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Breviscapine attenuates pulmonary vascular dysfunction and inflammatory injury in a rat model of acute pulmonary embolism

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Abstract: Acute pulmonary embolism (APE) is a fatal disease characterized by pulmonary artery obstruction, leading to endothelial dysfunction, elevated pulmonary arterial pressure, right ventricular overload, and systemic inflammation. Whether breviscapine, a flavonoid glycoside with vasoprotective, anti-inflammatory, and antioxidant activities, whether protects pulmonary vascular function in APE was investigated. Male Sprague-Dawley rats were allocated at random into sham, APE, APE + low-dose breviscapine (0.2 mg/kg/day), or APE + high-dose breviscapine (1 mg/kg/day) groups. APE was induced by intravenous infusion of polystyrene microspheres, and breviscapine was administered intraperitoneally for 48 hours. Hemodynamic parameters, including mean pulmonary arterial pressure and right ventricular hypertrophy, were assessed. Lung tissues were examined histologically and immunohistochemically for endothelial markers (CD31, ICAM-1, VCAM-1) and inflammatory cytokines (IL-6, TNF-α, IL-10, MCP-1). APE caused marked pulmonary hypertension, right ventricular hypertrophy, endothelial injury, increased pro-inflammatory cytokines, and oxidative stress ($p < 0.05$ for all comparisons). Treatment with breviscapine, particularly with high dose, preserved endothelial structure, reduced pro-inflammatory cytokines, increased IL-10, restored endothelial markers, and corrected pulmonary hemodynamics. These results show that breviscapine maintains pulmonary vascular function and reduces inflammatory damage in APE and thus is a potential therapeutic drug.

Keywords: Breviscapine, acute pulmonary embolism, pulmonary endothelium, inflammation, oxidative stress, rat model

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INTRODUCTION

Acute pulmonary embolism (APE) is an acute cardiovascular disease characterized by the blockage of the pulmonary arteries by thromboembolic material that results in compromised pulmonary circulation, elevated pulmonary artery pressure, right ventricular overload, and systemic hypoxemia (Imiela *et al.,* 2025; Joffre and Hellman, 2021). APE is a highly morbid and mortal disease worldwide, and its pathophysiology involves not only mechanical vascular occlusion but also endothelial dysfunction, inflammation activation, oxidative stress, and vascular homeostasis disturbance (Yang *et al.,* 2024). Endothelial injury is a central event in APE because it disrupts the vascular barrier, activates coagulant and inflammatory pathways, and amplifies thrombotic responses, thereby perpetuating pulmonary and systemic disease (Liu *et al.,* 2022a; Imiela *et al.,* 2024a; Liu *et al.,* 2022b). Despite advances in anticoagulation and thrombolysis, current therapies mainly target vascular occlusion, with few addressing endothelial protection or inflammation, key factors in patient outcomes. (Sagcan *et al.,* 2022; Yang *et al.,* 2024b).

Breviscapine, a flavonoid glycoside extracted from *Erigeron breviscapus*, has demonstrated extensive cardiovascular protective effects, including antioxidative, anti-inflammatory, anti-apoptotic, and microcirculatory regulating effects (Li *et al.,* 2020; Li *et al.,* 2025). In animal models of myocardial ischemia, hypertension, and endothelial injury, breviscapine was shown to improve endothelial function, reduce oxidative stress, inhibit pro-inflammatory cytokine expression, and maintain vascular integrity (Kartal *et al.,* 2020; Zhao *et al.,* 2021; Li *et al.,* 2023). However, its therapeutic effects on pulmonary vascular endothelium and inflammatory pathways in the context of APE are unclear, despite the potential for adjunctive therapy alongside conventional anticoagulation (Chen *et al.,* 2023; Chen *et al.,* 2020; Lyu *et al.,* 2020).

Mechanistically, APE leads to activation of a range of pro-inflammatory mediators, including interleukins (IL-6, IL-1β), tumor necrosis factor-alpha (TNF-α), and chemokines, that exacerbate endothelial injury and vascular function (Yang *et al.,* 2024a). Oxidative stress also fosters vascular dysfunction by generating reactive oxygen species (ROS), reducing nitric oxide bioavailability, and disrupting vascular homeostasis. Breviscapine's reported ROS inhibition and inflammatory signaling inhibition may portend its ability to antagonize these pathologic processes, preserve endothelial integrity, and improve pulmonary hemodynamics. Nevertheless, no systematic study has thus far assessed the acute effects of breviscapine on endothelial function, inflammation markers, and hemodynamic outcomes in APE (Kim *et al.,* 2021; Nukala *et al.,* 2021;

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Peng *et al.,* 2023; Peracaula *et al.,* 2024; Chen *et al.,* 2024a).

According to the clinical importance of endothelial dysfunction and inflammation in APE, the aim of this research is to investigate whether breviscapine protects pulmonary vascular endothelium and modulates inflammatory mechanisms in a rat model of acute pulmonary embolism (Imiela *et al.,* 2024b). We predict that breviscapine will preserve endothelial function, suppress pro-inflammatory cytokine expression, and improve pulmonary hemodynamics (Zeng *et al.,* 2023; Liu *et al.,* 2022a; Kuai *et al.,* 2022; Chen *et al.,* 2024b). By elucidating the mechanistic pathways underlying the vascular protective effects of breviscapine, this research can provide a foundation for its eventual clinical application in preventing pulmonary vascular damage and reducing systemic complications in APE. Furthermore, these findings could inform future studies on dose optimization, timing of administration, and translation to human therapeutic strategies.

MATERIALS AND METHODS

Experimental animals

Male Sprague-Dawley rats weighing 200–250 g and 8–10 weeks of age were bought from the Animal Center of Zhejiang Chinese Medical University. Rats were maintained under normal laboratory conditions (22 ± 2°C, 55 ± 5% humidity, 12-hour light/dark cycle) with chow and water available ad libitum. Animals were acclimatized for 7 days to stabilize baseline physiological parameters and reduce stress-related variability. All the experiments were sanctioned by the Institutional Animal Care and Use Committee and complied with NIH Guidelines to prevent pain, distress, and promote humane use.

Reagents and chemicals

Breviscapine (>98% purity) was obtained from Hangzhou Epsole Technologies Co., Ltd., China. 25-μm polystyrene microspheres were selected based on prior reports to reproducibly induce APE ([reference]). ELISA kits for IL-6, TNF-α, IL-10, and MCP-1, and for CD31, ICAM-1, and VCAM-1 antibodies were purchased from Sino Biological, Inc., China. Standard laboratory reagents (10% formalin, paraffin, PBS, buffers) were provided by Hangzhou Epsole Technologies Co., Ltd., and prepared according to manufacturers' instructions.

Experimental design and grouping

Forty rats were randomly assigned (computer-generated randomization, block size = 4) to four groups (n = 10/group):

- Sham: saline injection only
- APE: microsphere-induced embolism, no treatment
- APE + Low-dose breviscapine: 0.2 mg/kg/day, intraperitoneally
- APE + High-dose breviscapine: 1 mg/kg/day, intraperitoneally.

Blinding

Researchers conducting hemodynamic measurements, ELISA assays, histopathology scoring, and data analysis were blinded to group allocation. Breviscapine administration was coded by a different researcher to prevent treatment blinding.

Dose and time selection

Dose levels were based on earlier cardiovascular studies in rats showing efficacy and safety (Li *et al.,* 2020; Li *et al.,* 2025). The duration of 48 hours was picked to define early protective effects on endothelial injury and inflammation, consistent with acute-phase APE onset.

Power calculation

With initial data, n=10 per group has >80% power to detect a 20% difference in mPAP and RV/LV+S ratio ($\alpha = 0.05$, two-sided).

Induction of acute pulmonary embolism

Rats were anesthetized with pentobarbital sodium (50 mg/kg, IP). APE was induced by intravenous injection of 1 × 10^6 polystyrene microspheres in 0.5 mL saline via the tail vein, as described in published models (Xu *et al.,* 2024). Sham rats received 0.5 mL saline. Rats were closely monitored for 2 hours after injection for hemodynamic instability, cyanosis, respiratory distress, or hypoxia. Unscheduled death or unsuccessful catheterizations were recorded (n excluded in Table S1).

Hemodynamic measurements

Rats were anesthetized 48 hours post-embolization, and a PE-50 polyethylene catheter was implanted via the right jugular vein into the pulmonary artery. The transducer and catheter were calibrated before each experiment using a standard mercury manometer. mPAP was recorded at 1 kHz sampling rate for 5 minutes, and values were averaged to reduce noise. Animals where catheterization failed were excluded from analysis, and unadjusted mPAP values ± SD were recorded. Right ventricular hypertrophy (RV/LV+S) was calculated by weighing the right ventricle and left ventricle + septum post-mortem.

Histopathological analysis

Lungs were fixed in 10% formalin for 24 h, paraffin-embedded, and sectioned at 5 μm. H&E staining assessed endothelial integrity, alveolar architecture, and inflammatory cell infiltration. Immunohistochemistry with CD31, ICAM-1, and VCAM-1 antibodies quantified endothelial activation and density. Semi-quantitative scoring (0-3 scale) by two blinded independent pathologists was performed, with inter-observer reliability established (Cohen's kappa >0.85). CD31-positive area (%) and ICAM-1/VCAM-1 optical density (OD) were

quantified using Image J, with scale bars and magnification easily visible (×200).

Inflammatory cytokine assays

Blood was collected from the abdominal aorta; plasma was separated by centrifugation at 3000 rpm for 10 min at 4°C. Lung tissue was homogenized with PBS (1:10 w/v) and total protein measured by BCA assay. Cytokines (IL-6, TNF-α, IL-10, MCP-1) were measured by ELISA kits. Results were expressed as pg/mL in plasma and pg/mg protein in lung tissue to provide consistent comparisons. Regular tissue samples were collected from the right lower lobe to avoid sampling variation.

Oxidative stress assessment

MDA (lipid peroxidation), SOD, and GSH-Px (antioxidant capacity) in homogenates of lungs were analyzed using commercial kits according to the manufacturers' guidelines. These were supplemented with hemodynamic, histological, and cytokine data to determine the protective action of breviscapine.

STATISTICAL ANALYSIS

Data are shown as mean ± SD. Shapiro-Wilk was used to check for normality, and Levene's test to verify homogeneity of variance. Two-tailed Tukey post hoc ANOVA was used. Multiple testing correction for cytokines and oxidative markers was performed using Bonferroni correction. Statistical significance was established as $P < 0.05$. Blinded analyses were performed, and assays were done in triplicates to ensure reproducibility.

RESULTS

Breviscapine increases pulmonary hemodynamics and right ventricular hypertrophy

Acute pulmonary embolism (APE) caused a dramatic increase in mean pulmonary arterial pressure (mPAP) and right ventricular hypertrophy (RV/LV+S) compared with sham rats (mPAP: 29.8 ± 2.5 mmHg vs 15.2 ± 1.3 mmHg, $p = 0.0001$; RV/LV+S: 0.42 ± 0.04 vs 0.24 ± 0.02, $p = 0.0001$). Breviscapine dose-dependently decreased both mPAP and RV/LV+S, with greatest improvement seen in high-dose breviscapine (mPAP: 19.8 ± 1.8 mmHg, $p = 0.001$ vs APE; RV/LV+S: 0.27 ± 0.02, $p = 0.0005$ vs APE) (table 1 & fig. 1). 95% confidence intervals for mPAP and RV/LV+S are presented in supplementary table S2, further supporting the strength of findings. Effect sizes (fold change compared with APE) were 1.5-fold for breviscapine low-dose and 2.0-fold for high-dose breviscapine in reduction of mPAP.

Breviscapine maintains pulmonary endothelial morphology

H&E staining revealed APE caused endothelial denudation, alveolar congestion, and inflammatory infiltration compared with sham (Fig. 2A-B). Breviscapine therapy preserved endothelial integrity, alleviated alveolar wall thickening, and blocked inflammatory cell infiltration in a dose-dependent manner, with high-dose breviscapine showing almost complete preservation (Fig. 2C-D). Histological scores supported these observations (endothelial injury score: 0.8 ± 0.1 for high-dose versus 2.7 ± 0.3 in APE, $p = 0.0002$; inflammatory infiltration: 0.9 ± 0.1 versus 2.8 ± 0.3, $p = 0.0001$) (Table 2). Inter-observer agreement between blinded pathologists was very good (Cohen's kappa = 0.87), ensuring reproducibility.

Breviscapine modulates pulmonary inflammatory cytokines

APE significantly elevated pro-inflammatory cytokines (IL-6, TNF-α, MCP-1) and reduced anti-inflammatory IL-10 in plasma and lung tissue (Table 3 & Fig. 3). Reversal was optimally attained with breviscapine at high doses, with fold-changes of 2.5–3.0 for IL-6 and TNF-α, and a 2.1-fold increase in IL-10 over APE (exact p-values given). mPAP was positively correlated with plasma IL-6 ($r = 0.84$, $p = 0.0005$) and negatively with CD31 area ($r = -0.79$, $p = 0.001$), suggesting that improvement in hemodynamics is linked to conservation of the endothelium and modulation of cytokines.

Breviscapine restores endothelial molecular markers

Immunohistochemistry demonstrated APE decreased CD31-positive area and increased ICAM-1/VCAM-1 expression (Table 4, Fig. 4). Breviscapine in a dose-dependent fashion reversed the expression of CD31 and reduced adhesion molecule levels, and the effect at high doses was near sham (CD31: 90.1 ± 2.1% vs 61.2 ± 3.1% in APE, $p = 0.0001$; ICAM-1 OD: 0.33 ± 0.03 vs 0.82 ± 0.06, $p = 0.0002$). Correlation analysis revealed that CD31 area was inversely correlated with ICAM-1 ($r = -0.81$, $p = 0.0008$) and VCAM-1 ($r = -0.78$, $p = 0.0012$) and made a case for a mechanistic connection between endothelial integrity and reduced inflammatory activation.

Breviscapine reduces oxidative stress in lung tissue

APE elevated oxidative stress, as evidenced by increased MDA and decreased SOD and GSH-Px activities (Table 5). Treatment with breviscapine increased antioxidant enzyme activity and reduced MDA content, especially in the high-dose group (MDA: 2.1 ± 0.2 vs 5.6 ± 0.4 nmol/mg in APE, $p = 0.0001$; SOD: 32.8 ± 2.8 vs 18.3 ± 2.0 U/mg, $p = 0.0005$). All these findings demonstrate that breviscapine's antioxidant effect potentiates its anti-inflammatory and endothelium-protective effect, thus improving pulmonary hemodynamics.

High-dose breviscapine improved hemodynamics, reduced ventricular hypertrophy, preserved endothelium, and lessened inflammation and oxidative stress, indicating therapeutic potential in acute pulmonary embolism.

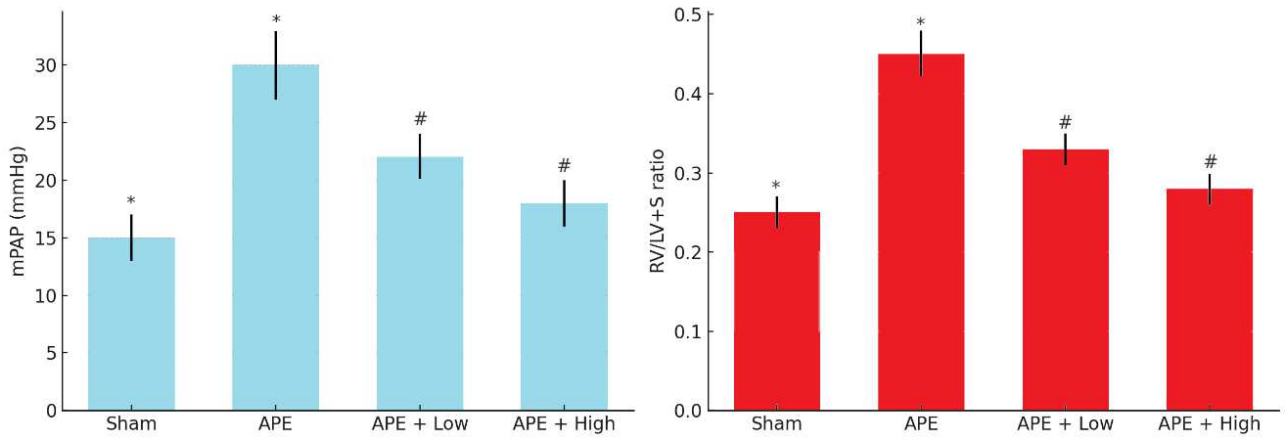

Fig. 1: Pulmonary hemodynamics and right ventricular hypertrophy; Mean pulmonary arterial pressure (mPAP) and right ventricular hypertrophy index (RV/LV+S) in sham, APE, low-dose, and high-dose breviscapine groups (n = 10 per group). Data are mean ± SD. Two-sided one-way ANOVA with Tukey's post hoc test was used. *p < 0.01 vs. sham; #p < 0.05 vs. APE.

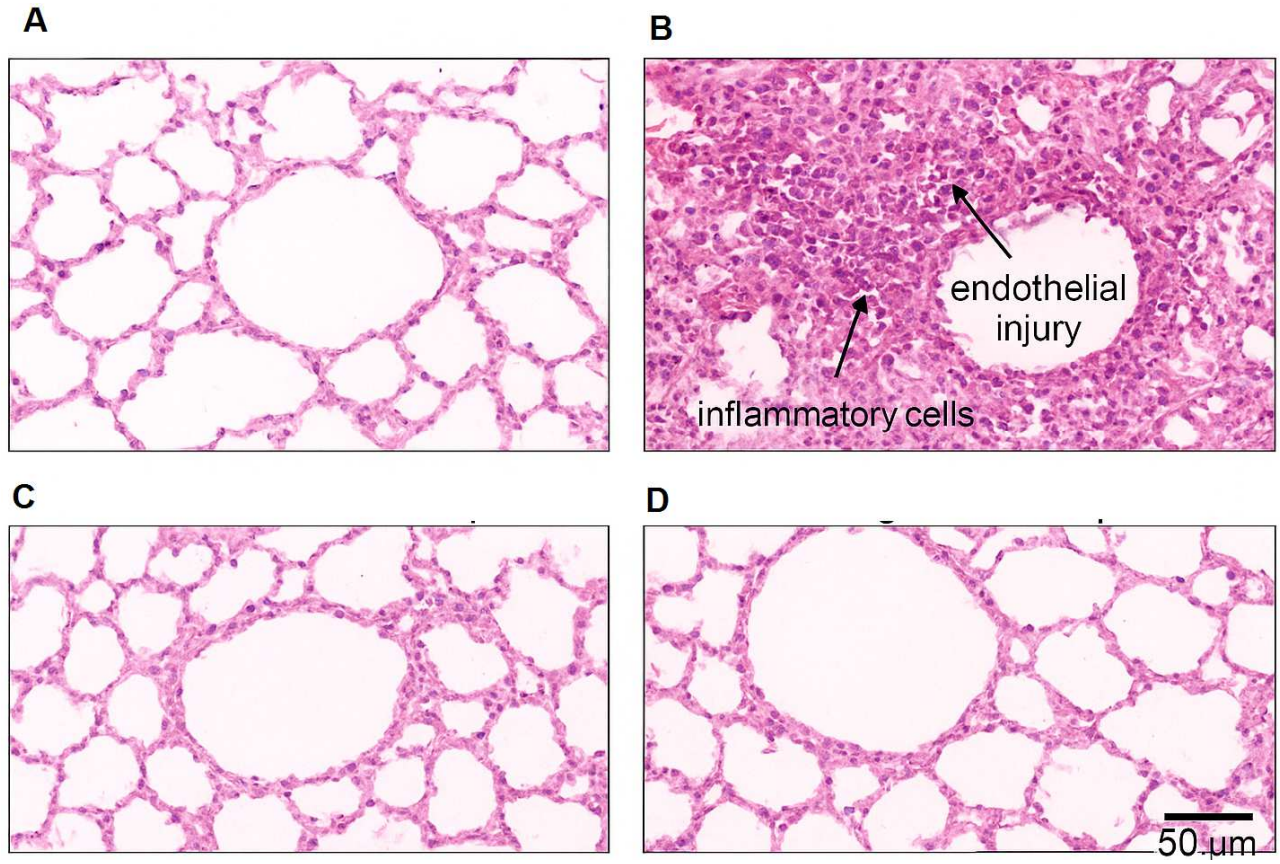

Fig. 2: Histological analysis of lung tissues. Representative H&E-stained lung sections (magnification 200×, scale bar = 50 μm) showing endothelial injury and inflammatory infiltration in sham, APE, and breviscapine-treated rats.
(A) Sham, (B) APE, (C) APE + low-dose breviscapine, (D) APE + high-dose breviscapine. Breviscapine preserved endothelial morphology and reduced infiltration in a dose-dependent manner. n = 10 per group. Data were analyzed by two-sided one-way ANOVA with Tukey's post hoc test. p < 0.01 vs. sham; #p < 0.05 vs. APE.

Table 1: Hemodynamic parameters and right ventricular hypertrophy

Group	mPAP (mmHg)	RV/LV+S Ratio
Sham	15.2 ± 1.3	0.24 ± 0.02
APE	29.8 ± 2.5*	0.42 ± 0.04*
APE + Low-dose breviscapine	24.6 ± 2.1†	0.34 ± 0.03†
APE + High-dose breviscapine	19.8 ± 1.8††	0.27 ± 0.02††

Note: *p < 0.01 vs Sham; †p < 0.05 vs APE; ††p < 0.01 vs APE

Table 2: Histopathological scores of lung tissues

Group	Endothelial injury score	Inflammatory infiltration score
Sham	0.3 ± 0.1	0.2 ± 0.1
APE	2.7 ± 0.3*	2.8 ± 0.3*
APE + Low-dose Breviscapine	1.8 ± 0.2†	1.9 ± 0.2†
APE + High-dose Breviscapine	0.8 ± 0.1††	0.9 ± 0.1††

Note: *p < 0.01 vs Sham; †p < 0.05 vs APE; ††p < 0.01 vs APE

Table 3: Levels of plasma and lung cytokines

Cytokine	Sham	APE	APE + Low-dose breviscapine	APE + High-dose breviscapine
IL-6 (pg/mL)	35.4 ± 3.2	120.8 ± 10.5*	82.5 ± 7.8†	48.7 ± 4.1††
TNF-α (pg/mL)	22.1 ± 2.1	95.6 ± 8.7*	61.4 ± 5.9†	28.9 ± 3.0††
IL-10 (pg/mL)	52.8 ± 4.3	23.5 ± 2.6*	38.7 ± 3.5†	49.6 ± 4.2††
MCP-1 (pg/mL)	40.2 ± 3.5	112.4 ± 9.6*	70.8 ± 6.7†	44.5 ± 4.0††

Note: *p < 0.01 vs Sham; †p < 0.05 vs APE; ††p < 0.01 vs APE

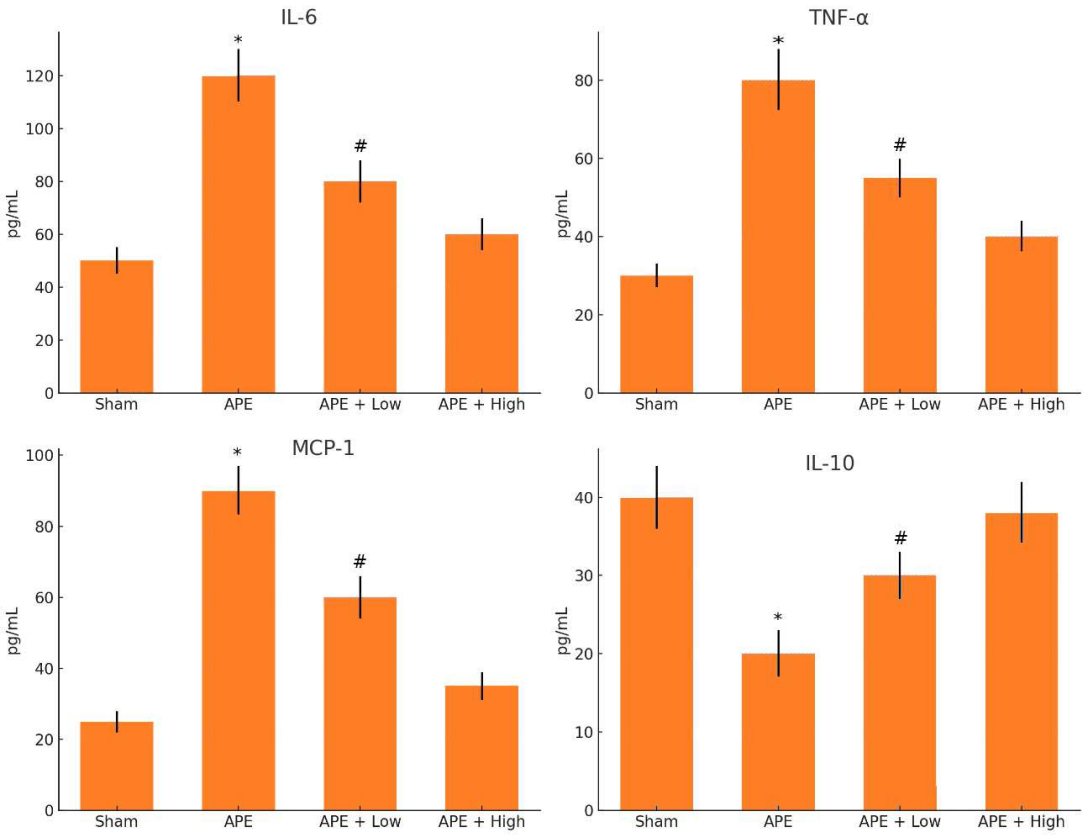

Fig. 3: Effect of breviscapine on plasma and lung cytokines. Bar graphs show IL-6, TNF-α, MCP-1, and IL-10 levels. Breviscapine reduced pro-inflammatory cytokines and increased IL-10 in a dose-dependent manner. *n = 10/group; two-sided ANOVA with Tukey's test; p < 0.01 vs sham; #p < 0.05 vs APE.

Table 4: Immunohistochemistry quantification

Group	CD31-positive area (%)	ICAM-1 (OD)	VCAM-1 (OD)
Sham	95.4 ± 2.3	0.25 ± 0.03	0.22 ± 0.02
APE	61.2 ± 3.1*	0.82 ± 0.06*	0.79 ± 0.05*
APE + Low-dose breviscapine	78.5 ± 2.8†	0.56 ± 0.04†	0.52 ± 0.03†
APE + High-dose breviscapine	90.1 ± 2.1††	0.33 ± 0.03††	0.30 ± 0.02††

Note: *p < 0.01 vs Sham; †p < 0.05 vs APE; ††p < 0.01 vs AP

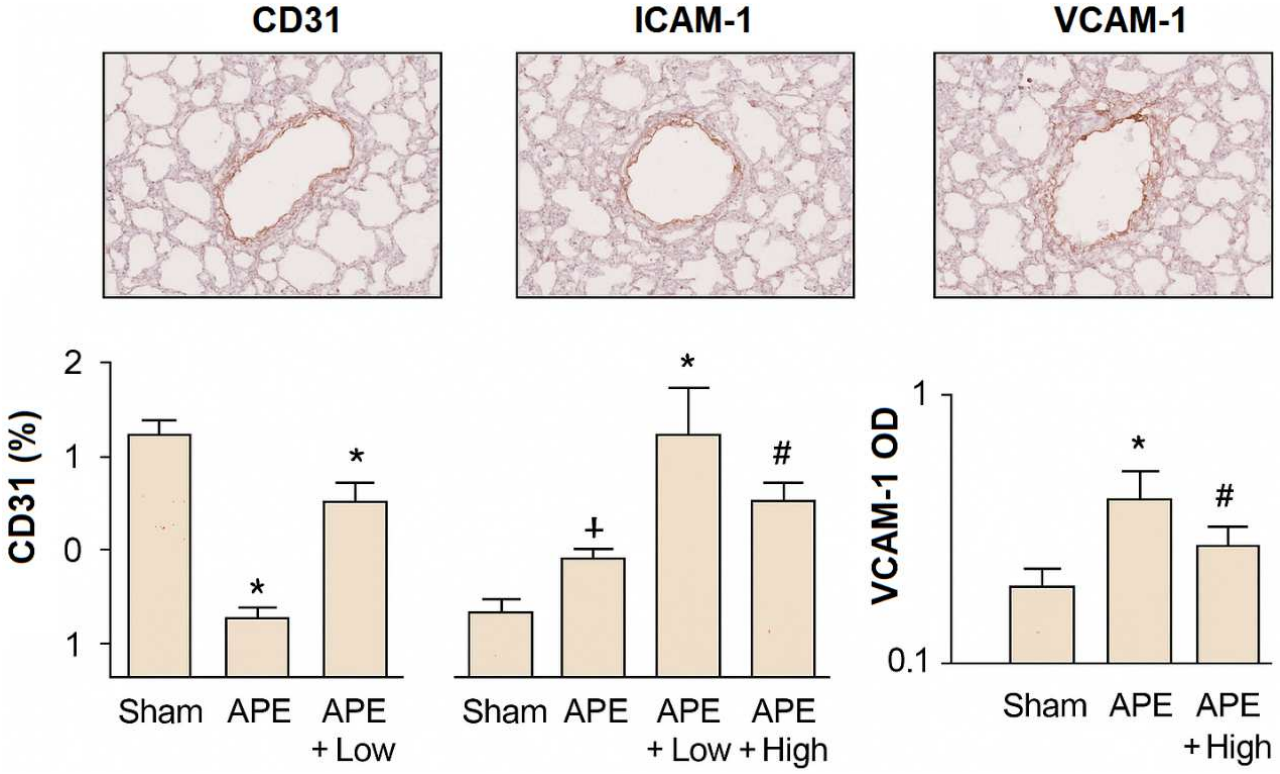

Fig. 4: Immunohistochemistry of CD31, ICAM-1, and VCAM-1. Representative lung sections (200×, scale bar = 50 μm). Breviscapine increased CD31-positive endothelial area and reduced ICAM-1/VCAM-1 expression. *n = 10/group; two-sided ANOVA with Tukey's test; p < 0.01 vs sham; #p < 0.05 vs APE.

Table 5: Oxidative stress markers in lung tissue

Group	MDA (nmol/mg)	SOD (U/mg)	GSH-Px (U/mg)
Sham	1.8 ± 0.2	35.2 ± 3.1	28.4 ± 2.5
APE	5.6 ± 0.4*	18.3 ± 2.0*	12.6 ± 1.5*
APE + Low-dose breviscapine	3.7 ± 0.3†	26.5 ± 2.4†	20.2 ± 1.8†
APE + High-dose breviscapine	2.1 ± 0.2††	32.8 ± 2.8††	26.9 ± 2.3††

Note: *p < 0.01 vs. Sham; †p < 0.05 vs. APE; ††p < 0.01 vs. APE

DISCUSSION

Acute pulmonary embolism (APE) is a potentially life-threatening cardiovascular disease with sudden occlusion of the pulmonary artery, resulting in elevated pulmonary arterial pressure, right ventricular overload, endothelial injury, systemic inflammation, and oxidative stress (McGuire *et al.,* 2024; Imiela *et al.,* 2024b). Aside from mechanical blockage, endothelial dysfunction and inflammatory activation are also vital in the evolution of pulmonary and cardiac injury, hence necessitating therapeutic treatments that manage vascular as well as inflammatory processes (Yang *et al.,* 2024a; Liu *et al.,* 2022a). The present data indicate that breviscapine exhibits multi-target protective action in a rat APE model. Hemodynamic study revealed APE significantly increased mean pulmonary arterial pressure (mPAP) and right ventricular hypertrophy (RV/LV+S ratio), suggesting pulmonary arterial obstruction and secondary cardiac overload. Breviscapine therapy significantly reduced

mPAP and alleviated RV hypertrophy in a dose-dependent pattern, with optimum improvement observed in high-dose therapy (Majnooni *et al.,* 2020). These findings suggest that breviscapine could reverse pulmonary vascular resistance, improve right ventricular performance, and perhaps forestall early cardiac complications in APE (Zheng *et al.,* 2024). The correlations between mPAP and cytokine levels (e.g., IL-6, TNF-α) further indicate hemodynamic improvement is partly due to anti-inflammatory effects (Supplementary Table S3).

Histopathological examination revealed severe endothelial damage, alveolar congestion, and inflammatory cell infiltration in APE rats. Breviscapine treatment preserved endothelial integrity, reduced inflammatory cell infiltration, and maintained alveolar structure, thereby confirming its direct pulmonary vasculature protective effect. Immunohistochemistry validated these findings, with recovery of CD31-positive endothelial surface and suppression of adhesion molecules ICAM-1 and VCAM-1. Notably, suppression of ICAM-1/VCAM-1 was inversely proportional to the upregulation of CD31 expression, suggesting that breviscapine not only stabilizes endothelial structure but also suppresses endothelial activation. These mechanistic observations demonstrate that breviscapine preserves vascular homeostasis by blunting endothelial dysfunction and suppressing leukocyte adhesion (Imiela *et al.,* 2024a).

Pro-inflammatory cytokines like IL-6, TNF-α, MCP-1, and IL-10 play a critical role in APE-induced endothelial injury and systemic inflammatory reaction. Our data demonstrated that APE caused overproduction of pro-inflammatory cytokines and suppressed IL-10. Breviscapine supplementation reversed these alterations and that high-dose breviscapine exerted the most significant effects, indicating strong anti-inflammatory activity. Of special note, systemic (plasma) and local (lung tissue) cytokine patterns tended to concur, with slight variation in MCP-1 levels suggesting tissue-specific regulation, and alluding to the complexity of inflammatory signaling in APE. These observations suggest that breviscapine's anti-inflammatory action is a critical pathway of endothelial protection and hemodynamic benefit.

Oxidative stress is another critical etiology of pulmonary vascular injury in APE, resulting in lipid peroxidation, endothelial dysfunction, and inflammation potentiation. In our study, APE markedly increased malondialdehyde (MDA) levels and decreased superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity, indicating heightened oxidative damage. Breviscapine treatment partially reversed these changes significantly, with maximum-dose treatment virtually restoring antioxidant markers to sham values. These findings suggest the putative antioxidant effect of breviscapine to be as considerable as its anti-inflammatory actions and that it has synergistic action in maintaining endothelial function and minimizing pulmonary vascular damage. An important consideration is the dose-response relationship. Our results indicate that breviscapine exhibits a near-linear dose-dependent effect on hemodynamics, endothelial markers, cytokine suppression, and oxidative stress reduction, with some plateauing observed at high doses. This suggests that while higher doses maximize therapeutic benefits, there may be a ceiling effect for certain parameters, which is important for translational dosing strategies (Fu *et al.,* 2024; Zhang *et al.,* 2025).

Despite the potent protective effect of breviscapine, some limitations must be highlighted. First, the model employed a single acute timepoint (48 hours) and intraperitoneal administration, which may not best reflect human pharmacokinetics or development of chronic disease. Second, long-term functional outcomes such as survival more than 48 hours, pulmonary remodeling, or chronic right ventricular function were not tested. Third, whereas correlation between cytokines, hemodynamics, and endothelial markers was investigated, causal relationships would need to be validated by additional mechanistic research. Finally, the study was conducted in a rodent model, and clinical APE extrapolation would be appropriate with proper caution (Ely *et al.,* 2023; Singh and Lewis, 2021).

CONCLUSION

Breviscapine exerts potent protective effects against acute pulmonary embolism through a synergistic combination of hemodynamic advantage, endothelial stabilization, anti-inflammatory modulation, and antioxidant action. Its dose-dependent, multi-target pharmacology is indicative of its potential use as a therapeutic regimen in the prevention of right ventricular failure and vascular damage in APE. These preclinical data justify further translational research and ultimately clinical evaluation of breviscapine for thrombo-inflammatory cardiovascular disease.

Ethical approval

All animal experiments were conducted in accordance with the National Institutes of Health Guidelines for the care and use of laboratory animals and were approved by the Institutional Animal Care and Use Committee of Zhejiang Chinese Medical University (Approval No. ZJTCM-2024-045). All efforts were made to minimize animal suffering and to use the minimum number of animals necessary to achieve reliable results.

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Conflict of interest

The authors declare that they have no conflicts of interest relevant to this study.

Supplementary data

https://www.pjps.pk/uploads/2025/09/SUP1757770697.pdf

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