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# Preventive effect of ursolic acid derivative on particulate matter 2.5-induced chronic obstructive pulmonary disease involves suppression of lung inflammation

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**Abstract**

Respiratory diseases like chronic obstructive pulmonary disease (COPD) are associated with the presence of particulate matter 2.5 (PM2.5) in the air. In the present study, the effect of synthesized ursolic acid derivatives on mice model of PM2.5-induced COPD was investigated in vivo. The mice model of COPD was established by the administration of 25 μL of PM2.5 suspension through intranasal route daily for 1 week. The levels of oxidative stress markers and inflammatory cytokines like tumor necrosis factors-α and interleukin-6 in the mice bronchoalveolar fluids increased markedly on administration with PM2.5. However, treatment with ursolic acid derivative caused a significant suppression in PM2.5-induced increase in oxidative stress markers and inflammatory cytokines in dose-dependent manner. Hematoxylin and eosin staining showed excessive inflammatory cell infiltration in pulmonary tissues in mice with COPD. The inflammatory cell infiltration was inhibited on treatment of the mice with ursolic acid derivative. The ursolic acid derivative treatment increased level of superoxide dismutase in mice with COPD. The lung injury induced by PM2.5 in mice was also prevented on treatment with ursolic acid derivative. Thus, ursolic acid derivative inhibits pulmonary tissues damage in mice through suppression of inflammatory cytokine and oxidative enzymes. Therefore, ursolic acid derivative can be of therapeutic importance for treatment of PM2.5-induced COPD.

**KEYWORDS**

anti-inflammatory, bronchitis, cell infiltration, chronic obstructive pulmonary disease, particulate matter

## 1 | INTRODUCTION

Pulmonary diseases are caused commonly by the inhalation of contaminated air in most of the regions of China and have adversely impacted human health. Increased concentration of particulate matter (PM), particularly PM2.5 in the atmosphere has led to a sharp rise in the mortality and morbidity rate because of respiratory

**Abbreviations:** BALF, bronchoalveolar fluids; COPD, Obstructive pulmonary disease; CrO3, Chromium trioxide; IL-6, interleukin-6; PM2.5, Particulate matter 2.5; TNF-α, Tumor necrosis factors-α; TCM, Traditional Chinese Medicine.

diseases.[1] The PM present in atmosphere having diameter greater than 2.5 μm is represented by PM2.5. The characteristic features of PM2.5 that make it harmful include its potential to aggregate toxic heavy metals, pollutants of organic nature, bacteria, and viruses from the air.[2,3] Moreover, PM2.5 remains in atmosphere for long duration and on inhalation deposits in lungs resulting in serious health diseases.[2,3] Studies have demonstrated that PM2.5 induces reactive oxygen species (ROS) and pro-inflammatory mediator production in lungs leading to lung damage and injury.[4–6] Histopathological examination of pulmonary tissues following PM2.5 inhalation has shown marked tissue damage.[7,8]

Chronic obstructive pulmonary disease (COPD) is associated with the blocking of lung airways because of degeneration of lung parenchyma and inflammation.[9] Over the past decade, the rate of morbidity and mortality of COPD patients has increased gradually which promoted knowledge about its pathogenesis globally.[9,10] The main causes of COPD are excessive exposure to cigarette smoking and atmosphere containing PM2.5.[2–4,11] PM having aerodynamic diameter ≤ 2.5 μm (PM2.5) has adversely impacted health of human beings worldwide. These small sized particles are responsible for respiratory system disorders as well as circulatory diseases. Researchers from the United States have shown that increase in PM2.5 concentration to 10 $\mu g/m^3$ will enhance mortality to 0.3–1.2% on short-term exposure and to 6–13% on long-term exposure.[12] According to researchers from Europe, mortality of the people exposed for long-term to air pollution will increase 7% with increase in PM2.5 concentration to 5 $\mu g/m^3$.[13] World Health Organization report reveals that globally 88% population is already exposed to PM2.5 level above 10 $\mu g/m^3$, which is harmful to humans.[14] In China and Japan, increased PM2.5 concentration is considered to be important environmental problem. The currently used antibiotics and traditional Chinese medicines (TCMs) are believed to inhibit respiratory diseases, including COPD through anti-inflammatory mechanism.[15–18] However, the presently available antibiotics have limitation of inducing side effects like weight loss, vomiting, diarrhea, and headaches.[19–21] There is urgent need for the development of effective treatment strategies for PM2.5-induced respiratory diseases because the emission of PM is increasing day-by-day. The controlling measures like PM2.5 emission reduction, the use of dust respirator, and planting more and more trees alone cannot solve the problem. Therefore, novel and effective strategies need to be developed for the treatment of PM2.5-induced respiratory diseases.

TCM derived from the plant source has been shown to be of importance for the treatment of respiratory diseases like chronic pneumonia, bronchitis, asthma, and COPD.[22–24] The mechanism of TCM is believed to involve antibacterial action, relaxing bronchial smooth muscle, and inhibition of inflammatory factors.[22–24] Triterpenes serve as potent molecules because of significant biological activities and presence of amenable functionalities. Three members of triterpene family, namely, betulinic, oleanolic, and ursolic acid are found abundantly in plants.[25] These three triterpenes possess promising anti-cancer,26a, b anti-inflammatory,26c and so forth, properties. Ursolic acid **1**, molecule has pentacyclic structure and present in abundance in the peels of *Malus pumila* Mill.[27] This molecule possesses anti-inflammatory, antiallergic, antibacterial, antiviral, antitumor, and cytotoxic activity.[28–32] The present study was designed to investigate the effect of ursolic acid derivatives on PM2.5-induced COPD in vivo in the mice model. The study demonstrated that ursolic acid derivative inhibited acute PM2.5-induced COPD through suppression of inflammation cytokines and by oxidative factors in the mice bronchoalveolar fluid (BALF). These data suggest that ursolic acid derivative acts as a potential candidate for the treatment of PM2.5-induced COPD (Figure 1).

## 2 | MATERIALS AND METHODS

### 2.1 | Synthesis of the compounds (7a-7o)

The ursolic acid was oxidized using chromium trioxide ($CrO_3$), sulfuric acid ($H_2SO_4$), and acetone to form the corresponding oxidized compound **4** in 98% yield (Scheme 1). The compound **4** was subjected to condensation reaction with $H_2NNH_2$ using potassium hydroxide as base in ethanol for 6 hr to afford the hydrazone **5**. The compound **5** was reacted with various substituted α,β-unsaturated ketones under acidic condition to form the library of compounds (***6a***-***6o***) in excellent yields. The compounds (***6a***-***6o***) were treated with palladium acetate

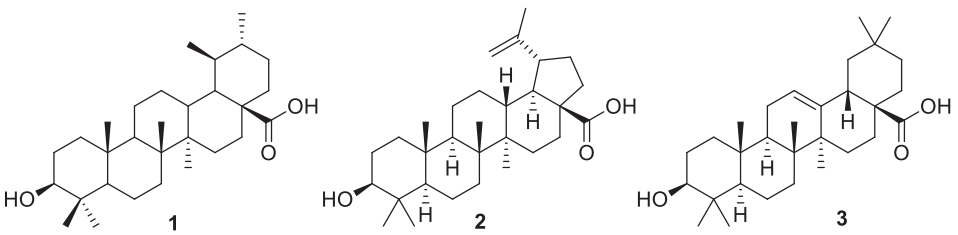
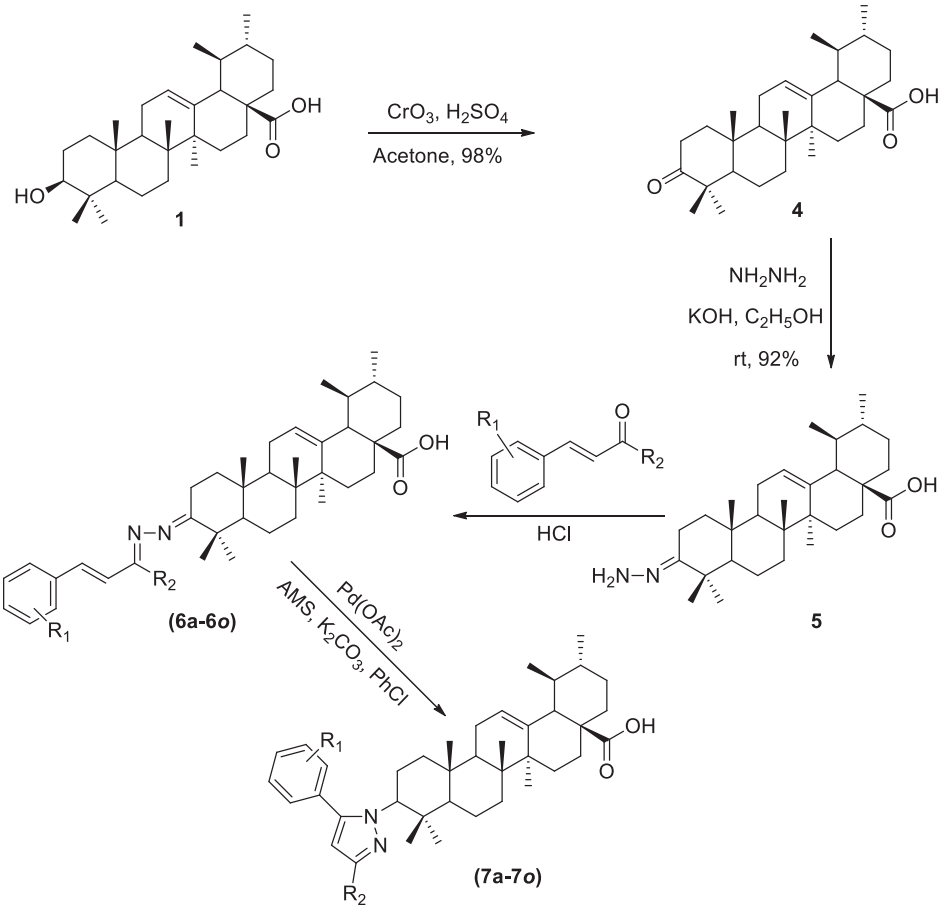



**FIGURE 1** Chemical structure of ursolic, betulinic, and oleonolic acids

**SCHEME 1** Synthesis of ursolic acid derivatives




and potassium carbonate in chlorobenzene containing molecular sieves to deliver the corresponding cyclized compounds (**7*a*-7*o***).

## 2.2 | Animals

A total of 50 adult male mice (age, 8 weeks and weight, 18–22 g) were obtained from the Experimental Animal Center of Soochow University (Suzhou, China).The mice were placed in pathogen-free conditions under 12 hr/12 hr light/dark cycles at room temperature (23 ± 2°C) and 50–70% humidity. The experimental protocols for the mice were performed according to the experimental practices and standards of the Animal Welfare and Research Ethics Committee, Zhangjiagang City, Jingfeng People's Hospital (Suzhou). The study was approved by the Animal Care Committee, Zhangjiagang City, Jingfeng People's Hospital (Suzhou).

## 2.3 | Collection of PM2.5

The Thermo Anderson sampler (PDR-1500; Thermo Fisher Scientific, Inc., Waltham, MA) was used for the collection of urban airborne PM2.5 over 2 weeks. The sampling filter membrane was partitioned into 2 × 2 cm sections and subsequently subjected to ultrasonic oscillation in the ultrapure water at room temperature (110 kHz; five times, 40 min each). The filtrate was collected by filtration through gauze and centrifuged for 25 min at 16,000× *g* at room temperature. After discarding, the supernatant precipitate collected was put in physiological saline (PS), sterilized in autoclave, and stored at 4°C after freeze-drying.

## 2.4 | Establishment of COPD mice model

Forty mice were administered 25 μL of PM2.5 suspension through intranasal route for 1 week daily. The mice in control group were given equal volumes of PS. The mice administered with PM2.5 suspension were divided randomly into four groups of 10 animals each: untreated group, low dose ursolic acid derivative (LUAD) treatment group (30 mg/kg ursolic acid derivative), medium dose ursolic acid derivative (MUAD) treatment group (50 mg/kg ursolic acid derivative), and high dose ursolic acid derivative (HUAD) treatment group (100 mg/kg ursolic acid derivative). The ursolic acid derivative was given for 1 week to the mice once daily. The mice were monitored daily to record their behavior like

condition of body hair, sensitivity, and respiratory murmur. On the 21st of PM2.5 administration, the mice were sacrificed to excise the lungs and collect the BALF.

## 2.5 | Collection and analysis of BALF

The 1 mL volumes of 1× phosphate buffer saline were injected to the mice lungs and maximum possible volumes were withdrawn for detection of various markers using the reported protocol.[16] The collected BALF was subjected to centrifugation for 20 min at 4°C using reported methodology.[16] Following centrifugation, the supernatants collected were subjected to analysis of lactate dehydrogenase (LDH), alkaline phosphatase (ALP), acidic phosphatase (ACP), nitric oxide (NO), nitric oxide synthase (NOS), malonyldialdehyde (MDA), and superoxide dismutase (SOD) levels using the commercially available kits in accordance with the manual protocol. The levels of TNF-α and IL-6 in the mice BALF were determined using ELISA kits as per manual protocol.

## 2.6 | Analysis of lung histology

The upper lobes of left lung were used for analysis of histopathological changes. The excised lung tissue samples were subjected to fixing for 24 hr with 10% buffered formalin at 25°C. Following fixing, the lung tissues were dehydrated using gradient ethanol, paraffin embedded, and then sliced into 2 μm thin sections. The slices were subjected to H&E staining for 20 min at room temperature to examine the infiltration of inflammatory cells. Examination of tissue sections was performed by light microscopy for analysis of inflammation, cell infiltration, tissue degeneration, and accumulation of pus cells.

## 2.7 | Statistical analysis

The values are presented as the mean ± *SD* of three experiments performed three times. The one-way analysis of the variance followed by Fisher's least significant difference test was used for comparison between groups. $p < .05$ was considered to indicate a statistically significant difference.

# 3 | RESULTS

## 3.1 | Synthesis of compounds

The library of 15 novel ursolic acid derivatives (**7*a*-7*o***) was synthesized using four-step procedure from ursolic acid and evaluated against COPD. Oxidation of ursolic acid **1** was carried out using Jones reagent at 0°C in acetone to get the C-3 oxidized compound **4** (Scheme 1). Condensation reaction of compound **4** with hydrazine to afford compound **5** was followed by reaction with α,β-unsaturated ketones under acidic condition to obtain the library of compounds (**6*a*-6*o***). Cyclization of the compounds (**6*a*-6*o***) was achieved on exposure to palladium acetate and potassium carbonate in chlorobenzene containing molecular sieves to obtain the corresponding cyclized compounds (**7*a*-7*o***; Table 1). All the synthesized compounds were screened against PM2.5-induced COPD that led to the identification of **7a** and **7 m** as the two most active compounds.

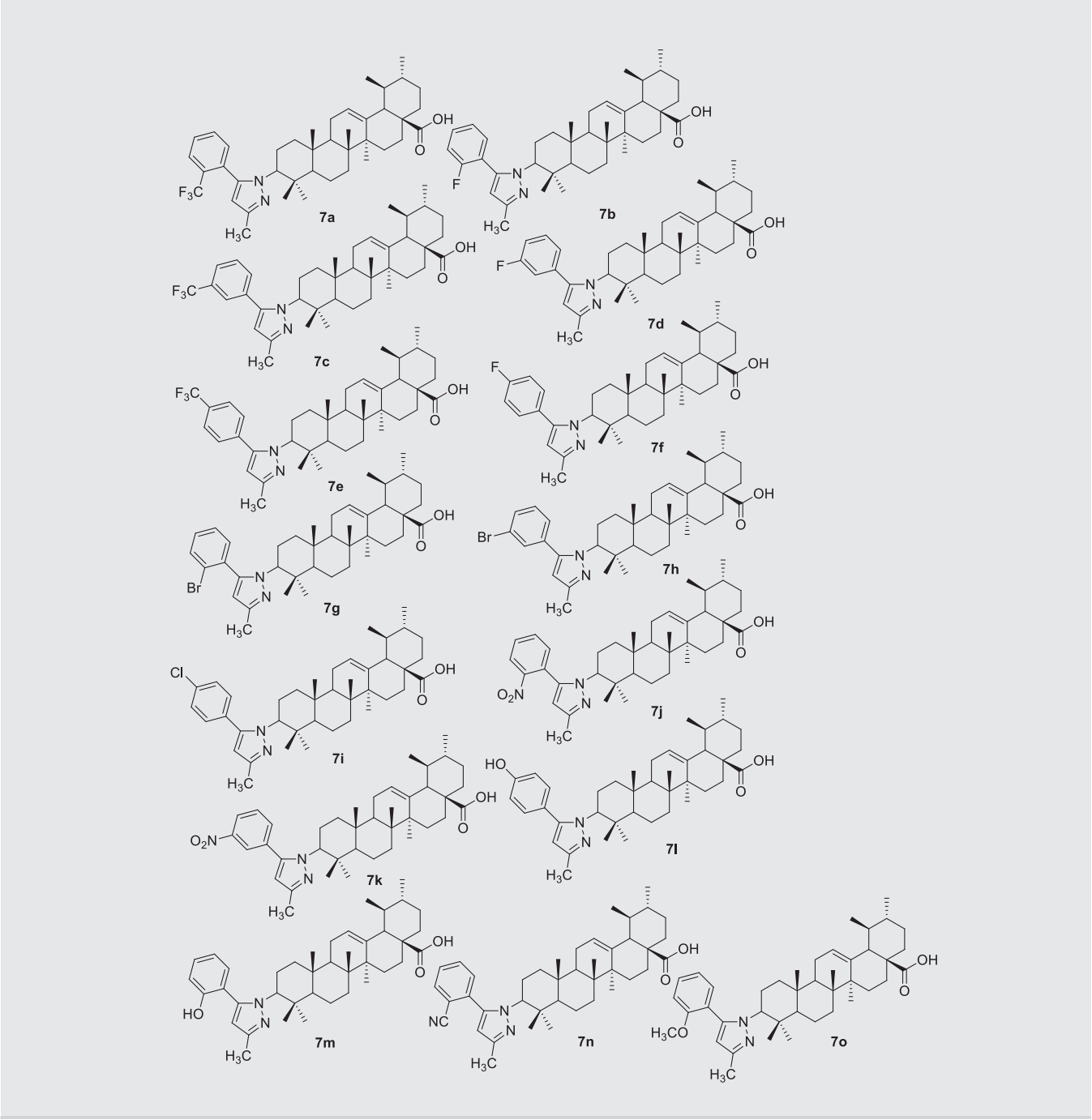
## 3.2 | Suppression of pulmonary inflammation by ursolic acid derivative (7a) in mice with PM-induced COPD

In the present study, effect of ursolic acid derivative (**7*a***) on LDH, ACP, ALP, and ALB in the BALF of mice with COPD was analyzed to determine the changes in lung biomembrane and parenchyma (Figure 2). The level of LDH, ACP, ALP, and ALB in the untreated mice was markedly higher compared to the normal group. This indicated higher pulmonary inflammation in the untreated mice than those in the normal group. In the ursolic acid derivative (**7*a***) treated mice, a significant reduction in LDH, ACP, ALP, and ALB level was observed in dose-based manner compared to the untreated group. The reduction of LDH, ACP, ALP, and ALB level was maximum in the mice treated with 100 mg/kg dose of ursolic acid derivative (**7*a***).

## 3.3 | Suppression of oxidative stress marker level by ursolic acid derivative (7a) in mice with PM-induced COPD

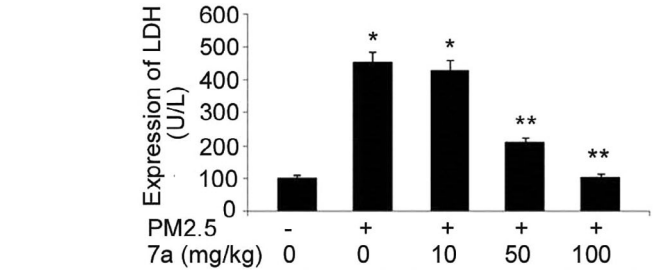
Effect of ursolic acid derivative (**7*a***) on SOD and NOS activity and level of NO and MDA in BALF of mice with COPD was analyzed using ELISA kits (Figure 3). Treatment of the mice with ursolic acid derivative (**7*a***) lead to a significant increase in the SOD activity compared to untreated group. The activity of NOS was decreased in the mice with COPD on treatment with ursolic acid derivative (**7*a***) in dose-dependent manner. Ursolic acid derivative (**7*a***) treatment of the mice with COPD also decreased the levels of NO and MDA in BALF significantly ($p < .05$) in comparison to the untreated group. Thus, ursolic acid derivative (**7*a***) suppresses PM-induced oxidative stress in the mice with COPD.

**TABLE 1** The library of ursolic acid derivatives synthesized




## 3.4 | Suppression of inflammatory cytokines by ursolic acid derivative (7a) in mice with PM-induced COPD

The present study analyzed the effect of ursolic acid derivative (***7a***) on TNF-α and IL-6 level in the BALF of mice with PM-induced COPD using ELISA kits (Figure 4). The level of TNF-α and IL-6 in the BALF of untreated mice was significantly higher in comparison to the normal group. Ursolic acid derivative (***7a***) treatment of the mice caused a marked decrease in the level of both TNF-α and IL-6 in dose-based manner. Treatment of the mice with PM-induced COPD with ursolic acid derivative (***7a***) decreased TNF-α and IL-6 level to minimum at 100 mg/kg dose.



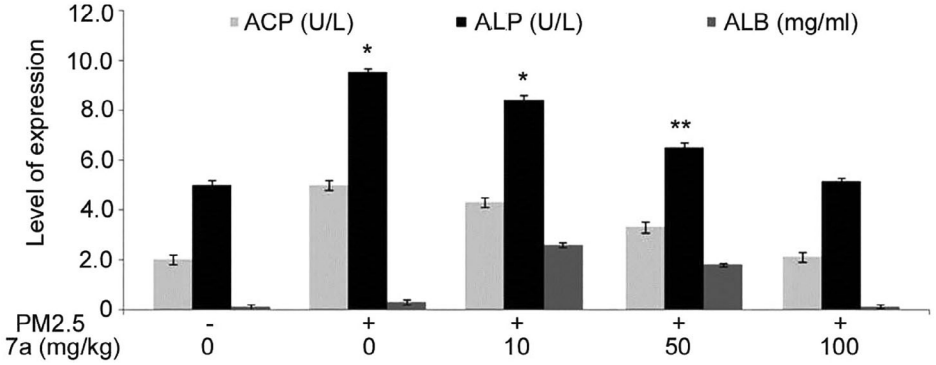




**FIGURE 2** Ursolic acid derivative (**7*a***) decreases PM-induced increase in LDH, ACP, ALP, and ALB levels in mice with COPD. In the mice BALF levels of LDH, ACP, ALP, and ALB were measured using ELISA kits. *$p < .05$ and **$p < .02$ versus the normal group

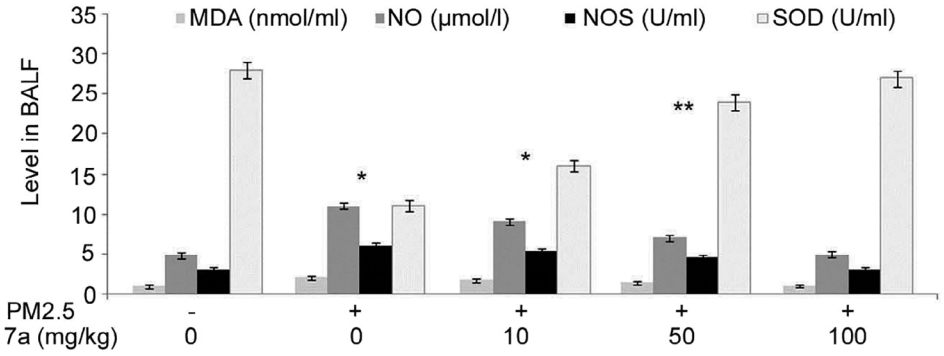
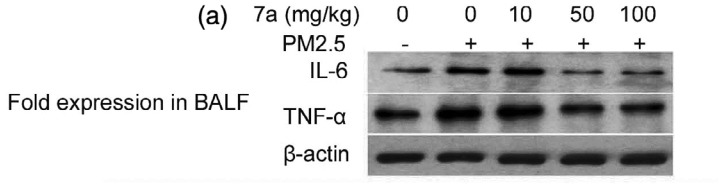



**FIGURE 3** Ursolic acid derivative (**7*a***) regulates PM-induced changes in MDA, NO, NOS, and SOD, in mice with COPD. In the mice BALF levels of MDA, NO, NOS, and SOD were measured using ELISA kits. *$p < .05$ and **$p < .05$ versus the normal group



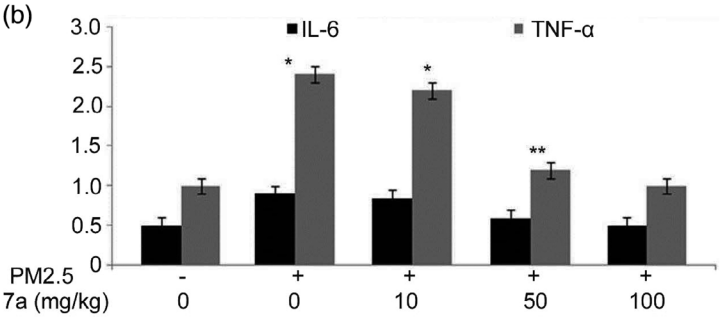




**FIGURE 4** Ursolic acid derivative (**7*a***) decreases PM-induced TNF-α and IL-6 level in mice with COPD. The mice BALF was analyzed for TNF-α and IL-6 levels using (a) western blot assay (b) ELISA kits, respectively. *$p < .05$ and **$p < .05$ versus the normal group

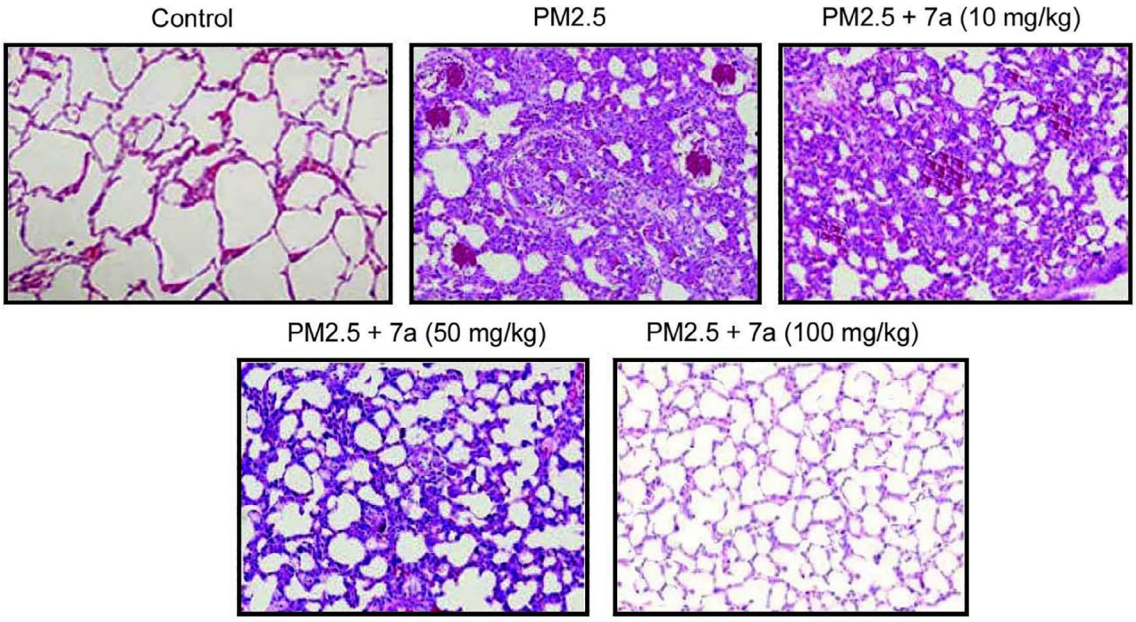



**FIGURE 5** Ursolic acid derivative (***7a***) suppresses PM-induced inflammation of pulmonary tissues in mice with COPD. Pulmonary tissue histopathological changes were examined using hematoxylin and eosin staining of tissue samples in the control, model, and treatment groups. Magnification, ×200

### 3.5 | Inhibition of pulmonary inflammation and damage by ursolic acid derivative (7a) in mice with PM-induced COPD

H&E staining revealed excessive infiltration of the inflammatory cells, accumulation of pus, and degradation of the alveolar septae in the untreated mice (Figure 5). There was no inflammatory cell infiltration and pus accumulation in the mice of normal group. Treatment of the mice with ursolic acid derivative (***7a***) markedly inhibited inflammatory cell infiltration, accumulation of pus, and pulmonary tissue degradation. The pulmonary histological features of mice treated with 100 mg/kg doses of ursolic acid derivative (***7a***) were almost similar to those in the normal control group. This data proved that ursolic acid derivative exhibits therapeutic effect on PM2.5-induced COPD through suppression of inflammatory cytokines and oxidative factors. Therefore, ursolic acid derivative has potential to be developed as the therapeutic agent for respiratory disease treatment.

## 4 | DISCUSSION

Taking into consideration, the wide range of biological activities of ursolic acid, its availability in abundance, and bioavailability in the living systems, the present study was designed to synthesize and evaluate a series of ursolic acid derivatives against the PM2.5-induced COPD in mice model in vivo.

PM present in the air is the leading cause of ROS generation and results in the thickening of bronchial alveolar wall.[33] Exposure to the PM, particularly to PM2.5 for long-term is linked with the development of respiratory diseases. It is reported that PM2.5 causes chronic inflammation in the lungs, which leads to various pulmonary diseases like COPD, pulmonary hypertension, and so forth.[34] There has been a gradual rise in the incidence rate of respiratory diseases like pneumonia, asthma, and COPD over past decade because of increase in percentage of PM2.5 in the air. The PM2.5-induced respiratory diseases are serious concern worldwide and therefore efforts are put forward to treat these diseases using TCMs.[35–37] It is reported that inflammation of lungs induced by cigarette smoke is prevented by tuberostemonine treatment via suppression of chemokine expression and inflammatory cell infiltration.[38] Resveratrol treatment of the house dust mite-induced asthma prevents inflammation of pulmonary airways.[16] The functioning of lungs is improved in the mouse model of PM2.5-induced lung injury through inhibition of inflammatory cell infiltration by GubenZhike.[39] Mechanistic studies have shown that environmental toxin inoculation leads to allergic airway inflammation and identified B cells and antigen-specific IgG1 as the potent target for treatment of pulmonary diseases.[4,40] The present study explored the effect of ursolic acid derivative (***7a***) on LDH, ACP, ALP, and ALB in the BALF of mice with COPD. Treatment of the PM-induced

COPD mice with ursolic acid derivative (***7a***) significantly reduced LDH, ACP, ALP, and ALB level in dose-based manner compared to the untreated group. Thus, ursolic acid derivative (***7a***) treatment of mice with PM-induced COPD exhibited therapeutic effect on pulmonary damage by inhibiting cell infiltration and pulmonary tissue damage.

Studies have demonstrated that exposure to PM2.5 leads to innate immune cell and epithelial cell activation resulting in release of inflammatory cytokines, proteases, and expression of antibacterial protein.[36,41,42] The xanthine oxidase reduction to uric acid and $H_2O_2$ was measured by analyzing the formation of nitroblue tetrazolium-formazan for determination of SOD activity.[23] In the current study, the level of TNF-α and IL-6 in the BALF of untreated mice was significantly higher in comparison to the normal group. It was found that ursolic acid derivative (***7a***) reduced the activity of NOS in mice with COPD. The secretion of NO and MDA in BALF of mice with COPD was significantly reduced on treatment with ursolic acid derivative (***7a***). It has been demonstrated that inhalation of excessive smoke leads to the depletion of pulmonary anti-oxidant potential in chain smokers.[27,28] Alterations in the lung histology of mice with PM-induced COPD following ursolic acid derivative (***7a***) treatment were examined using the reported methodology.[26,27] In the present study, ursolic acid derivative (***7a***) inhibited excessive infiltration of the inflammatory cells, accumulation of pus, and degradation of the alveolar septae in mice with PM-induced COPD.

## 5 | CONCLUSION

In summary, ursolic acid derivative has potential to inhibit the PM2.5-induced pulmonary damage through suppression of inflammatory cytokines and anti-oxidant molecule level. Thus, ursolic acid derivative may be developed as an effective therapeutic agent for COPD treatment.

## ACKNOWLEDGMENT

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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