Tropical Journal of Pharmaceutical Research February 2023; 22 (2): 313-319
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v22i2.13

Original Research Article

Decursinol angelate attenuates lipopolysaccharide-induced acute lung injury by regulating AKT/NF-κB pathway

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Sent for review: 7 November 2022 *Revised accepted: 30 January 2023*

Abstract

Purpose: *To investigate the effect of decursinol angelate in acute lung injury induced by lipopolysaccharide treatment.*
Methods: *Human bronchial epithelial cells (BEAS-2B cells) and human pulmonary artery endothelial cells (HPAECs) were exposed to lipopolysaccharide to induce cell injury and then treated with 20, 40, or 60 μM decursinol angelate. Cell viability was quantified using a cell counting assay, while cell apoptosis was evaluated by western blot and flow cytometry. Colorimetric and enzyme-linked immunosorbent assay (ELISA) was used to measure oxidative stress. Expressions of tumor necrosis factor-alpha (TNF-α), interleukin-1β, and interleukin-6 were evaluated using quantitative real-time-polymerase chain reaction (qRT-PCR) and enzyme-linked immunosorbent assay (ELISA). Phosphorylation levels of p65, IκBα, AKT, and phosphatidylinositol 3-kinase were assessed by western blot, while the entry of p65 into the nucleus was investigated by indirect immunofluorescence assay.*
Results: *Treatment with 40 or 60 μM decursinol angelate increased cell viability after lipopolysaccharide-induced damage. B-cell lymphoma 2 (Bcl2) and Bax expression were regulated, and the rate of apoptosis was inhibited. The concentration of superoxide dismutase and glutathione was elevated, and the density of malondialdehyde and myeloperoxidase decreased significantly. Inflammation was also suppressed by decursinol angelate by regulating TNF-α, interleukin-1β, and interleukin-6 expressions. Furthermore, decursinol angelate significantly decreased the phosphorylation of p65, IκBα, AKT, and phosphatidylinositol 3-kinase. Finally, decursinol angelate inhibited p65 entry into the cell nucleus.*
Conclusion: *Decursinol angelate alleviates cell damage and apoptosis, reduces oxidative stress, and attenuates inflammation after lipopolysaccharide-induced acute lung injury by inhibiting AKT/NF-κB signaling pathway. Thus, decursinol angelate is a potential candidate for the treatment of lung injury.*

Keywords: *Decursinol angelate, Inflammation, Lung injury, NF-κB, Oxidative stress, AKT/NF-κB signaling pathway, Cell damage, Apoptosis*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are common, but serious clinical conditions seen in intensive care units worldwide that cause high morbidity and mortality in critically ill patients [1]. Patients with ALI or ARDS present with acute exacerbations,

progressive hypoxemia, bilateral lung infiltrates on chest radiographs, increased work of breathing, and non-cardiac respiratory failure [2]. Despite significant advances in treatment strategies and an increased understanding of the associated respiratory physiology, patients with ALI or ARDS still have an annual mortality rate of 40 % [3]. Acute lung injury is a ubiquitous inflammatory disease characterized by the overproduction of proinflammatory mediators, inflammatory cell infiltration, and apoptosis of alveolar epithelial cells [4]. Control of abnormal inflammation and apoptosis greatly contributes to improved prognosis [5].

Angelica sinensis has long been used as a traditional Chinese medicine that promotes blood circulation, has analgesic and antipyretic effects, and inhibits airway inflammation [6]. Decursinol angelate (DA) is the active ingredient isolated from the root of *A. sinensis*. Among other effects, DA has antitumor and anti-inflammatory effects and reduces adipogenesis. Decursinol angelate blocks cancer cell migration and blocks activation of inflammatory factors by inhibiting phosphatidylinositol 3-kinase (PI3K), extracellular signal-regulated kinase (ERK), and NF-κB activation [7]. Decursinol angelate treatment improves colitis symptoms by modulating T cell responses [8] and can inhibit lipopolysaccharide (LPS)-induced macrophage polarization by modulating NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways [9]. Whether DA is therapeutic against LPS-induced ALI has not yet been elucidated.

EXPERIMENTAL

Cell culture

Human bronchial epithelial cells (BEAS-2B cells) were cultured in Dulbecco's Modified Eagle Medium with 10 % fetal bovine serum. Human pulmonary artery endothelial cells (HPAECs) were cultured in Endothelial Basal Medium-2 containing 10 % fetal bovine serum. The cells were grown in a 37 °C incubator supplied with 5 % CO_2.

Lipopolysaccharide exposure

Lipopolysaccharide (L2630, Sigma-Aldrich, St. Louis, MO, USA) was used to induce cell injury. BEAS-2B cells or HPAECs at 80 % confluence were exposed to 5 μg/mL lipopolysaccharide for 24 h at 37 °C with 5 % CO_2.

Cell viability assay

BEAS-2B cells and HPAECs were exposed to lipopolysaccharide to induce cell injury and then treated with 20, 40, or 60 μM DA (130848-06-5, Sigma-Aldrich). Cell viability was determined with the Cell Counting Kit-8 (CA1210, Solarbio Life Sciences, Beijing, China). Absorbance value was collected using a spectrophotometer at 450 nm, and the cell viability ratio was calculated.

Western blot assay

BEAS-2B cells and HPAECs were cultured in lipopolysaccharide to induce cell injury and then treated by with 20, 40, or 60 μM DA. Cellular protein was extracted cell lysis with radioimmunoprecipitation assay lysis buffer (89901, Thermo Fisher Scientific, Waltham, MA, USA). The protein samples were electrophoresed on SDS–PAGE gel and transferred to a PVDF membrane. Then the proteins on the membrane were incubated with the antibodies listed in table 1 at 4 ℃ for 12 h followed by horseradish peroxidase-conjugated goat anti-rabbit IgG (1:5000; B900210, Proteintech Group, Rosemont, IL, USA) at room temperature for 2 h. Finally, the target bands were visualized with ECL Western Blotting Detection Kit (Solarbio Life Sciences). The western blot signal was quantified by measurement of the relative intensity of each band using ImageJ software, and the relative expression levels were normalized to the relative β-actin levels.

Table 1. Antibody information

Protein	Cat. no.	Manufacturer	Dilution
Bcl2	ab196495	Abcam, Cambridge, United Kingdom	1:2000
Bax	ab8227	Abcam, Cambridge, United Kingdom	1:3000
p65	ab32536	Abcam, Cambridge, United Kingdom	1:3000
p-p65	3033S	Cell Signaling Technology, Danvers, MA, USA	1:1000
IκBα	4814	Cell Signaling Technology, Danvers, MA, USA	1:2000
p-IκBα	9246S	Cell Signaling Technology, Danvers, MA, USA	1:1000
AKT	ab8805	Abcam, Cambridge, United Kingdom	1:500
p-AKT	ab38449	Abcam, Cambridge, United Kingdom	1:1000
PI3K	ab154598	Abcam, Cambridge, United Kingdom	1:3000
p-PI3K	ab278545	Abcam, Cambridge, United Kingdom	1:2000
β-actin	ab8227	Abcam, Cambridge, United Kingdom	1:5000

Table 2: Primers for quantitative real-time polymerase chain reaction

Target gene	Forward sequence (5′→3′)	Reverse sequence (5′→3′)
TNF	CCCAGGCAGTCAGATCATCTTC	AGCTGCCCCTCAGCTTGA
IL6	GGTACATCCTCGACGGCATCT	GTGCCTCTTTGCTGCTTTCAC
IL1B	AACAGGCTGCTCTGGGATTC	AGTCATCCTCATTGCCACTGT
ACTB	GTCTGCCTTGGTAGTGGATAATG	TCGAGGACGCCCTATCATGG

Flow cytometry

Apoptosis was measured in BEAS-2B cells and HPAECs using an apoptosis detection kit (BD Biosciences, San Jose, CA, USA) based on annexin V-fluorescein isothiocyanate (FITC) and propidium iodide staining in accordance with the manufacturer's instructions. BEAS-2B cells and HPAECs were cultured in LPS to induce cell injury and then treated with 20, 40, or 60 μM DA. Then the cells stained with FITC and PI were analyzed using a FACS Calibur flow cytometer (BD Biosciences). The data were analyzed using FlowJo software (BD Life Sciences, Franklin Lakes, NJ, USA).

Enzyme-linked immunosorbent assay (ELISA)

The concentrations of superoxide dismutase (SOD), glutathione (GSH), malondialdehyde (MDA), and myeloperoxidase (MPO) in BEAS-2B cells and HPAECs were evaluated using a colorimetric activity assay for SOD (EIASODC, Thermo Fisher Scientific) and enzyme-linked immunosorbent assay (ELISA) kits for GSH (MBS265674, MyBioSource Inc., San Diego, CA, USA), MDA (ab238537, Abcam, Cambridge, United Kingdom), and MPO (MBS564055, MyBioSource Inc.). The concentrations of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6 were determined using ELISA kits (SEKR-0009, SEKR-0002, and SEKR-0005, respectively, Solarbio Life Sciences). The 100 μL BEAS-2B cells or HPAECs were incubated for 2 h in wells of an ELISA plate. Each well was washed five times, and then the cells were incubated for 1 h with 100 μL detection antibody. Each well was again washed five times, and then the cells were incubated for 30 min with 100 μL enzyme working reagent. Then each well was washed five times, and the cells were incubated for 30 min with 100 μL 3,3′,5,5′-tetramethylbenzidine. Finally, the reaction was terminated by the addition of 50 μL stop solution. The absorbance values were read at 450 nm using a spectrophotometer.

Quantitative real time-polymerase chain reaction (Qrt-pcr)

Total RNA was isolated from BEAS-2B cells and HPAECs using TRIzol reagent (15596026, Thermo Fisher Scientific) following the manufacturer's protocol. Reverse transcription was conducted with 500 ng RNA using the PrimeScript RT Reagent Kit (Takara Bio Inc., Kusatsu, Japan). Quantitative real-time PCR (qRT-PCR) was performed with the iTaq Universal SYBR Green Supermix (1725121, Bio-Rad Laboratories Inc., Hercules, CA, USA). The transcription of the target genes, *TNF*, *IL1B*, and *IL6* (that encode the proteins TNF-α, IL-1β, and IL-6, respectively), was determined by $2^{-\Delta\Delta CT}$, and the relative transcription was normalized to the transcription level of the *ACTB* gene, which encodes the β-actin protein. The PCR primer sequences are listed in Table 2.

Indirect immunofluorescence assay

BEAS-2B cells were seeded on 96-well microplates and exposed to LPS, followed by 40 μM DA. The cells were fixed with 4 % paraformaldehyde and permeabilized with 0.1 % Triton X-100. The cells were incubated with anti-p65 antibody, washed three times with phosphate-buffered saline, and stained with FITC-conjugated goat anti-rabbit IgG. After washing three times with phosphate-buffered saline, the cells were stained with 4′,6-diamidino-2-phenylindole and then examined under a fluorescence microscope (Eclipse TE2000-U, Nikon, Tokyo, Japan).

Statistical analysis

Statistical analysis was performed using GraphPad Prism 8. Data are presented as mean ± standard error of the mean (SEM) from three replicates. The differences were analyzed by *t*-test. $P < 0.05$ was considered statistically significant.

RESULTS

Decursinol angelate alleviated lipopolysaccharide-induced lung cell damage

The structure of DA is shown in Figure 1A. To study the effect of DA on damaged lung cells, the viability of BEAS-2B cells and HPAECs was investigated. First, LPS induced damage to BEAS-2B cells and HPAECs. Despite no significant improvement in cell viability after 20 μM DA treatment, 40 and 60 μM DA significantly

increased the cell viability of both BEAS-2B cells and HPAECs after LPS exposure (Figure 1 B).

Next, cell apoptosis in BEAS-2B cells and HPAECs was studied to clarify how DA increased cell viability after LPS exposure. Western blots were performed to measure the expression of Bcl2 and Bax. As is reported that Bcl2 protein is one of the most important inhibitors of programmed cell death [10], and Bax may stimulate cell apoptosis [11]. Bcl2 expression was reduced when damage was induced with LPS; 20, 40, or 60 μM DA significantly increased Bcl2 expression after LPS-induced damage. Bax expression was increased in LPS-treated cells and decreased significantly after treatment with 20, 40, or 60 μM DA after LPS-induced damage (Figure 1 C).

Flow cytometry was also used to evaluate cell apoptosis in BEAS-2B cells and HPAECs. Cell apoptosis was increased in LPS-treated cells compared with control cells. The proportion of apoptotic BEAS-2B cells decreased significantly after treatment with 20, 40, or 60 μM DA. The proportion of apoptotic HPAECs decreased significantly after treatment with 40 or 60 μM DA (Figure 1 D). Thus, DA improved cell viability and suppressed apoptosis of BEAS-2B cells and HPAECs after LPS-induced cell damage.

Decursinol angelate reduced lipopolysaccharide-induced oxidative stress

The expression of superoxide dismutase was downregulated after LPS-induced injury. However, this downregulation was alleviated by DA. Cells damaged by LPS and treated with 40 or 60 μM DA had significantly increased Superoxide dismutase expression compared with LPS-treated cells that had no DA treatment. Glutathione concentration decreased after cell injury but significantly upregulated after treatment with 20, 40, or 60 μM DA. The concentration of Malondialdehyde was increased after LPS-induced injury, and 20, 40, or 60 μM DA decreased MDA level compared with LPS-treated cells that had no DA treatment. Myeloperoxidase expression was elevated after LPS treatment, and this was weakened after DA treatment (Figure 2). Therefore, DA reduced LPS-induced oxidative stress in BEAS-2B cells and HPAECs.

Decursinol angelate attenuated lipopolysaccharide-induced inflammation

The mRNA and protein levels of three inflammation-related molecules, TNF-α, IL-1β, and IL-6, were quantified in BEAS-2B cells and HPAECs damaged by LPS with or without DA treatment.

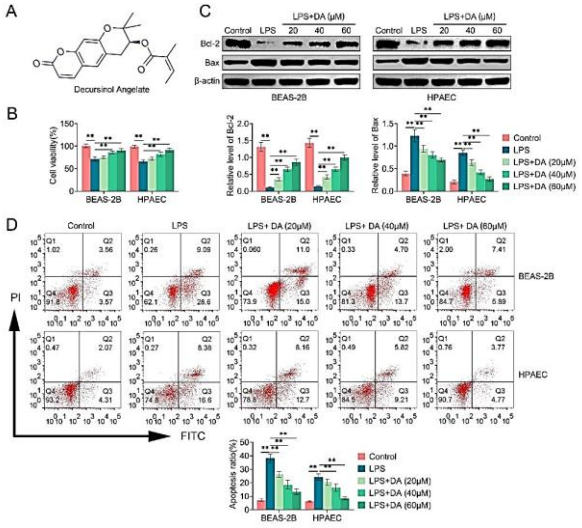

Figure 1: DA alleviated LPS-induced lung cell damage. (A) Chemical structure of DA. (B) Cell viability of BEAS-2B cells and HPAECs. (C) The expression of Bcl2 and Bax in BEAS-2B cells and HPAECs induced by LPS followed by DA treatment. (D) The apoptosis ratio of BEAS-2B cells and HPAECs induced by LPS followed by DA treatment. ***P* < 0.01

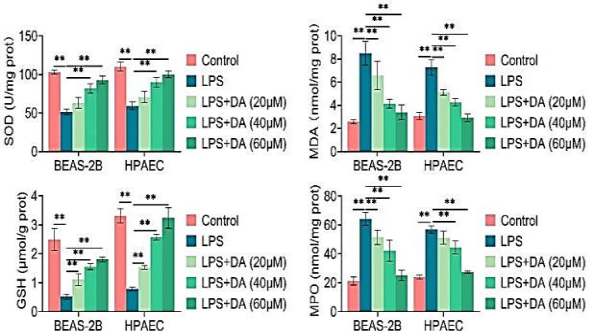

Figure 2: DA reduced LPS-induced oxidative stress in lung cells. The colorimetric assay or ELISA data to indicate the concentrations of SOD, MDA, GSH, and MPO in BEAS-2B cells and HPAECs induced by LPS followed by DA treatment. SOD: Superoxide dismutase; MDA: Malondialdehyde; GSH: Glutathione; MPO: Myeloperoxidase. ***P* < 0.01

Firstly, qRT-PCR was performed to measure the transcription of the *TNF*, *IL1B*, and *IL6* genes. The mRNA expression levels of *TNF*, *IL1B*, and *IL6* were markedly elevated after LPS treatment, which indicates that inflammation was induced in cells damaged by LPS treatment. This inflammation was weakened by DA, as the mRNA expression levels of *TNF*, *IL1B*, and *IL6* were significantly reduced after DA treatment.

Then, the protein expression levels of TNF-α, IL-1β, and IL-6 were determined using ELISA.

Consistent with the mRNA data, the expressions of TNF-α, IL-1β, and IL-6 proteins increased after LPS-induced cell damage, and DA treatment subsequently decreased the protein expression (Figure 3). Thus, DA attenuated LPS-induced inflammation in lung cells.

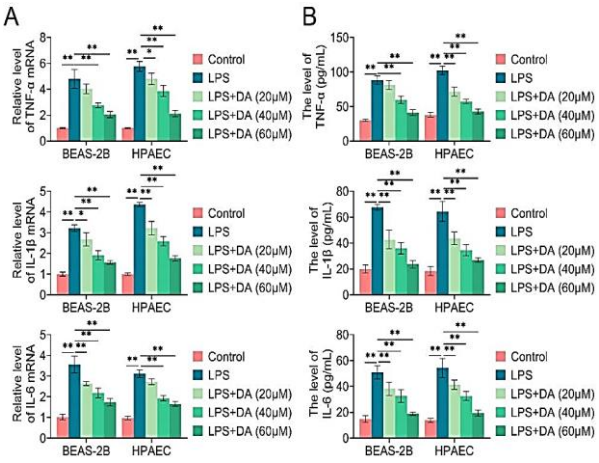

Figure 3: DA attenuated LPS-induced inflammation in lung cells. (A) The mRNA levels of *TNF*, *IL1B*, and *IL6* genes in the supernatant of BEAS-2B cells and HPAECs. (B) The protein expression levels of TNF-α, IL-1β, and IL-6 in BEAS-2B cells and HPAECs. $^{**}P < 0.01$

Decursinol angelate inhibited the AKT/NF-κB signaling pathway

As is known that inflammation is associated with AKT/NF-κB signaling pathway. Here, western blot was conducted to measure the phosphorylation and expression of four related molecules including p65, IκBα, AKT, and PI3K. The data demonstrated that LPS induction or DA treatment regulated the phosphorylation of p65, IκBα, AKT, and PI3K instead of their protein expression. Specifically, the phosphorylation levels of p65, IκBα, AKT, and PI3K were increased in LPS group than in the control, and 40 or 60 μM DA could significantly decline the phosphorylation of p65, IκBα, and AKT. For PI3K, its phosphorylation was significantly decreased in 20, 40, and 60 μM DA (Figure 4 A).

An indirect immunofluorescence assay was also performed to investigate the transportation of p65 into the nucleus of BEAS-2B cells. More p65 was observed in the nuclei of cells damaged by LPS treatment, which means that LPS promoted the entry of p65 into the nucleus. However, p65 significantly declined in the nuclei of cells treated with LPS and DA compared with those treated with LPS alone, which indicates that DA treatment reduced the entry of p65 into the nucleus. Thus, DA inhibited LPS-induced activation of the AKT/NF-κB pathway.

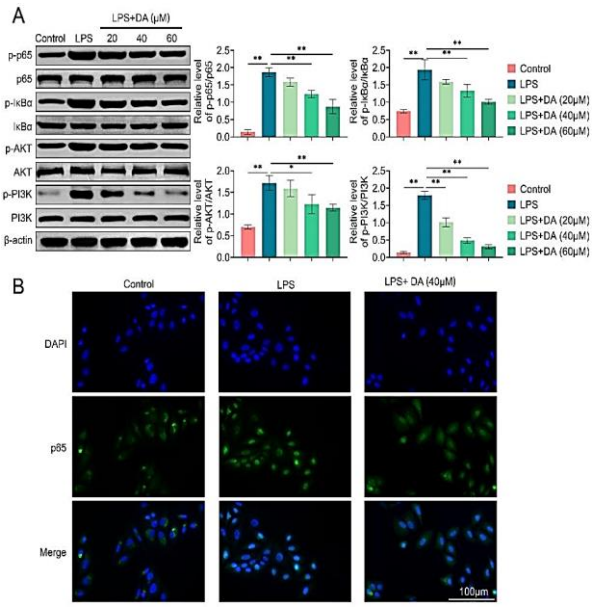

Figure 4: DA inhibited the AKT/NF-κB signaling pathway. (A) The phosphorylation and expression levels of p65, IκBα, AKT, and PI3K in BEAS-2B cells and HPAECs. (B) An indirect immunofluorescence assay was performed in BEAS-2B cells to investigate the transportation of p65 into the nucleus. LPS: LPS induction; LPS+DA: LPS induction followed by DA treatment. $^{*}P < 0.05$, $^{**}p < 0.01$

DISCUSSION

There are millions of cases of ALI every year, with an annual mortality rate of 40 % [3], it is important to develop more effective clinical treatments for ALI. Exposure to LPS results in airway inflammation and injury [12]. In this work, 5 μg/mL of LPS induced injury to BEAS-2B cells and HPAECs. This model of LPS-induced damage has been widely used in ALI studies. And this model was used to measure cell viability, which revealed that DA promoted restoration of the viability of lung cells after LPS treatment.

Next, the apoptosis rate was investigated to elucidate the mechanism of DA enhancing cell viability after LPS-induced damage. A similar compound, decursin, can protect against cytotoxicity and apoptosis by suppressing caspase-3 activity and regulating the ratio of Bcl2 to Bax [13]. Despite DA-induced apoptosis in some types of tumor cells, inhibition of tumor cell replication would in fact serve to normalize cell growth. So, it makes sense that DA attenuates apoptosis and improves the viability of lung cells.

The regulation of oxidative stress was also investigated. Decursinol angelate upregulates GSH levels and its antioxidant enzyme activity in PC12 cells [13]. Decursin also inhibits cytotoxicity and apoptosis, reactive oxygen species production, and mitochondrial release of cytochromes [13]. These findings are consistent with the conclusion of this study. In this section, four molecules including Superoxide dismutase, Glutathione, Malondialdehyde, and Myeloperoxidase were used as indicators of oxidative stress. Superoxide dismutase is a biochemical marker of oxidative stress in diabetic patients [14]. Malondialdehyde is a presumptive biomarker for nutritionally induced oxidative stress [15]. Lipopolysaccharide-induced damage in BEAS-2B cells and HPAECs reduced the level of Superoxide dismutase and Glutathione, while increasing the quantity of Malondialdehyde and Myeloperoxidase [16]. Thus, it is reasonable to suggest that the expression of these proteins regulates oxidative stress.

Acute lung injury is a ubiquitous inflammatory lung disease characterized by the overproduction of proinflammatory mediators, inflammatory cell infiltration, and apoptosis of alveolar epithelial cells [4,17]. Cho and others showed that the anti-inflammatory effect of DA is regulated by heme oxygenase-1 expression [18]. Decursinol angelate also suppresses LPS-induced inflammatory responses by blocking the NF-κB and MAPK pathways [9]. Thus, it is necessary to investigate the inflammation response after LPS-induced injury. The data in this work also showed an inhibitory role of DA on inflammation. Furthermore, the effect of DA on AKT/NF-κB pathway involved in inflammation regulation was investigated. The phosphorylation of p65, IκBα, AKT, and PI3K was downregulated after LPS-induced cell damage. Numerous studies have shown that DA inhibits AKT/NF-κB pathway. For example, DA inhibits LPS-induced macrophage polarization by modulation of NF-κB and MAPK pathways [9]. Decursinol Angelate also blocks inflammation of tumor cells by inhibition of PI3K, ERK, and NF-κB activation [7]. So, it is logical to conclude that DA inhibits inflammation via inhibiting the AKT/NF-κB pathway.

CONCLUSION

The findings of this study demonstrate that DA alleviates cell damage and inhibits cell apoptosis to promote the viability of BEAS-2B cells and HPAECs. Decursinol angelate also reduces oxidative stress and attenuates inflammation by inhibiting AKT/NF-κB signaling pathway. Therefore, DA is a promising candidate for the management of lung injury.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Qiaosu Xiao designed the study and carried out the experiments. Qiaosu Xiao, Ting Li, and Wenyang He supervised the data collection, analyzed the data, interpreted the data, prepared the manuscript for publication, and reviewed the draft of the manuscript. All authors read and approved the manuscript.

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