Molecular and Cellular Biomedical Sciences, Vol.10 No.3, November 2026, p. 131-91
Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v10i3.811

RESEARCH ARTICLE

MCBS
Mol Cell Biomed Sci. 2026; 10(3): 175-83
DOI: 10.21705/mcbs.v10i3.811

Inhalable Nanoemulgel Combining Extracts of *Artocarpus heterophyllus* Peel Waste and *Sonchus arvensis* L. Leaves Reduces Interleukin-6, Alveolar Septal Thickening, and Hemorrhage in a Bleomycin-Induced Rat Model of Acute Lung Injury

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Background: Anti-inflammatory therapies for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) remain limited. Natural products are promising sources of bioactive compounds; *Artocarpus heterophyllus* (AH; jackfruit) peel waste and *Sonchus arvensis* L. (SA; tempuyung) leaves contain phytochemicals with anti-inflammatory potential. This study evaluated an inhalable nanoemulgel containing both extracts in bleomycin- induced ALI rats.

Materials and methods: AH peel and SA leaves were separately macerated in 70% ethanol for 24 h and 96% ethanol for 72 h, respectively. The extracts were combined (25% each) in a sodium alginate nanoemulgel prepared using aqueous alginate and PEG 7-virgin coconut oil phases, $CaCl_2$-mediated gelation, and centrifugation. Male Wistar rats (n = 24) were randomized to healthy controls or bleomycin-induced groups receiving no extract or nebulized nanoemulgel (400 or 800 mg/kg; n = 6/group). ALI was induced by intratracheal bleomycin (0.75 U/kg). Lung IL-6, alveolar septal thickening, and pulmonary hemorrhage were assessed by ELISA and hematoxylin-eosin staining.

Results: Bleomycin increased lung IL-6, alveolar septal thickening, and pulmonary hemorrhage compared with healthy controls (all $p<0.0001$). Compared with untreated bleomycin-induced rats, 400 mg/kg nanoemulgel reduced IL-6 ($p<0.001$) and hemorrhage ($p<0.0001$), but not septal thickening. The 800 mg/kg dose reduced IL-6 and hemorrhage (both $p<0.0001$) and septal thickening ($p<0.001$).

Conclusion: Nebulized AH-SA nanoemulgel reduced lung IL-6 and pulmonary hemorrhage at both doses, whereas alveolar septal thickening was reduced only at 800 mg/kg. These findings warrant further evaluation of this inhalable formulation for ALI.

Keywords: *: jackfruit skin, tempuyung leaves, acute lung injury, bleomycin*

Submission: May 08, 2026
Last Revision: July 19, 2026
Accepted for Publication: July 27, 2026

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Introduction

Acute respiratory distress syndrome (ARDS) is a noncardiogenic pulmonary edema with rapid progression from initial manifestations of dyspnea, tachypnea, and hypoxemia.[1] The etiology of ARDS is very diverse, including aspiration, inhalation injury, contusion, pneumonia, sepsis, non-cardiogenic shock, transfusion, and trauma.[2] Recent studies have revealed that the most common causes of ARDS are sepsis, pneumonia, and aspiration of gastric contents, with a percentage of >85%.[3] In Indonesia, ARDS has a mortality rate of approximately 40% in patients treated in hospital intensive care unit (ICU).[4] A milder form of ARDS is acute lung injury (ALI), and the use of the term ALI only describes this disease in experimental animals and generally according to the 2012 Berlin criteria.[5]

A literature review further explains that sepsis influences the incidence of death in ARDS patients.[6] The incidence of sepsis itself reaches 437 cases per 100,000 patients globally, while the risk of death in sepsis patients with ARDS is 20-50%.[7,8] Essentially, the severe inflammatory response caused by sepsis can affect vascular permeability (the exudative phase of ARDS), resulting in acute pulmonary edema.[9] Increased membrane permeability is associated with the release of the acute inflammatory mediator Interleukin (IL)-6, which triggers exudate in the alveoli.[10,11] One concept that can be utilized to observe ARDS is the bleomycin-induced (BLM) animal model due to the similarity of the processes involved in the development of this disease.[12] The bleomycin-induced ALI model were extensively utilized to investigate sepsis-associated lung injury, as bleomycin provokes a pronounced inflammatory response characterized by inflammatory cell recruitment and increased pro-inflammatory cytokine expression.[13] Currently, there is no pharmacological therapy available for patients with ARDS. Existing treatments are intended solely for the prevention of primary lung disease.[6] An unfavorable situation also occurs in ARDS patients who appear very thin with an average weight loss of 18% upon discharge from the hospital after treatment.[14]

Plant-derived extracts are increasingly investigated as chemically diverse sources of anti-inflammatory agents for ALI.[15] In this context, the valorization of agro-industrial by-products and medicinal plants may provide bioactive-rich materials for pulmonary therapeutic development. Jackfruit peel (*Artocarpus heterophyllus*), an underutilized fruit-processing waste, contains phenolic and flavonoid constituents, whereas tempuyung leaves (*Sonchus arvensis* L.), an Indonesian medicinal plant, contain several flavonoid derivatives. Resveratrol and quercetin have been reported as representative constituents of jackfruit peel and tempuyung leaves, respectively.[16–18] Previous evidence that an inhalable quercetin-alginate nanogel attenuated experimental ALI further supports the pulmonary delivery of plant-derived anti-inflammatory agents.[15]

However, the therapeutic effects of combined *A. heterophyllus* peel and *S. arvensis* L. leaf extracts delivered as an inhalable nanoemulgel have not been investigated in ALI. Therefore, this study evaluated whether the combined extract-loaded nanoemulgel could reduce pulmonary IL-6 concentrations, alveolar septal thickening, and hemorrhage in bleomycin-induced Wistar rats.

Materials and methods

Plant Authentication and Extract Preparation

A. heterophyllus peel and *S. arvensis* L. leaves were authenticated by the Herbal Laboratory of Materia Medica, East Java Provincial Health Office, Indonesia (No. 000.9.3/1366/102.20/2025 and 000.9.3/1367/102.20/2025, respectively). The plant materials were cleaned, oven-dried to a moisture content below 10%, and milled into powder. Each powdered material was macerated at a plant-to-solvent ratio of 1:10 (w/v). *A. heterophyllus* peel was extracted with 70% ethanol for 24 h, whereas *S. arvensis* L. leaves were extracted with 96% ethanol for three consecutive 24-h cycles.[19,20] The filtrates were concentrated under reduced pressure using a rotary evaporator to obtain the crude extracts.

Preparation of A. heterophyllus and S. arvensis Extract-Loaded Nanoemulgel

The nanoemulgel was prepared at the Faculty of Pharmacy, Universitas Hang Tuah, Surabaya, Indonesia, using a modified previously reported method.[15] Sodium alginate (Cat. No. A2033; Sigma-Aldrich, St. Louis, USA) was dissolved in demineralized water at 45 °C under magnetic stirring for 6 h to prepare the aqueous phase. The oil phase, consisting of liquid paraffin (Cat. No. 18512; Sigma-Aldrich, St. Louis, USA), PEG-7 glyceryl cocoate (Cetiol® HE, Product No. 30528395; BASF SE, Ludwigshafen, Germany), and virgin coconut oil (VCO; Cat. No. W530155; Sigma-Aldrich, St. Louis, USA), was stirred at 500 rpm

Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v10i3.811

for 30 min. The aqueous phase was then added dropwise to the oil phase at 0.75 mL/min and stirred for 60 min. *A. heterophyllus* peel and *S. arvensis* L. leaf extracts were incorporated at equal concentrations (25% each), followed by the addition of an ethanolic $CaCl_2$ solution. The mixture was centrifuged to separate the gel-rich fraction from the liquid phase (Table 1).

Study Design, Animals, and Group Allocation

This post-tes-only randomized controlled animal study was conducted at the Experimental Animal Laboratory, Faculty of Medicine, Universitas Wijaya Kusuma Surabaya, Surabaya, Indonesia. Twenty-four healthy male Wistar rats (*Rattus norvegicus*), approximately 10 weeks old and weighing 120-175 g, were randomly allocated to four groups (n = 6/group; Figure 1).

Bleomycin-Induced Acute Lung Injury and Nanoemulgel Treatment

Rats were housed three per cage (33×27.5×13 cm) under controlled conditions: a 12-h light/dark cycle, temperature of 21±5 °C, and relative humidity of 50 ± 5%, with standard chow and water provided ad libitum.[21] ALI was induced using a previously described bleomycin protocol. Rats were anesthetized with ketamine-xylazine administered intramuscularly and received a single intratracheal instillation of bleomycin (0.75 U/kg; PT Kalbe Farma, Jakarta, Indonesia). After recovery from anesthesia, the animals were returned to their cages.[22]

Table 1. Composition of the *A. heterophyllus-S. arvensis* extract-loaded nanoemulgel formulation.

Composition	Formulation Concentration
A. heterophyllus extract	25%
S. arvensis L. extract	25%
Sodium Alginate	1%
PEG-7	35%
VCO	5%
Aquadest	*q.s*
Alcohol	*q.s*

The healthy control group received no bleomycin or nanoemulgel, whereas the untreated BLM-induced group received bleomycin without nanoemulgel treatment. The INEG4 and INEG8 groups received bleomycin followed by nebulized nanoemulgel at 400 and 800 mg/kg body weight, respectively. Treatment commenced 120 min after bleomycin instillation on the first intervention day and continued over the 7-day intervention period. The INEG4 and INEG8 groups were exposed to nebulized nanoemulgel for 30 and 60 min per treatment session, respectively. Nebulization was conducted in an adapted exposure chamber (38×24×22 cm) designed to maintain airflow and permit simultaneous group exposure, based on a previously reported model (Figure S1).[23] Body weight was recorded daily.

Lung Tissue Collection for Histopathological and IL-6 Analyses

On day 14, rats were deeply anesthetized with intramuscular ketamine-xylazine, and the lungs were collected by thoracotomy at the Central Laboratory of Animal Research and Diagnostics, Satwa Sehat Malang Animal Clinic, Malang, Indonesia. The left lung was rinsed with 0.9% NaCl and fixed in 10% neutral-buffered formalin for 24 h before hematoxylin-eosin staining. The right lung was perfused with phosphate-buffered saline (PBS) and stored at −40 °C until IL-6 analysis.[21]

Lung Tissue Histopathology by Hematoxylin–Eosin Staining

The left lung was dehydrated through graded ethanol, cleared in xylene, and embedded in paraffin. Transverse sections (5 µm) were stained with hematoxylin and eosin and examined using a Nikon Eclipse Ei light microscope (Nikon Corporation, Tokyo, Japan) equipped with an Optilab SIGMA MTN020 imaging system (PT Miconos, Yogyakarta, Indonesia). Histological images were analyzed using ImageJ software (National Institutes of Health, Bethesda, USA) for quantitative assessment of tissue alterations. Alveolar septal thickening and pulmonary hemorrhage were graded using a previously described semiquantitative scale: 0, absent; 1, involving < one-third of the field; 2, involving one-third to two-thirds of the field; and 3, involving>two-thirds of the field.[24] Histopathological scores were analyzed using the Kruskal-Wallis test followed by Dunn's multiple-comparison test and are reported as median with interquartile range.

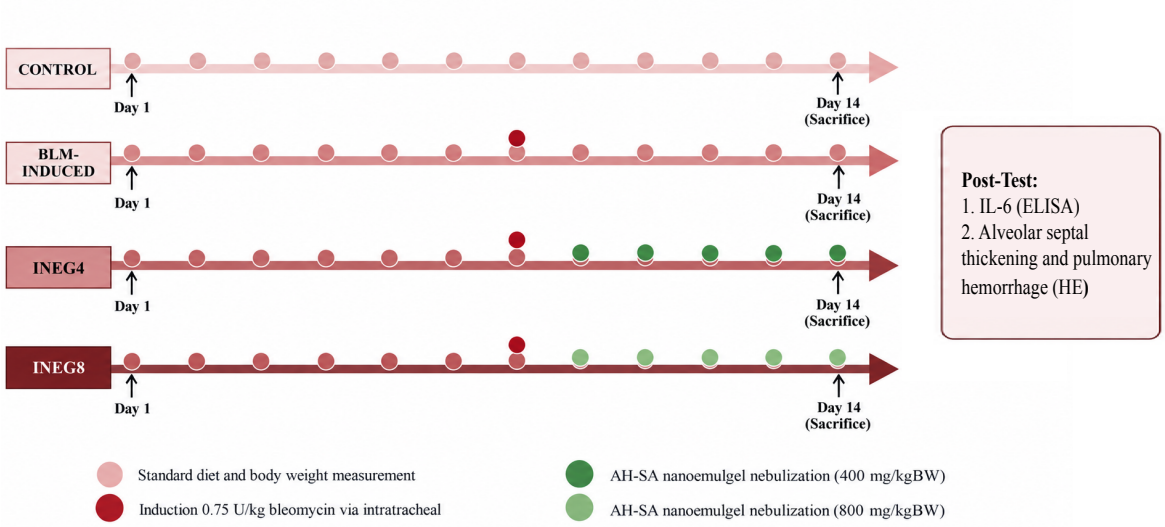


Figure 1. Experimental design and treatment schedule. Rats were assigned to control, BLM-induced, INEG4, or INEG8 groups (n = 6/group). The BLM-induced, INEG4, and INEG8 groups received intratracheal bleomycin (0.75 U/kg); INEG4 and INEG8 additionally received nebulized AH-SA nanoemulgel at 400 or 800 mg/kg, respectively, for 7 days. Body weight was recorded daily, and lungs were collected for IL-6 quantification and histopathological assessment. BLM: bleomycin; AH-SA: *A. heterophyllus-S. arvensis* L.; INEG4: BLM-induced rats treated with 400 mg/kg nanoemulgel; INEG8: BLM-induced rats treated with 800 mg/kg nanoemulgel.

IL-6 Quantification by ELISA

The PBS-perfused right lung was homogenized in ice-cold PBS containing protease inhibitors and centrifuged at 10,000 rpm for 15 min at 4°C. IL-6 concentrations in the supernatant were quantified using a rat IL-6 sandwich ELISA kit (Cat. No. E0135Ra; Bioassay Technology Laboratory, Shanghai, China) according to the manufacturer's instructions. Absorbance was measured at 450 nm using a DR-200Bc microplate reader (Wuxi Huawei Diatek Instrument Co., Ltd., Jiangsu, China), and IL-6 concentrations were expressed as ρg/mL.[15,21,22] IL-6 data were assessed for normality using the Shapiro-Wilk test and analyzed using one-way ANOVA followed by Tukey's multiple-comparison test. Data are presented as mean ± standard deviation (SD). All analyses were performed using GraphPad Prism version 10.4.1 for Windows, with two-sided $p<0.05$ considered statistically significant.

Results

Extract Yield of A. heterophyllus and *S. arvensis*

The extraction yields differed markedly between the two plant materials, with *A. heterophyllus* peel showing an approximately two-fold higher yield than *S. arvensis* L. leaves. This difference indicates a substantially greater recovery of crude extract from *A. heterophyllus* under the applied extraction conditions (Table 2).

Nanoemulgel Droplet Size and Polydispersity

The droplet size and polydispersity index (PDI) of the nanoemulgel were determined by dynamic light scattering using a BIOBASE BK-802N particle size analyzer. The formulation exhibited a mean droplet size of 118.17 nm and a PDI of 0.4911. The observed droplet size was within the nanoscale range reported for nanoemulsion-based formulations, whereas the PDI indicated a moderately broad droplet-size distribution.[25,26]

Table 2. Extraction yields of *A. heterophyllus* peel and *S. arvensis* L. leaf extracts.

Plant	Weight of Powdered Simplex (g)	Extract Weight (g)	Yield Value (%)
A. heterophyllus	510	163.10	32
S. arvensis L.	1000	161.40	16.14

Print ISSN: 2527-4384, Online ISSN: 2527-3442
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Effects of A. heterophyllus-S. arvensis Nanoemulgel on Body Weight in Bleomycin-Induced Rats

Changes in body weight were monitored from the final day of acclimatization through the intervention period to evaluate the effects of intratracheal bleomycin (0.75 U/kg) and the *A. heterophyllus-S. arvensis* L. nanoemulgel. Body weight increased progressively in the Control group but declined in the BLM-induced group. The INEG4 and INEG8 groups showed an initial reduction in body weight after bleomycin instillation, followed by gradual recovery during nanoemulgel treatment. Body-weight recovery was most evident in the INEG4 group relative to the BLM-induced group (Figure 2).

Inhalable A. heterophyllus-S.varvensis Nanoemulgel Attenuates BLM-Induced Pulmonary Inflammation and Histopathological Changes

Bleomycin induction significantly increased lung IL-6 concentrations (p<0.0001 vs control; Figure 3A), alveolar septal thickening (p<0.001 vs control; Figure 3B), and pulmonary hemorrhage (p< 0.0001 vs control; Figure 3C) in the BLM-induced group compared with the Control group. Relative to the BLM-induced group, INEG4 significantly reduced IL-6 (p<0.001 vs BLM-induced) and hemorrhage (p<0.0001 vs BLM-induced), but did not significantly reduce septal thickening (p = 0.1476). INEG8 significantly reduced IL-6 and hemorrhage (both p<0.0001 vs BLM-induced) and alveolar septal thickening (p<0.001 vs BLM-induced). Representative hematoxylin-eosin-stained lung sections showed marked septal thickening and hemorrhage in the BLM-induced group, with attenuation of these lesions after nanoemulgel treatment, particularly in INEG8 (Figure 3D-G).

Discussion

The principal finding of this study was that nebulized nanoemulgel containing combined *A. heterophyllus* peel and *S. arvensis* L. leaf extracts attenuated inflammatory and histopathological changes in bleomycin-induced lung injury. Both 400 and 800 mg/kg reduced pulmonary IL-6 concentrations and hemorrhage scores compared with untreated bleomycin-exposed rats. However, a significant reduction in alveolar septal thickening was observed only at 800 mg/kg. These findings suggest that suppression of inflammatory signaling and pulmonary microvascular injury may occur at both treatment levels, whereas measurable preservation of alveolar architecture may require greater exposure to the formulation.

The increases in pulmonary IL-6, alveolar septal thickening, and hemorrhage after bleomycin administration confirm successful induction of ALI. These findings are consistent with the inflammatory phase of the bleomycin model, during which epithelial and endothelial injury promotes cytokine release, inflammatory-cell recruitment, disruption of the alveolar-capillary barrier, and tissue edema or hemorrhage. Previous studies using bleomycin-induced lung injury have similarly reported increased inflammatory mediators and marked histopathological abnormalities, including alveolar septal thickening and hemorrhage.[22,27–29] The present study extends these observations by showing that inhaled delivery of the combined plant-extract formulation partially attenuated these responses.

In our study, administration of nebulized nanoemulgel containing combined *A. heterophyllus* peel and *S. arvensis* L. leaf extracts at both 400 (INEG4) and 800 (INEG8) mg/kg resulted in a marked decrease in IL-6. The reduction

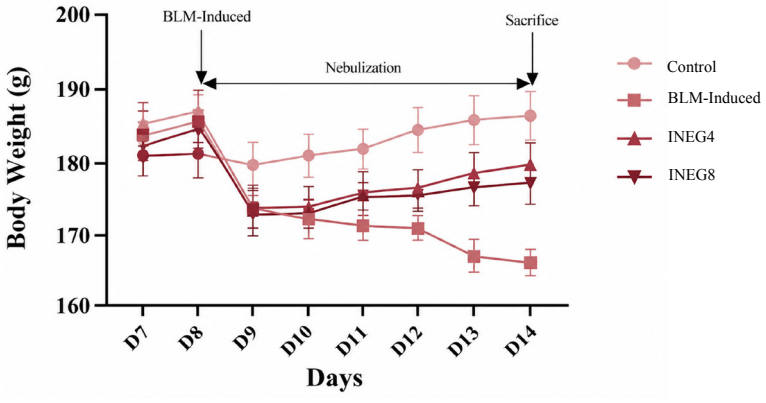


Figure 2. Body-weight changes during bleomycin-induced acute lung injury and nanoemulgel treatment. On day 8, the BLM-induced, INEG4, and INEG8 groups received intratracheal bleomycin (0.75 U/kg). INEG4 and INEG8 subsequently received nebulized *A. heterophyllus-S. arvensis* L. nanoemulgel at 400 and 800 mg/kg, respectively. Data are presented as mean ± SD (n = 6/group).

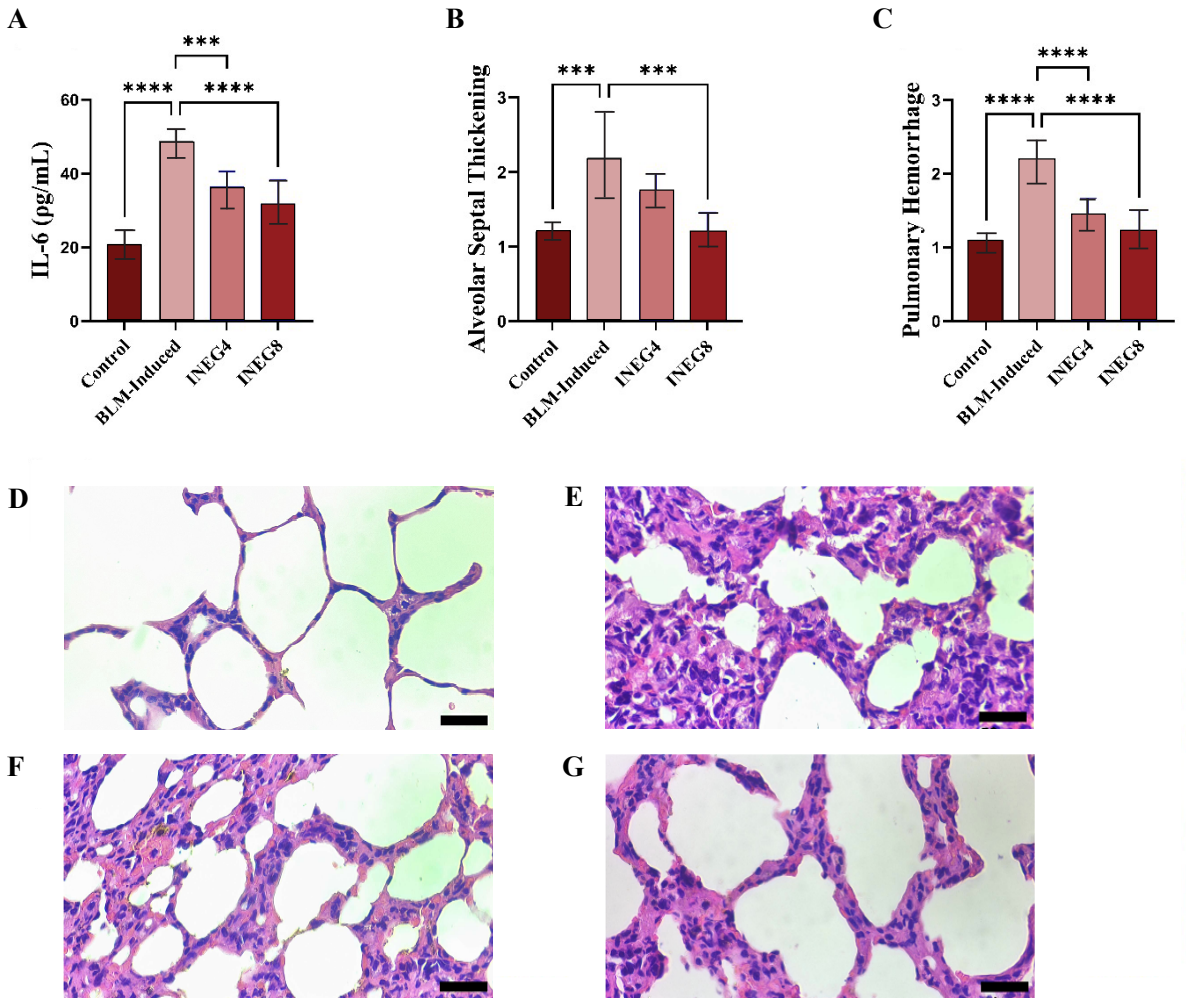


Figure 3. Effects of *A. heterophyllus*-*S. arvensis* nanoemulgel on lung IL-6 and histopathology in bleomycin-induced rats. Lung IL-6 concentration (A), alveolar septal-thickening score (B), pulmonary-hemorrhage score (C), and representative H&E-stained sections from the Control (D), BLM-induced (E), INEG4 (F), and INEG8 (G) groups. INEG4 and INEG8 received nebulized nanoemulgel at 400 and 800 mg/kg, respectively, after intratracheal bleomycin (0.75 U/kg). Histopathological lesions were scored from 0 to 3. Data are mean±SD for IL-6 and median with interquartil range for histopathological lesions (alveolar septal thickening and pulmonary hemorrhage). n = 6/group. ***p<0.001; ****p<0.0001. BLM, bleomycin; H&E, hematoxylin and eosin; IL-6, interleukin-6; INEG4, BLM-induced rats treated with 400 mg/kg nanoemulgel; INEG8, BLM-induced rats treated with 800 mg/kg nanoemulgel. Black bar = 50 µm.

in lung IL-6 provides evidence of an anti-inflammatory effect of the combined formulation. *A. heterophyllus* peel and *S. arvensis* L. leaves contain chemically diverse phenolic and flavonoid constituents that may act through complementary inflammatory pathways.[30,31] Resveratrol and quercetin have been reported as representative constituents of *A. heterophyllus* peel and *S. arvensis* L., respectively, and previous experimental studies have shown that these compounds can suppress inflammatory signaling associated with NF-κB activation, NLRP3 inflammasome activity, and pro-inflammatory cytokine production.[18,32–35] These observations provide possible mechanism for the reduction in IL-6 observed in this study. Nevertheless, resveratrol, quercetin, and related constituents were not quantified in the

Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v10i3.811

extracts, and NF-κB or NLRP3 signaling was not directly examined.

The histopathological findings were broadly consistent with the IL-6 results. Both doses reduced pulmonary hemorrhage, whereas only the 800 mg/kg treatment significantly reduced septal thickening. Hemorrhage may respond relatively rapidly to attenuation of inflammation and alveolar-capillary barrier injury, whereas septal thickening reflects a broader combination of edema, cellular infiltration, and early tissue remodeling.[13,22] The different responses of these outcomes may therefore indicate that structural recovery requires a stronger or more sustained treatment effect.

Pulmonary or inhalation delivery may have contributed to the observed effects by placing the formulation in direct contact with the respiratory tract.[36,37] Previous work demonstrated that an inhalable quercetin-alginate nanogel attenuated experimental ALI, supporting the feasibility of alginate-based pulmonary delivery of plant-derived anti-inflammatory compounds.[15] In the present study, the formulation had a mean droplet size of 118.17 nm, confirming nanoscale dispersion, although the PDI of 0.4911 indicates a relatively broad size distribution. Importantly, droplet size measured by dynamic light scattering does not establish aerosol performance or pulmonary deposition. Measurements such as emitted dose, aerodynamic diameter, fine-particle fraction, nebulization stability, and regional lung deposition are required before the formulation can be considered optimized for inhalation.

Several limitations should be acknowledged. First, the study did not include bleomycin-induced groups treated with each extract separately. The individual contribution of each extract and whether their combination produced additive or synergistic effects therefore remain unknown. Healthy animals receiving the individual extracts or the extract-loaded nanoemulgel were also not included, preventing assessment of baseline pulmonary tolerability. Second, a vehicle nanoemulgel control and a pharmacological positive-control group were absent, limiting attribution of the effects specifically to the plant extracts and comparison with established anti-inflammatory interventions. Third, the extracts were not comprehensively characterized or standardized according to their principal bioactive constituents. Fourth, the evaluation was restricted to IL-6 and two semiquantitative histopathological outcomes at a single time point in male rats. Additional studies should assess pulmonary function, bronchoalveolar lavage fluid, inflammatory-cell profiles, alveolar permeability, oxidative stress, multiple cytokine pathways, and systemic or pulmonary toxicity in both sexes. Finally, larger studies with standardized delivered doses and equivalent nebulization durations are needed to establish a reliable dose–response relationship.

Conclusion

Nebulized nanoemulgel containing *A. heterophyllus* peel and *S. arvensis* leaf L. extracts attenuated bleomycin-induced acute lung injury in rats, as evidenced by reduced pulmonary IL-6 and hemorrhage, with improvement in alveolar septal thickening also observed. These findings support the potential of this formulation as an inhalable plant-based anti-inflammatory agent. Further studies are warranted to identify its active constituents, characterize its inhalation performance, evaluate its safety, and establish its translational relevance.

Acknowledgment

The authors thank the Lembaga Penelitian dan Pengabdian kepada Masyarakat (LPPM), Universitas Wijaya Kusuma Surabaya, Surabaya, Indonesia, for institutional and financial support through the 2025 Research Grant Program. The authors also thank Johanes Aprilius Falerio Kristijanto for technical assistance, language editing, and constructive feedback on the manuscript.

Authors' Contributions

AT conducted the preparation of the research methodology design, comprehensive animal experiments, sample collection, ELISA parameter examination, statistical analysis, data visualization, and prepared the draft manuscript; MWS and HA conducted the histopathological parameter examination, directed the experiment, and revised the draft manuscript comprehensively; RDT conducted the animal experiments, *A. heterophyllus* and *S. arvensis* L. extraction experiments, nanoemulgel formulation, and and prepared the draft manuscript; NK and MRA formulated the research objectives, directed the experiment comprehensively, and revised the draft manuscript.

Ethical Statement

All animal procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Research Ethics Committee, Faculty of Medicine, Universitas Wijaya Kusuma Surabaya, Surabaya, Indonesia (approval no. 7/SLE/FK/UWKS/2025).

Conflict of Interest

The authors declare no conflict of interest.

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