treatment, markedly improved SOD activity compared to LPS group (P<0.01 to P<0.001). Improvement effect of FA, 20 mg/kg on SOD activity was markedly higher than FA, 5 and10 mg/kg (P<0.01 and P<0.001). FA (10 and 20 mg/kg) administration reversed CAT activity and thiol level compared to the LPS group (P<0.05 to P<0.005). Improvement effect of FA 20 mg/kg on CAT activity was higher than FA 5 mg/kg (P<0.05). Also, reversing effect of FA 20 mg/kg on thiol level was higher than FA 5 and 10 mg/kg groups (P<0.05 to P<0.01), (Figure 5).

## Lung Tissue Histopathological Evaluation

LPS administration markedly increased inflammation (P<0.01), hemorrhage (P<0.001), lung edema (P<0.05) and alveolar damage (P<0.001) severity score in lung tissue compared to the control group. Treatment with FA (5, 10, and 20 mg/kg) had no remarkable effect on the inflammation, edema and alveolar damage indexes. However, treatment with FA (20 mg/kg) improved hemorrhage severity compared to LPS group (P<0.01). Improvement effect of FA (20 mg/kg) on hemorrhage score was markedly higher than FA (5 mg/kg), Figures 6 and 7 illustrate a specimen photograph of lung histopathology in each studied group (Figure 8).

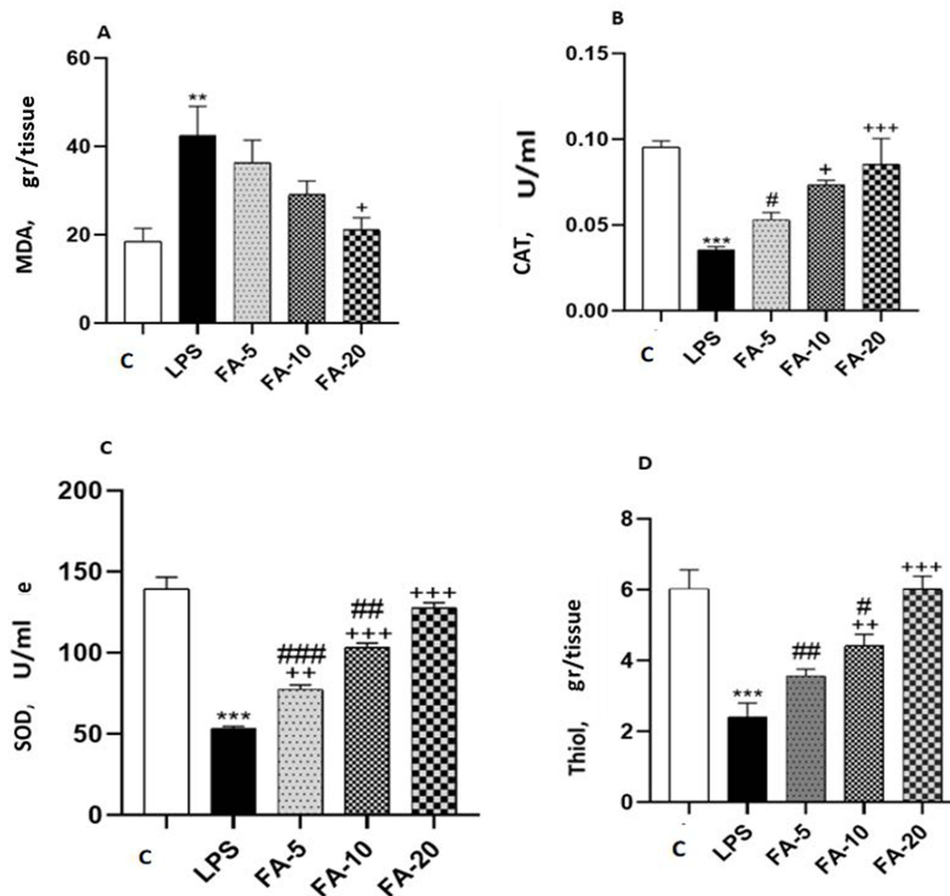


**Figure 5** Lung oxidative stress markers. MDA (**A**) CAT (**B**) SOD (**C**) and thiol (**D**). LPS versus control group; **p <0.01 and ***p <.001. Treatment groups versus LPS challenged group; +p < 0.05, ++p <0.01 and +++p <.001. High dose of FA versus other treated groups; #p <.05, ## p<0.01 and ### p<0.001. In each group, 10 rats were examined and the results were expressed as mean ± SEM. One-way ANOVA followed by Tukey's multiple comparison test was applied for comparisons among different groups.

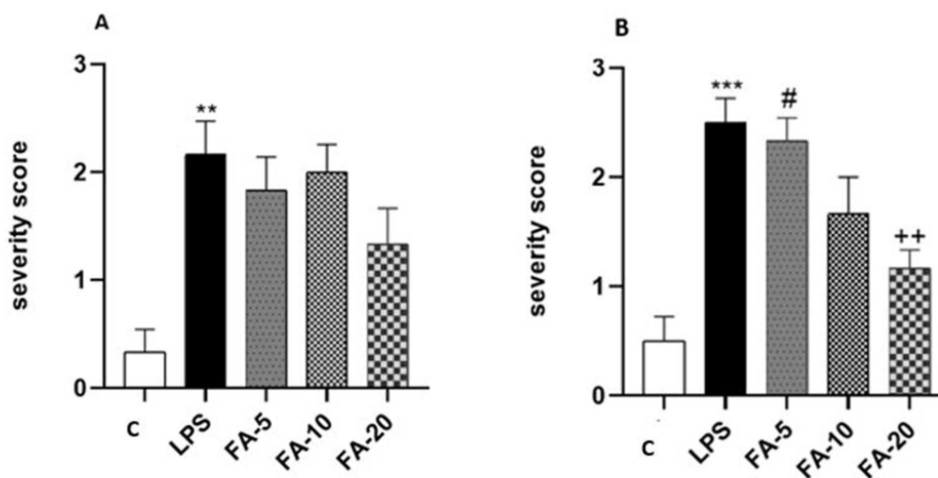


**Figure 6** Inflammation (**A**) and hemorrhage (**B**) severity score. LPS versus control group; **p <0.01 and ***p <.001. Treatment groups versus LPS challenged group; ++p <0.01. High dose of FA versus other treated groups; #p <.05. In each group, 10 rats were examined and the results were expressed as mean ± SEM. One-way ANOVA followed by Tukey's multiple comparison test was applied for comparisons among different groups.

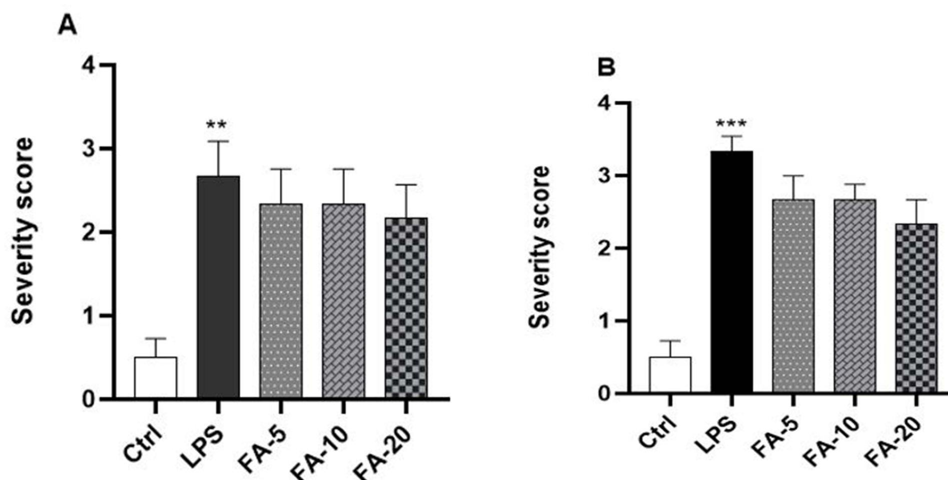


**Figure 7** Alveolar edema (**A**), Alveolar damage (**B**). LPS versus control group; **p <0.01 and ***p < 0.001. In each group, 10 rats were examined and the results were expressed as mean ± SEM. One-way ANOVA followed by Tukey's multiple comparison test was applied for comparisons among different groups.

# Discussion

In this preclinical investigation, the potential effects of FA in experimental model of LPS-induced lung damage were evaluated. Evidence from our study showed that FA can improve lung damage caused by systemic administration of LPS, probably due to its anti-inflammatory and antioxidant effects.

Cytological evaluation of BALF in LPS-challenged rats revealed increased counts of total and differential WBC, which confirmed remarkable inflammatory response in the lung tissue. BALF cellular analysis is known as a dynamic tool for detecting the cytological change during lung pathological process and also a method to evaluate the response to therapy and follow-up of lung disease process.[14] Several mechanisms for the mentioned findings based on previous experimental reports could be proposed. For example, it is postulated that TLR-LPS interaction may trigger leucocyte recruitment in to lung alveolar space. In an animal model of acute lung injury, inhaled LPS induced chemokine receptor 2 (CXCR2) expression, which induced neutrophil migration into the BALF.[15] In another preclinical report, Anfossi R et al showed that LPS induced ICAM-1 (Intercellular Adhesion Molecule 1) and VCAM-1 (Vascular Cell Adhesion Molecule 1) expression in cardiac fibroblast-neutrophil co-culture and also stimulated neutrophil recruitment and

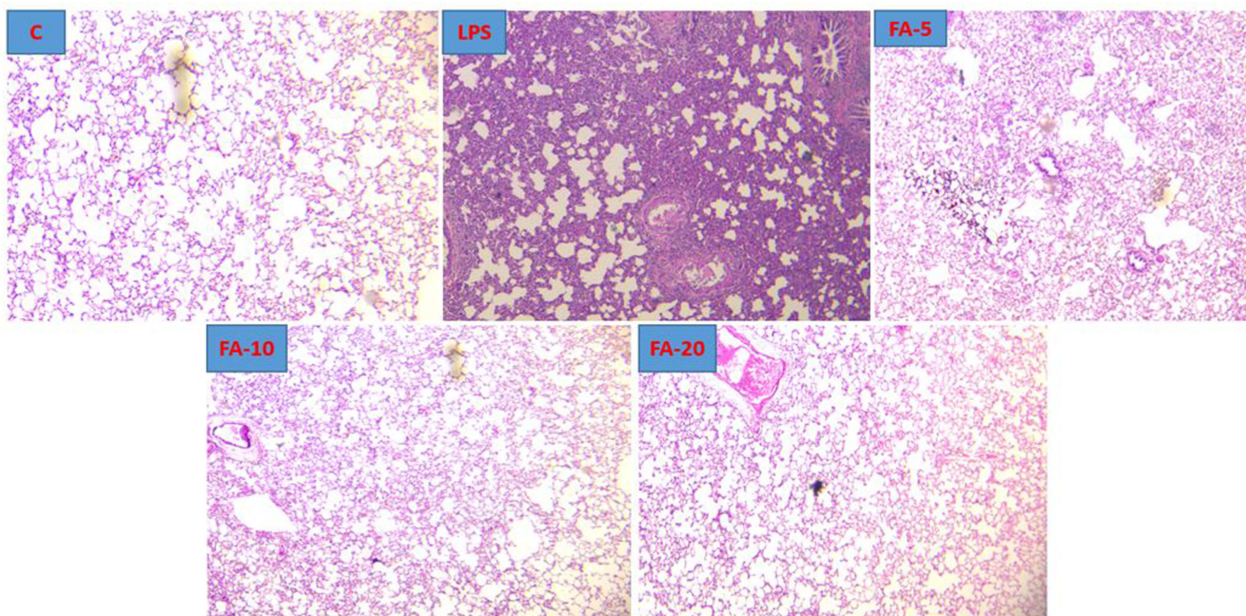


**Figure 8** Photographs of a lung sample of group C, LPS challenged group and treated groups with FA-5, FA-10, and FA-20 mg/kg. (Scale bar = 100 μm, magnification, ×100).

Matrix metalloproteinases (MMPs) activity.[16] Exposure to LPS also upset the dynamic equilibrium between oxidant-antioxidant balance in lung tissue by increasing MDA level and decreasing the activities of SOD and CAT and also thiol level. During LPS-challenge, macrophage TLR activation can trigger ROS generation, which can reveal inflammatory-oxidative damage interaction in this condition.[17]

Pathological alterations were also observed following animal exposure to LPS further supporting the profound lung injury due to LPS exposure. Numerous previous studies also showed lung pathological changes after LPS administration with various dose and duration[18,19] which support the findings of the present study.

The results of the present study may provide compelling evidence for the beneficial effects of FA in the context of LPS-induced lung injury with possible antioxidant and anti-inflammatory effect of FA. Treatment with FA reversed total and differential WBC in the BALF, oxidative stress markers in the lung and lung pathological changes induced by LPS. Recently, lung protective property of FA confirmed in preclinical and clinical studies. In line with our finding, in rats with lung ischemia- reperfusion injury, treatment with FA (5, 10, 20 mg/d for 1 week) reduced pulmonary inflammation by suppressing IL-8 and TNF-α secretion in lung tissue.[20] In another study, FA supplementation (5 mg/kg) suppressed oxidative stress, inflammation and histopathological changes in sepsis induced lung damage model.[21] In an in-vitro investigation, FA supplementation protect human bronchial epithelium cells (BEAS-2B) from high glucose–induced oxidative stress and inflammation.[22] In addition to this, evidence from a clinical research (case–control study) also confirms the lung protective effects of FA in patients with chronic obstructive pulmonary disease (COPD).[23] Moreover, in a retrospective cohort study, FA administration in patients with traumatic brain injury (TBI) reduced the risk of hospital acquired pneumonia (HAP).[24] In two clinical reports, FA deficiency was associated with poor prognosis in patient with COVID-19 and pneumonia occurrence.[25,26] Recently, results from a systematic review and meta-analysis on diabetic patients showed remarkable anti-inflammatory effect of FA administration[27] that was in line with our pre-clinical finding. In this work, a dose-dependent effect of FA on a number of indicators was observed. It seems that further studies should evaluate these therapeutic effects of FA in different doses for determination of best effective dose of FA. Also, pretreatment effects of FA were assessed in the present study, but future studies using new administration protocols design studying preventive or treatment were recommended. In this work, for the first time based on a comparative approach, oxidative stress indices in the lung tissue and BALF, which is probably indicative of their relationship to one another, and proves the effectiveness of BALF as a tool to reflect the pathological condition of the lung in clinic was

shown. The effective dose of LPS in the present study was chosen according to previous studies, but it may not be in the sepsis induction scale. Also, the study of various doses of LPS should be considered in future studies for defining of more suitable dose of this agent. In addition, as a limitation, we only used cellular analysis of BALF for inflammatory response detection, therefore more inflammatory biomarkers and specific signaling pathways should be considered by researchers to determine the lung protective effects of FA, as well as the use of new targeted drug delivery techniques with the aim of altering FA metabolism in lung cells. It is also suggested that the effects of this agent should be investigated in comparison to a standard drug.

## Conclusion

This experimental report is among the first to demonstrate lung protective effect of FA in LPS-induced lung damage. FA not only improved lung oxidant/antioxidant balance but suppressed inflammatory response and histopathological change in lung tissue in a dose-dependent manner. These findings provide evidence for the pulmonary protective effects of nutritional supplements in systemic inflammatory conditions such as sepsis, but further experimental and clinical studies are required.

## Disclosure

The authors report no conflicts of interest in this work.

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