

Sesamin Alleviates Asthma Airway Inflammation by Regulating Mitophagy and Mitochondrial Apoptosis

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ABSTRACT: Bronchial asthma poses a considerable burden on both individual patients and public health. Sesamin is a natural lignan that relieves asthma. However, the potential regulatory mechanism has not been fully validated. In this study, we revealed the mechanism of sesamin in inhibiting airway inflammation of asthma. In cockroach extract (CRE)-induced asthmatic mice, sesamin efficiently inhibited inflammatory cell infiltration, expressions of total and CRE-specific IgE in serum, and inflammatory cytokines (including IL-4, 5, 13) in bronchoalveolar lavage fluid. Further study revealed that sesamin inhibited Th2 cells in the mediastinal lymph nodes and spleen, the expression of PTEN-induced putative kinase 1 (PINK1) and Parkin, and apoptosis of lung airway epithelial cells. *In vitro*, sesamin had no significant cytotoxicity to BEAS-2B cells. Sesamin significantly increased TNF- α /IL-4-induced superoxide dismutase (SOD), catalase (CAT), heme oxygenase 1 (HO-1), and nuclear factor erythroid 2 related factor 2 (Nrf2), and decreased malondialdehyde. Sesamin also inhibited TNF- α /IL-4-induced mitochondrial reactive oxygen species, increased mitochondrial membrane potential, and reduced cell apoptosis as well as PINK1/Parkin expression and translocation to mitochondria. Conclusively, sesamin may relieve asthma airway inflammation by inhibiting mitophagy and mitochondrial apoptosis. Thus, sesamin may become a potential therapeutic agent for asthma.

KEYWORDS: sesamin, mtROS, mitophagy, apoptosis, asthma

■ INTRODUCTION

Asthma is considered to be an inflammatory disease characterized by chronic airway inflammation and airway hyperresponsiveness (AHR).¹ There are about 358 million asthma patients around the world, and the prevalence has increased by 12.6% since 1990.² The pathological changes of asthmatic lungs consist of excessive mucus production, increased infiltration of inflammatory cells, and airway obstruction.³

Oxidative stress caused by reactive oxygen species (ROS) plays a critical role in airway inflammation and remodeling.⁴ Cao et al. demonstrated that in cadmium-induced airway inflammation, cadmium increased intracellular ROS by activating the mitochondrial-mediated endogenous apoptotic pathway and caused cellular oxidative stress, and the activation of JNK, ERK, and p38 MAPK signal transduction, which finally promoted apoptosis of bronchial epithelial cells (BEAS-2B).⁵ Therefore, ROS scavenging effects are important in inhibiting mitochondrial damage and apoptosis, thereby inhibiting airway inflammation in asthma. In addition, excessive ROS can also promote mitochondrial autophagy (mitophagy).⁶ Mitophagy is generally considered to be a key physiological process for maintaining mitochondrial homeostasis, but in allergen-induced asthma, mitophagy will eventually lead to mitochondrial bioenergy imbalance.⁶ Mitophagy is mainly carried out through the PINK1/Parkin autophagy pathway.⁷ Li et al. reported that PM2.5 activated mitochondrial fission and mitophagy induced by the PINK1/Parkin pathway by

activating AMP protein kinase, thereby aggravating airway inflammation.⁸ Zhang et al. showed that the mitochondrial-targeted calcium/calmodulin-dependent protein kinase II inhibitors inhibited mitochondrial autophagy, including the expression of PINK1 and Parkin, also reduced cockroach allergen-induced asthma.⁴ However, the regulatory mechanism of mitochondrial autophagy in asthma remains to be further studied.

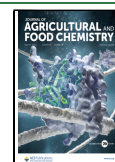
Sesamin is a fat-soluble lignan that has antioxidant, antiapoptotic, antihypertensive, anticancer, and hypolipidemic effects.⁹ Sesamin also has protective effects on bronchial asthma. Studies have shown that sesamin can reduce ovalbumin (OVA) induced allergic airway inflammation by inhibiting macrophage-derived chemokine expression,¹⁰ and T(H)2 responses;¹¹ however, its role in cockroach extract (CRE)-induced asthmatic inflammation has not been reported. Sesamin is reported to inhibit H₂O₂-mediated oxidative stress through SIRT1/SIRT3/FOXO3a axis in human neuronal cells.¹² It can also achieve antioxidant function by upregulating the Nrf2/HO-1/(NAD(P)H quinone oxidoreductase 1 (NQO1) pathway in intestinal ischemia-reperfusion induced

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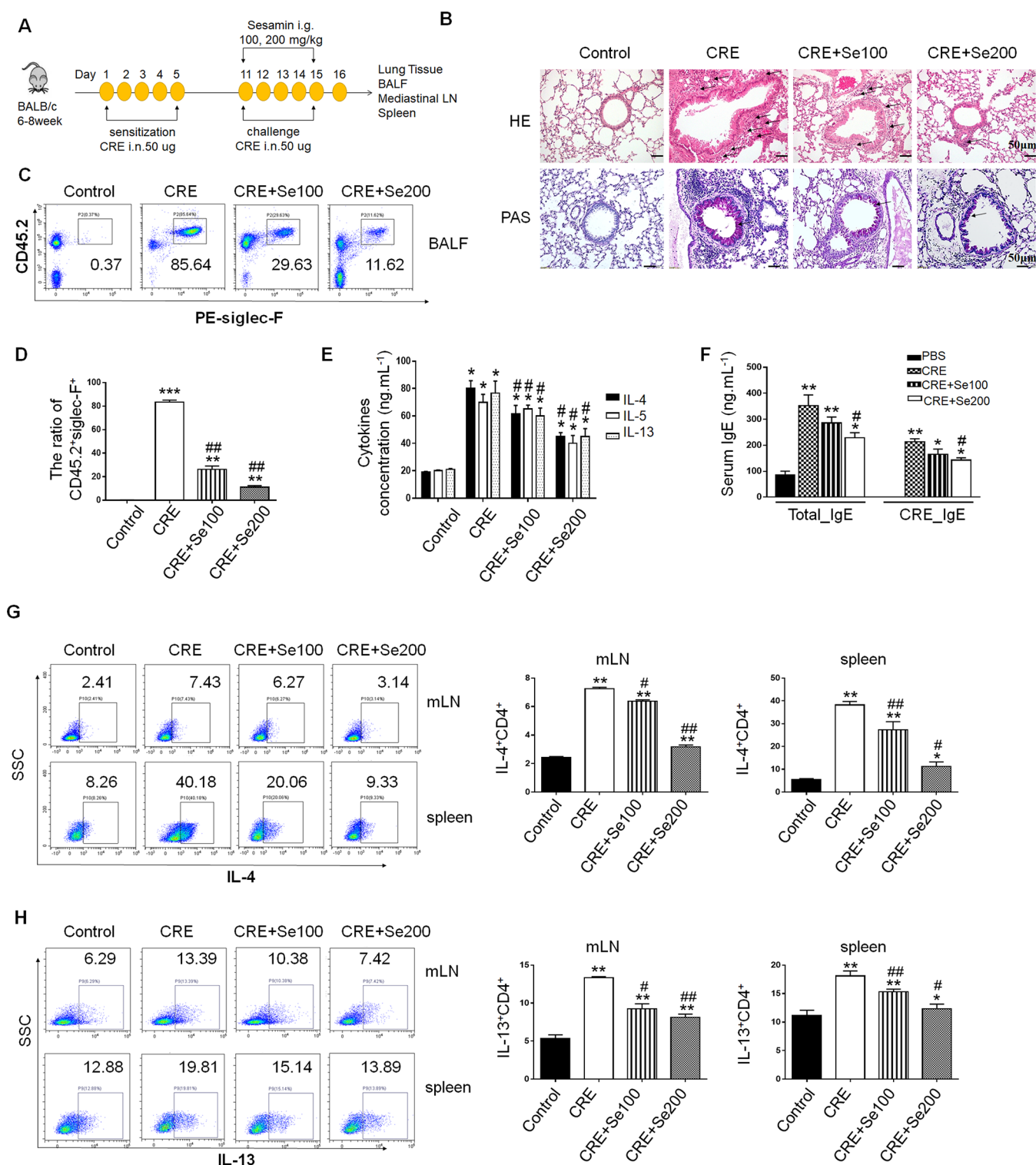


Figure 1. Sesamin inhibits airway inflammation, goblet cell proliferation, and Th2 development in asthmatic mice. (A) Schematic diagram of CRE and sesamin treatment. (B) HE and PAS staining of lung sections. Arrows indicate inflammatory cells around the airway and mucus secretion of goblet cells in the airway epithelium, respectively. Magnification = 100 $\times$. Scale bar = 50 μ m. (C) CD45.2⁺ CD11c⁻ siglec-F⁺ cells (eosinophils) were gated in BALF. (D) Ratio of CD45.2⁺ CD11c⁻ siglec-F⁺ cells in BALF. (E) IL-4, IL-5, IL-13 in the supernatant of BALF. (F) IgE levels in the serum of mice. (G) Ratio of CD4⁺ IL-4⁺ cells in mediastinal lymph nodes (mLN) and spleen was measured by flow cytometry. Representative and quantitative results were shown. (H) Ratio of CD4⁺ IL-13⁺ cells in mLN and spleen was measured by flow cytometry. Representative and quantitative results were shown. * P < 0.05, ** P < 0.01 compared with the control group. # P < 0.05, ## P < 0.01 compared with CRE group.

cell/tissue injury.¹³ Lee et al.¹⁴ found that sesamin significantly inhibited the production of intracellular ROS and SOD (superoxide dismutase), alleviated apoptosis, and restored

dysfunctions including intracellular calcium accumulation, mitochondrial membrane potential (MMP), mitochondrial cytochrome c (Cyo-c) release, and caspase-3 activation. Roustia

et al.¹⁵ believed that sesamin attenuated the lipopolysaccharide-induced acute kidney injury through inhibiting the inflammatory response, oxidative stress, and apoptosis. The research by Fan et al.¹⁶ also indicated that sesamin regulated the levels of B-cell lymphoma-2 (Bcl-2) and BCL-2-associated X (Bax) in myocardial infarction through the JNK/NF- κ B axis. However, it is unclear whether sesamin affects allergic airway inflammation in asthma by regulating mitophagy and mitochondrial apoptosis.

Both OVA and CRE are allergens used to replicate asthma in animal models. OVA is an egg white extract with strong immunogenicity and has the characteristics of convenient source, low cost, and simple operation. However, there is a lack of structural validity in the acute nature of the challenge. In addition, passive respiratory exposure to OVA will result in inhalation tolerance.¹⁷ CREs are common in our daily life as environmental contaminants and can cause oxidative damage to airway epithelial cells.¹⁸ CRE-induced asthma in mice have many common pathological features with human asthma. Therefore, we utilized CRE to induce asthma in this study.

Here, in this study, we investigated the inhibitory effect of sesamin on asthma and the underlying mechanism involving mitochondrial apoptosis and mitophagy. Our results indicated that sesamin improved asthma by reducing mitophagy and mitochondrial apoptosis, and ultimately reduced airway inflammation in asthma. These findings further confirm the antioxidant properties of sesamin for asthma. Therefore, sesamin may become a promising therapeutic agent for asthma.

MATERIALS AND METHODS

Mice. Thirty-two female BALB/c mice (specific pathogen free, 8-week-old, weight 20–22 g) were purchased from the Feeding Department of Yanbian University Health Science Center (Animal License [JI] 2020–00093, Yanji, China). All mice were bred under conditions with relative humidity 50–60%, 22 ± 2 °C room temperature, and 12 h dark and light cycle. They had free access to regular chow (3–7 g/day) and strictly autoclaved water. All animal experimental processes were applied in accordance with the Regulations on the Administration of Laboratory Animals and approved by the Ethics Committee of School of Medicine, Yanbian University (approval number (SYXK(JI)2020–0009)).

Asthma Model and Grouping. Animal grouping was designed as 4 groups ($n = 8$) including control group, Cockroach Extract (Cockroach German RMB46P) group, and the sesamin treated (low and high dose) groups. As previously described,¹⁸ the CRE group mice were intranasally (i.n.) sensitized with 50 μ g of CRE (German cockroach, *Blattella germanica*) and 50 μ L of a mixed solution of sterile saline on days 1–5, respectively (Figure 1A). The control group received the 50 μ L of saline. On days 11–15, mice were challenged once a day with 50 μ g of CRE in 50 μ L of saline (i.n.) under light anesthesia for 5 days. Sesamin group mice were intragastrically administered with sesamin (100 and 200 mg/kg, S890228, MacklinLnc, Shanghai, China)¹⁰ for 5 days once a day after challenge. The 50 μ L of saline was used in the control group.

Sample Collection. After 24 h post last challenge (day 16), the mice were sacrificed for bronchoalveolar lavage fluid (BALF) collection. One milliliter of cold PBS was used in lavaging the airways. Approximately 800 μ L of BALF was collected. After centrifuging at $400 \times g$ for 10 min, the cell pellet was resuspended for eosinophil analysis by flow cytometry detailed below, and the supernatant was taken to detect cytokines. The peripheral blood, right lung, mediastinal lymph nodes (mLN), and spleen were also collected.

ELISA. Cytokines were detected using ELISA kits (R&D Systems, Minneapolis, MN, USA). The sensitivities for IL-4, IL-13, and IL-5 were all 2.0 pg/mL. The allergen-specific IgE and IgG1 in the serum

were also measured by the corresponding ELISA.¹⁹ The expression levels of MDA, CAT, and SOD in cell culture supernatant were detected by corresponding ELISA kits (A003–1–2, A007–1–1, and A001–3–2; Nanjing Jiancheng Bioengineering Institute, China), and the relevant optical densities were measured by a microplate reader (BioTek).

Histological Analysis. Lung tissues were stained with hematoxylin and eosin (#G1120, Solarbio, Beijing, China) to observe inflammatory cell infiltration. PAS staining was performed with Glycogen PAS staining solution kit (G1281, Solarbio, Beijing, China) to analyze proliferation of goblet cells around airways and the secretion of airway mucus.

Immunohistochemistry. First, lung tissue sections were deparaffinized, followed by dehydration in gradient ethanol. Then citric acid was used for antigen retrieval. For analyzing cleaved caspase-3, lung sections were incubated with rabbit cleaved caspase-3 (9664, 1:2000, CST, USA) followed by incubating with goat antirabbit IgG H&L (HRP) (6721, 1:2000, Abcam, USA). Images were captured using light microscope (Eclipse Ni-U, Nikon, Japan).

Cell Culture and Treatment. BEAS-2B cell line were obtained from Cell Resource Center of Shanghai Institute of Life Sciences, Chinese Academy of Sciences (Shanghai, China). Cells were cultured in DMEM (Gibco, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum (Gibco), 100 g/mL streptomycin and 100 U/mL penicillin at 37 °C, 5% CO₂.

For *in vitro* stimulation, cells (1×10^5) were administrated with 20 and 40 μ M of sesamin²⁰ for 1 h and then incubated with both 10 ng/mL of TNF- α (78157, STEMCELL, Technologies Inc. Vancouver, Canada) and 10 ng/mL of IL-4 (78047, STEMCELL) for 24 h.²¹ For siRNA transfection, siRNAs specific for human PINK1 (sc-44598) and Parkin (sc-42158) were bought from Santa Cruz Biotechnology (CA, USA). After the cells were pretreated with sesamin for 1 h, siRNAs were transfected using Lipofectamine RNAiMAX reagent (13778150, Invitrogen, USA) for 72 h.

MTT Assay. BEAS-2B cells (5000 cells per well; 200 μ L in total) were treated with sesamin (10, 20, 40, and 60 μ M) for 24 and 48 h. Then 100 μ L of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) solution (0.5 mg/mL, C0009S, Beyotime, China) was added per well. After 4 h, the DMSO (dimethyl sulfoxide) (150 μ L/well) (D8371, Solarbio, China) was added, and 10 min later, a microplate reader (BioTek) was used to detect the absorbance at 563 nm. Percentage of cell viability = (OD value of sesamin treated cells/OD value of control cells) $\times$ 100.

Transmission Electron Microscopy (TEM). Cells were fixed with 2.5% glutaraldehyde for 2 h followed by washing with PBS, 3 times, 10 min per time. The subsequent sample preparation was performed by the Pathology Department of Yanbian University according to routine procedure. Finally, pictures were photographed by TEM (HT7700 Hitachi, Japan) at 6000 $\times$ magnification.

ROS. A DCFH-DA (10 μ M, #S0033S, Beyotime, Shanghai, China) fluorescent probe was used for cellular ROS detection, 10 min at 37 °C. ROS positive cells were measured by both flow cytometry (Cytotex, Beckman Coulter, Inc., CA, USA) and pictured by a Cytation 5 Cell Imaging Microplate Detection System (BioTek, Inc., Winooski, VT, USA). For ROS measurement of lung tissues, the lung sections were stained with DHE (10 μ M, #S0063, Beyotime) solution, at 37 °C for 5 min. For intracellular mitochondrial ROS (mtROS) detection, cells were stained with MitoSOX Dye (5 μ M, # M36008, Thermo Fisher Scientific, Massachusetts, USA), at 37 °C for 10 min. The data were normalized to the control group.

Mitochondrial Membrane Potential Assay. The JC-1 (5 μ M, #C2006, Beyotime) solution was incubated with treated cells, at 37 °C for 15 min, and then cells were observed with Cytation 5. The degree of mitochondrial depolarization was calculated as red/green fluorescence and normalized to the control group.

TUNEL Assay. Apoptosis was measured using the DeadEnd Fluorometric TUNEL System kit (C1089, Beyotime). Briefly, the lung sections were deparaffinized in xylene for 10 min and then hydrated with gradient ethanol. Then the samples were treated with DNase free proteinase K (20 μ g/mL, ST532, Beyotime) at 37 °C for

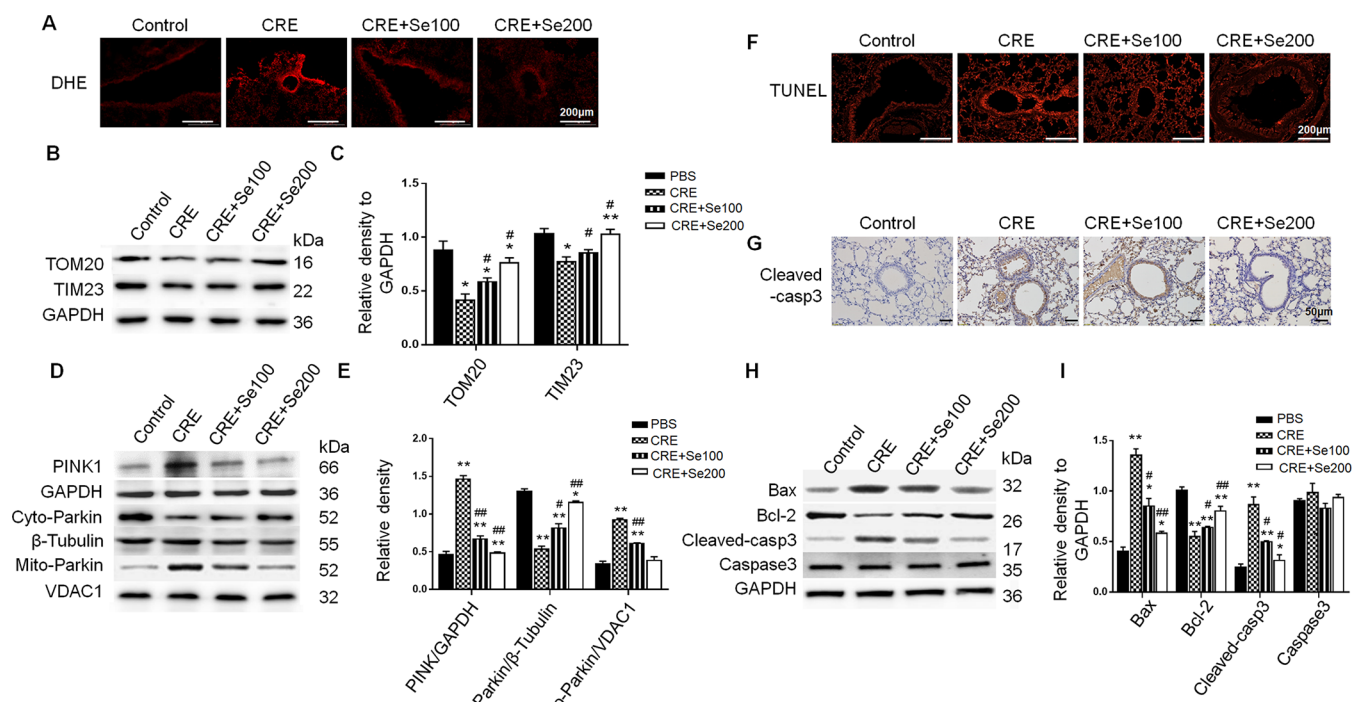


Figure 2. Sesamin inhibits mitophagy and mitochondrial apoptosis in CRE-induced asthmatic mice. (A) Fluorescence assay on lung section for ROS generation. Magnification = 100 $\times$. Scale bar = 200 μ m. (B) Western blot of TOM20, TIM23, and GAPDH. (C) Relative density was calculated using Quantity One software. (D) Western blot of PINK1, GAPDH, Cyto-Parkin, β -Tubulin, Mito-Parkin, and VDAC1. (E) Relative density was calculated. (F) TUNEL assay of lung tissues. Magnification = 100 $\times$. Scale bar = 200 μ m. (G) Immunohistochemical staining of cleaved-caspase 3. Magnification = 100 $\times$. Scale bar = 50 μ m. (H) Western blot of cleaved caspase-3, Bax, Bcl-2, and GAPDH. (I) Relative density of Bax, Bcl-2, cleaved caspase-3 was calculated. * P < 0.05, ** P < 0.01 compared with the control group. # P < 0.05, ## P < 0.01 compared with CRE group.

30 min. Then 50 μ L of TUNEL solution was applied in the dark for 60 min at 37 $^{\circ}$ C. For cellular TUNEL assay, paraformaldehyde (4%) was used to fix treated cells for 30 min. After permeabilization with 0.3% of TritonX-100, TUNEL was added for 5 min of incubation. All samples were observed under Cy3 channels using Cytaion5.

Mitochondria and Cytoplasmic Protein Isolation. The isolations of cytoplasmic proteins and mitochondria were carried out using a cellular mitochondrial isolation kit (#C3606, Beyotime). Briefly, 50–100 mg of fresh lung tissues was homogenized in 10 volumes of precooled mitochondrial isolation reagent A on ice. The homogenate samples were centrifuged (1000 $\times$ g) for 5 min at 4 $^{\circ}$ C. Supernatant was further centrifuged (11 000 $\times$ g) at 4 $^{\circ}$ C for 10 min. Cell pellet was the isolated mitochondria. At this step, mitochondria-depleted cytoplasmic protein was prepared by the centrifugation of supernatant at 12 000 $\times$ g for 10 min at 4 $^{\circ}$ C.

Western Blot. Proteins were extracted, and 20 μ g of total proteins were separated by SDS-PAGE. Then incubation with primary antibodies, including anticaspase-3 (9664, CST, USA), β -tubulin (2128, CST, USA), caspase-3 (9662, CST, USA), voltage-dependent anion channel 1 (VDAC1, 4661, CST, USA), glyceraldehyde-3-phosphate dehydrogenase (GAPDH, 5174, CST, USA), PINK1 (DF7742, Affinity, USA), translocase of the outer membrane 20 (TOM20, 186735, Abcam, USA), TIM23 (230253, Abcam, USA), Parkin (A0968, Abclonal, USA), Nrf2 (12721, CST, USA), HO-1 (189491, Abcam, USA), Bax (182858, Abcam, USA), and Bcl-2 (17509, Abcam, USA), was performed. The secondary antibodies used were HRP-goat antirabbit antibody (S151, CST, USA) and HRP-antimouse antibody (S257, CST, USA). Protein levels were calculated by Quantity One software (BioRad, Hercules, CA, USA).

Flow Cytometry. Apoptosis was detected by Annexin-V Apoptosis Detection Kit I (BD Biosciences, CA, USA) and flow cytometry. For measuring the proportion of eosinophils in BALF and the proportion of IL-4 $^{+}$ CD4 $^{+}$ cells and IL-13 $^{+}$ CD4 $^{+}$ cells in mLN and spleen, the collected BALF cells and lymphocytes were first

stained with FITC-CD4 antibody (11–0041–82; Invitrogen, USA), PE-Siglec-F antibody (552126; BD, USA), APC-CD45.2 antibody (558702; BD Biosciences, USA), Percp-Cy5.5 CD3e antibody (45–003182; Invitrogen), and Percp-Cy5.5 CD11c (45–0114–82, Invitrogen, Carlsbad, CA, USA). Then cells were treated using the Intracellular Fixation and Permeabilization kit (88–8824–00; Invitrogen) and then stained with intracellular antibodies including PE-Cy7 IL-4 antibody (25–7042–41; Invitrogen, USA) and APC-IL-13 antibody (32007; Invitrogen, USA). The CD45.2 $^{+}$ CD11c $^{-}$ siglec-F $^{+}$ cells were defined as eosinophils, and the IL-4 $^{+}$ CD4 $^{+}$ cells and IL-13 $^{+}$ CD4 $^{+}$ cells were gated CD3e $^{+}$ CD4 $^{+}$ cells. All samples were measured by the Cytoflex flow cytometer (Beckman Coulter, Inc., CA, USA) and analyzed using Cytoexpert 2.4.

Immunofluorescence Assay. Cells were fixed, permeabilized, and stained with primary antibodies, including rabbit antimouse PINK1 (DF7742, Affinity, USA), rabbit antimouse Parkin (A0968, Abclonal, USA), and TOM20 (283317, Abcam, USA), overnight. After rinsing, cells were incubated with antibodies of AlexaFluor488 goat antirabbit (R37118, lifetechnologies, USA) and goat antimouse IgGHampL (Cy3) (97035, Abcam, USA) for 1 h at 37 $^{\circ}$ C. For translocation assay, mitochondrial marker MitoTracker Red (M7512, Thermo Fisher Scientific, Massachusetts, USA) probe was incubated with cells for 30 min at 37 $^{\circ}$ C, followed by incubation with anti-PINK1, anti-Parkin, and AlexaFluor488 goat antirabbit antibodies. Images were acquired by Cytaion5.

Molecular Docking. The crystal structures of PINK1 (PDB ID: 5OAT) and Parkin (PDB ID: 5CV9) were obtained from the protein database (PDB, <https://www.rcsb.org/>). For molecular docking, the Discovery Studio 2020 Server was used. Docking of the active sites of PINK1 was set as follows: the coordinates of center was x 1/4 89.5252, y 1/4 31.6317, and z 1/4 119.213, and the radius was 41.7 spheres. Docking of the active site of Parkin was set as follows: the coordinates of center was x 1/4 0.772764, y 1/4 23.4744, and z 1/4 30.2789, and the radius was 9.7 spheres.

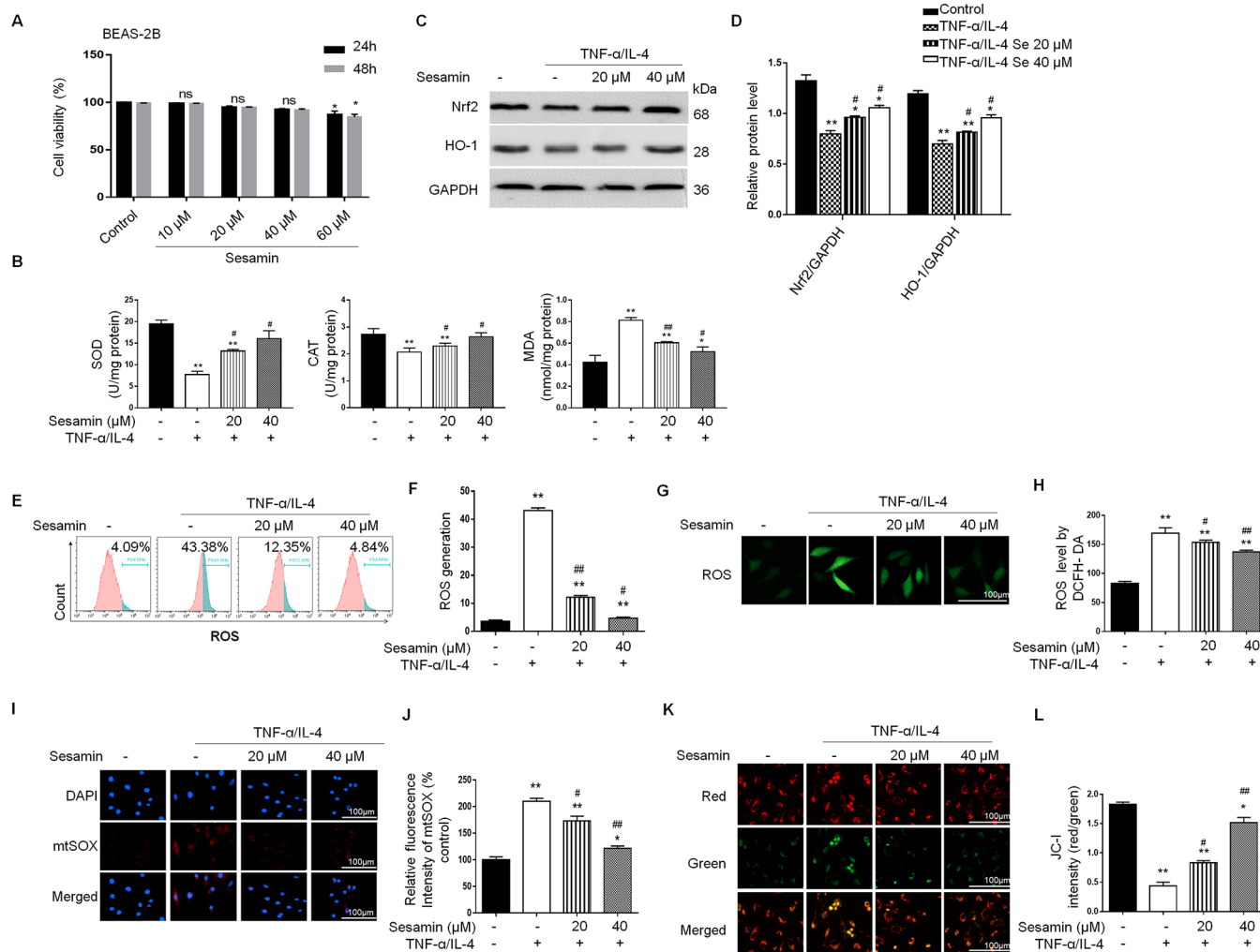


Figure 3. Sesamin inhibits mtROS production and up-regulates mitochondrial membrane potential in BEAS-2B cells exposed to TNF- α /IL-4. BEAS-2B cells (1×10^5) were treated with different concentration of sesamin (20 μ M and 40 μ M) for 1 h and then stimulated with TNF- α /IL-4 (10 ng/mL) for 24 h. (A) MTT assay assessing cell viability. (B) SOD, CAT, and MDA levels analyzed by ELISA. (C, D) HO-1 and Nrf2 expression by WB and their relative density. (E) ROS generation was detected using DCFH-DA (10 μ M) and with flow cytometry. (F) ROS generation was calculated and normalized to the control group. (G) ROS was detected using DCFH-DA (10 μ M) and observed under fluorescence microscope. Scale bar = 100 μ m. (H) Green fluorescence intensity was measured using Cytation 5 software 5.0 and normalized to the control group. (I) mtSOX production was performed using MitoSOX Dye (5 μ M). Magnification = 200 $\times$. Scale bar = 100 μ m. (J) Relative mtSOX fluorescence intensity was calculated and normalized to the control group. (K) Mitochondrial membrane potential was measured by JC-1 probe. Magnification = 100 $\times$. Scale bar = 100 μ m. (L) Ratio of red to green fluorescence intensity was calculated. * P < 0.05, ** P < 0.01 compared with the control group. # P < 0.05, ## P < 0.01 compared with TNF- α /IL-4 group.

Statistical Analysis. The data were expressed as the mean $\pm$ standard deviation of three independent experiments. The significance of differences between two groups was determined by Student t test of SPSS 19.0 software (IBM Co., Armonk, NY, USA). Multiple comparisons were performed using ANOVA or Wilcoxon's rank-sum test. A P -value < 0.05 was considered statistically significant.

RESULTS

Sesamin Inhibits Airway Inflammation, Goblet Cell Proliferation, and Th2 Development in Asthmatic Mice. HE staining of lung tissue displayed a great accumulation of inflammatory cells around airways in the asthma model induced by CRE, while sesamin treatment inhibited the infiltration of inflammatory cells (Figure 1B). Meanwhile, PAS staining showed that sesamin inhibited the increase in mucus secretion and goblet cell proliferation in the airway epithelium induced by CRE (Figure 1B). The proportion of eosinophils (CD45.2⁺ CD11c- siglec-F⁺) in BALF was greatly reduced

after sesamin treatment (Figure 1C,D). Moreover, the Th2 cytokines in BALF were obviously reduced by sesamin (Figure 1E). Serum levels of total and CRE-specific IgE were also significantly inhibited by sesamin (Figure 1F). In addition, in mLN and spleen, compared with the CRE group, sesamin treatment significantly inhibited the ratio of IL-4⁺CD4⁺ cells and IL-13⁺CD4⁺ cells in mLNs and the spleen (Figure 1H). The above results indicate that sesamin may reduce CRE-induced asthma by inhibiting airway inflammation, IgE levels, and Th2 development.

Sesamin Inhibits CRE-Induced Mitophagy and Mitochondrial Apoptosis in Asthmatic Mice. To study the regulation of sesamin on mitophagy in asthma, we analyzed the ROS levels in lung, and the expression of mitophagy proteins, including mitochondrial membrane proteins TOM20 and TIM23, and mitochondrial proteins PINK1 and Parkin. The results revealed that compared with the CRE group, sesamin

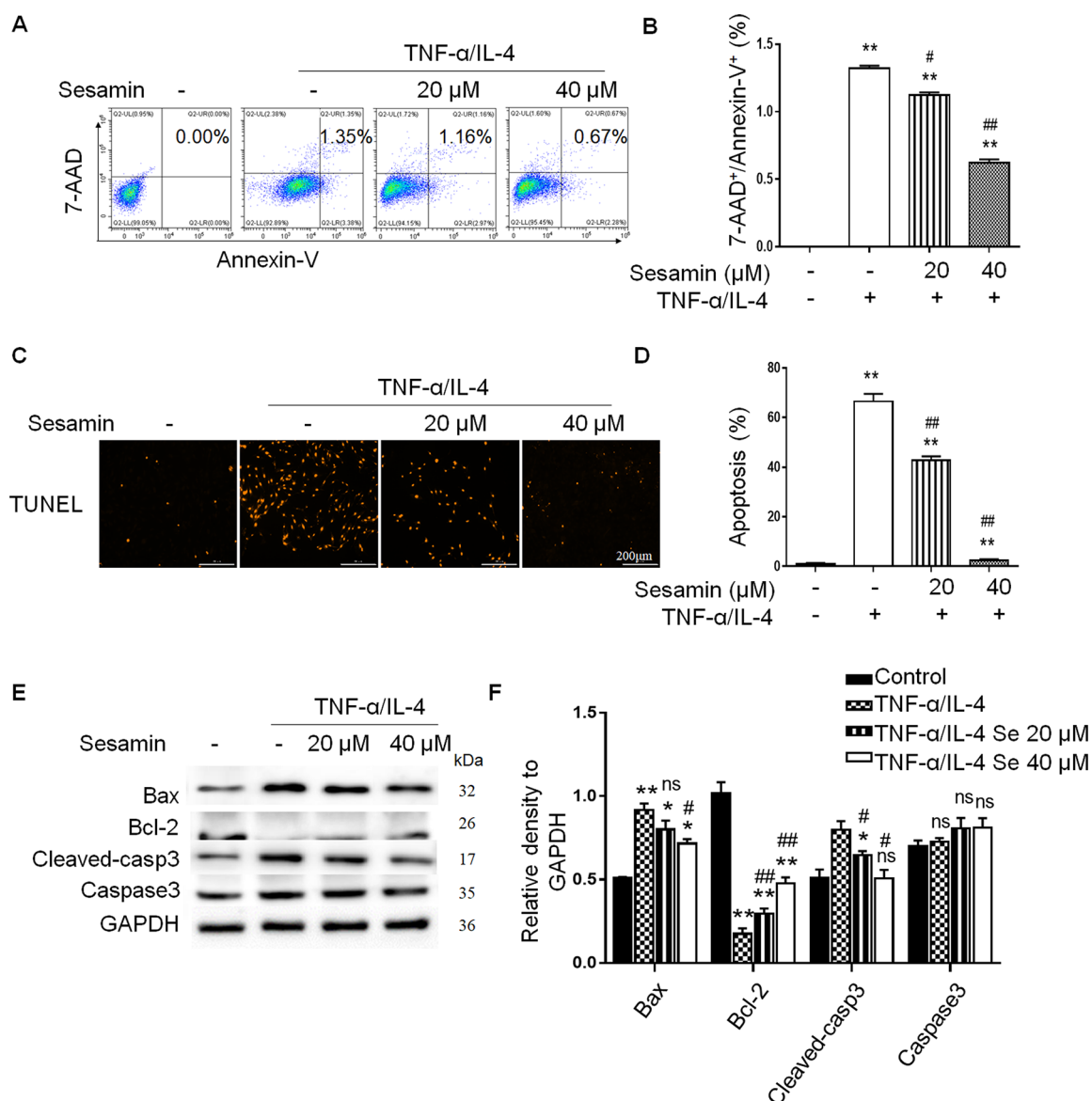


Figure 4. Sesamin inhibits TNF- α /IL-4 induced apoptosis in BEAS-2B cells. (A) Gating strategy of apoptosis using 7-AAD/Annexin-V by flow cytometry. (B) Ratio of 7-AAD⁺ to Annexin-V⁺ was calculated. (C) TUNEL assay was performed to evaluate apoptosis. Magnification = 100 $\times$. Scale bar = 200 μ m. (D) Ratio of apoptotic cells was evaluated. (E) Western blot of caspase-3, cleaved caspase-3, Bax, Bcl-2, and GAPDH. (F) Relative density of above proteins. * P < 0.05, ** P < 0.01 versus control group. # P < 0.05, ## P < 0.01 versus TNF- α /IL-4 group.

decreased ROS generation around the airway in lung section (Figure 2A), and obviously upregulated TOM20 and TIM23 levels, reflecting the reduction of mitophagy (Figure 2B,C). In addition, sesamin treatment reduced the level of PINK1 and mitochondrial Parkin but increased the cytoplasmic Parkin (Figure 2D,E), indicating that sesamin inhibited the transfer of Parkin from the cytoplasm to the mitochondria.

To verify the effect of sesamin on mitochondrial apoptosis in asthmatic mice, we performed TUNEL assay. Compared with the CRE group, we found that the red fluorescence in bronchial epithelial cells was obviously reduced after sesamin treatment (Figure 2F). Immunohistochemical results showed the expression of cleaved caspase-3 in lung tissue was obviously reduced after sesamin treatment (Figure 2G). Correspondingly, after sesamin treatment, the protein levels of cleaved caspase-3 and Bax in the lung tissue were obviously reduced, while the level of Bcl-2 increased (Figure 2H,I). These results

indicate that sesamin may reduce mitophagy and mitochondrial apoptosis in asthmatic mice.

Sesamin Inhibits ROS and mtROS Production and up-Regulates Mitochondrial Membrane Potential in BEAS-2B Cells Treated with TNF- α /IL-4. First, we examined cell viability using the MTT assay (Figure 3A). The results indicated that compared to control, cell viability after intervention with sesamin (10, 20, and 40 μ M) was not significantly different, suggesting that sesamin (10, 20, and 40 μ M) has no significant cytotoxicity to BEAS-2B cells. Then to determine whether sesamin reduced intracellular oxidative stress, we measured SOD, CAT, and MDA by ELISA. The results showed that sesamin significantly increased cellular SOD and CAT production but decreased MDA (Figure 3B). In addition, sesamin could significantly increase Nrf2 and HO-1 production after challenge with TNF- α /IL-4 (Figure 3C,D). Moreover, we detected ROS expressions by flow cytometry and fluorescence (Figure 3E–H). The results indicated that

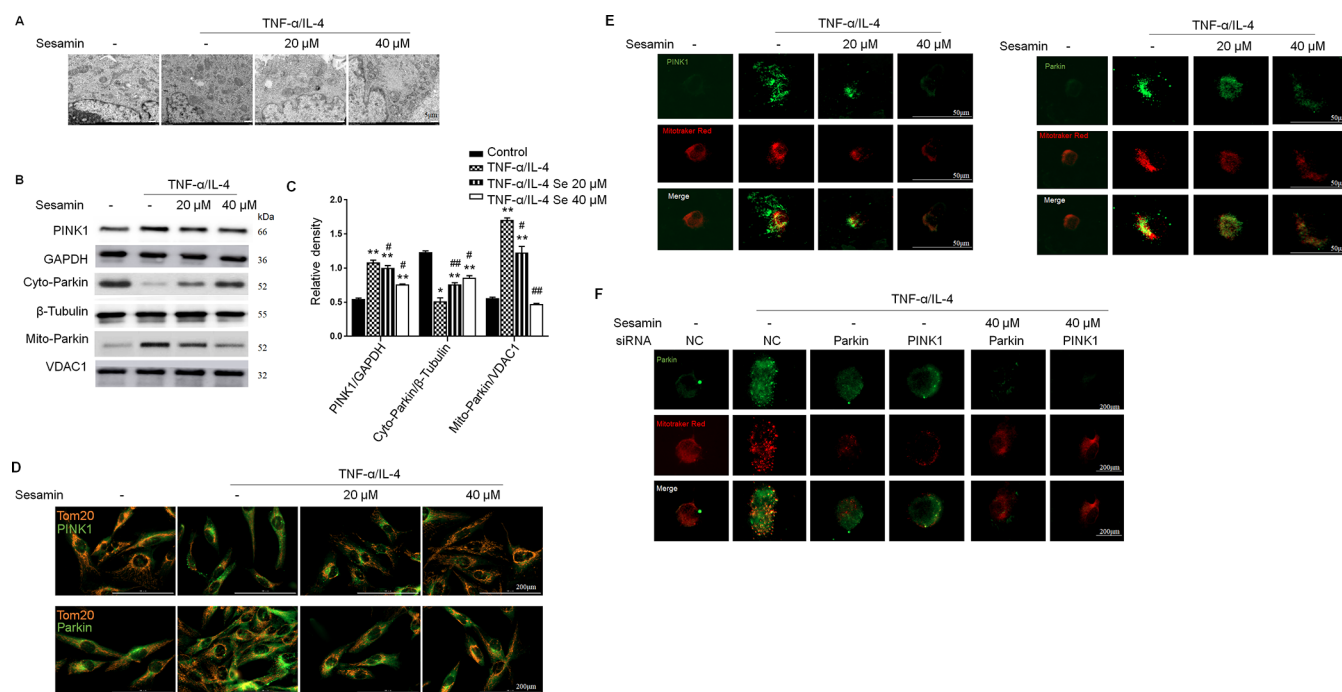


Figure 5. Sesamin reduces mitophagy in TNF- α /IL-4 BEAS-2B cells. (A) Mitochondrial morphology was observed by transmission electron microscope. Scale bar = 5 μ m. (B) Western blot analysis of PINK1, GAPDH, Cyto-Parkin, β -Tubulin, Mito-Parkin, and VDAC1 was performed. (C) Their relative density was calculated by Quantity One software. * P < 0.05, ** P < 0.01 versus control group. # P < 0.05, ## P < 0.01 versus TNF- α /IL-4 group. (D) Immunofluorescence assay was performed for PINK1 (green), TOM20 (orange), and Parkin (green). Magnification = 400 $\times$. Scale bar = 200 μ m. (E) Immunofluorescence assay was performed for MitoTrackerRed (red) and Parkin or PINK1 (green) colocalization. (F) Immunofluorescence assay was performed for MitoTrackerRed (red) and Parkin or PINK1 (green) colocalization after siRNA PINK1 or siParkin transfection. Images were acquired by Cytation 5. Magnification = 400 $\times$. Scale bar = 50 μ m.

sesamin efficiently reduced the production of ROS in cells. We also detected mtROS with mitoSOX Dye and found that sesamin significantly inhibited the production of mtROS (Figure 3I,J).

Excessive ROS production could result in mitochondrial dysfunction and decrease of mitochondrial membrane potential, which in turn causes PINK1/Parkin activation and triggers mitophagy.⁶ After JC-1 staining for mitochondrial membrane potential (MMP) assay, the ratio of red/green fluorescence decreased after TNF- α /IL-4 treatment, while sesamin significantly alleviated the decrease, implying the restoration of membrane potential (Figure 3K,L). The above results indicate that sesamin may protect mitochondrial functions by increasing SOD, CAT, Nrf2, and HO-1, decreasing MDA, reducing ROS/mtROS accumulation, and increasing mitochondrial membrane potential.

Sesamin Inhibits BEAS-2B Cell Apoptosis Induced by TNF- α /IL-4. Increased ROS/mtROS can stimulate the death receptor pathway and induce apoptosis.⁴ To explore whether sesamin can reduce the apoptosis induced by TNF- α /IL-4 exposure in BEAS-2B cells, we performed apoptosis assay using 7-AAD/Annexin-V dye. We suggested that sesamin treatment effectively inhibited the apoptosis of bronchial epithelial cells (Figure 4A,B). Similarly, TUNEL assay also revealed that sesamin significantly inhibited cell apoptosis (Figure 4C,D). The protein levels of mitochondrial apoptotic proteins, cleaved caspase-3, and Bax reduced, while the expression of Bcl-2 was increased (Figure 4E,F). The above results indicate that sesamin could be able to suppress the apoptotic changes of bronchial epithelial cells exposed of TNF- α /IL-4.

Sesamin Could Reduce Mitophagy *In Vitro* Induced by TNF- α /IL-4.

The decrease of mitochondrial membrane potential can induce mitophagy, which is usually mediated by the PINK1 and Parkin pathways.⁷ Ultrastructural changes of BEAS-2B cells were analyzed by transmission electron microscopy (Figure 5A). The results revealed that sesamin reversed the mitochondrial swelling and degeneration in BEAS-2B cells after challenge. Next, we measured PINK1, as well as changes in mitochondrial and cytoplasmic Parkin with Western blot (Figure 5B,C), which showed that compared with stimulation of cells alone, PINK1 and mitochondrial Parkin in BEAS-2B cells treated with sesamin were obviously decreased. However, the expression of Parkin in the cytoplasm increased significantly. In addition, we also detected the levels of PINK1 and Parkin by cellular immunofluorescence. We observed that PINK1 and Parkin were obviously enhanced by TNF- α /IL-4 stimulation alone, while sesamin inhibited this enhancement (Figure 5D). Then we observed the translocation of PINK1 and mitochondrial Parkin under TNF- α /IL-4 stimulation and treated them with different doses of sesamin. The results revealed that the translocation of PINK1 and mitochondrial Parkin was markedly decreased in BEAS-2B cells treated with sesamin compared to cells treated with TNF- α /IL-4 alone. This suggests that sesamin can inhibit the translocation of PINK1 and mitochondrial Parkin from the cytoplasm to the mitochondria (Figure 5E). Furthermore, after silencing PINK1 or Parkin, sesamin significantly decreased their translocation (Figure 5F). These data suggest that sesamin might alleviate asthmatic airway inflammation through inhibiting PINK1/Parkin-mediated mitophagy.

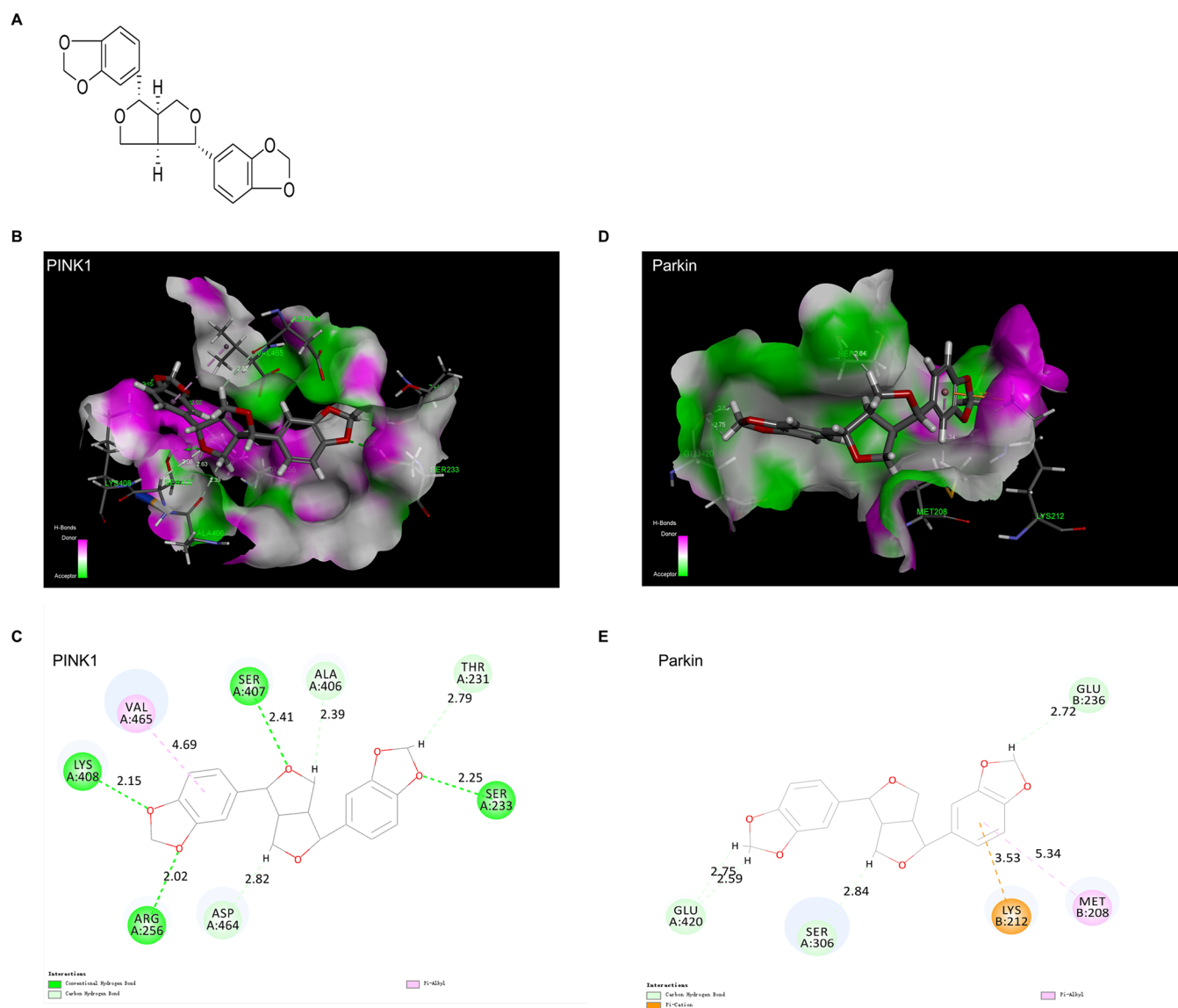


Figure 6. Docking results of sesamin with PINK1 (PDB ID: 5OAT) and Parkin (PDB ID: 5C9 V). (A) Chemical structures of sesamin. (B) Key residues of binding sites in PINK1 for binding with sesamin. (C) Molecular docking model in 2D showing the binding of sesamin with PINK1. (D) Key residues of binding site of Parkin for binding with sesamin. (E) Molecular docking model in 2D showing the binding of sesamin with Parkin.

Molecular Docking. To explore the binding of sesamin with PINK1 and Parkin, we conducted molecular docking. [Figure 6A](#) shows the chemical structure of sesamin. The PINK1 molecule formed four conventional hydrogen bonds and three carbon–hydrogen bonds with sesamin, which were located at Lys408, Arg256, Asp464, Ser233, Thr231, and Ala406, respectively ([Figure 6B,C](#)). Similarly, Parkin and sesamin formed three carbon–hydrogen bonds and other chemical bonds ([Figure 6D,E](#)), locating at Glu420, Ser306, Glu236, Lys212, and Met208, respectively. The docking score of PINK1 was 32.8759 kcal/mol, and that of Parkin was 28.1107 kcal/mol.

■ DISCUSSION

In this study, we explored the mechanism of sesamin in influencing mitophagy and mitochondrial apoptosis. We revealed that sesamin not only inhibited CRE-induced infiltration of airway eosinophils, serum total IgE, CRE-specific IgE, and BALF Th2 cytokines. Furthermore, sesamin also

inhibited the Th2 expression in mLN and spleen. Sesamin inhibited the PINK1 and mitochondrial Parkin expression and mitochondrial apoptosis in the lung tissue of asthmatic mice. *In vitro*, sesamin effectively increased SOD, CAT, Nrf2, and HO-1 levels, decreased MDA level, and inhibited the production of ROS/mtROS in BEAS-2B cells induced by TNF- α /IL-4, increased the mitochondrial membrane potential, and reduced the expression of cleaved caspase-3 and Bax, and PINK1/Parkin, thus inhibiting mitophagy and mitochondrial apoptosis.

Excessive ROS and oxidative stress are related to CRE-induced bronchial epithelial cell damage and the development of asthma.²² Studies have shown that antioxidant defense mechanisms can protect CRE-induced oxidative lung injury and airway inflammation in asthmatic mice.^{4,23} Sesamin is lignan extracted from sesame seeds, which has anti-inflammatory and antioxidant effects in various diseases.^{24,25} Gouveia et al.²⁵ found that the antioxidant effect of sesamin may regulate the concentration of vitamin C and vitamin E in the blood, and antioxidant enzymes, like SOD, glutathione,

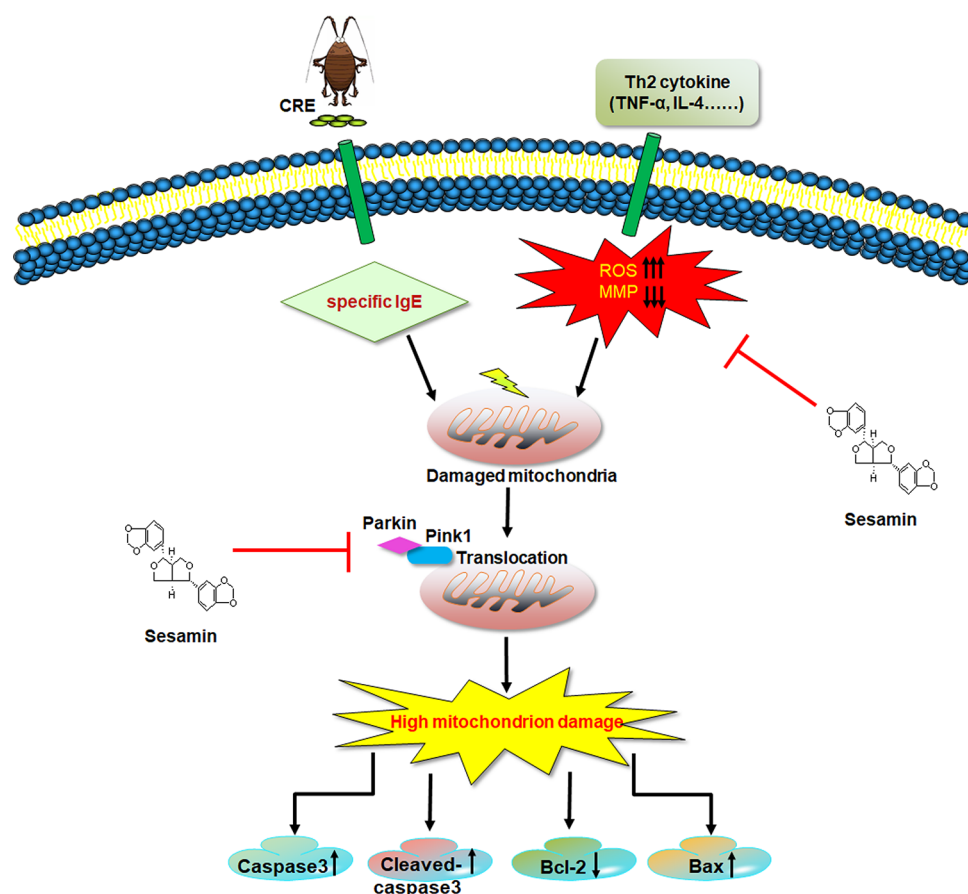


Figure 7. Sesamin may alleviate airway inflammation in asthma by inhibiting mitophagy and mitochondrial apoptosis. *In vivo*, CRE could activate PINK1/Parkin-mediated mitophagy, affecting apoptosis of lung airway epithelial cells. *In vitro*, TNF- α /IL-4 could damage mitochondria by increasing reactive oxygen species (ROS) generation and decreasing mitochondrial membrane potential (MMP), which could further trigger mitophagy through PINK1 and Parkin pathway and promote apoptosis in BEAS-2B cells. Sesamin could inhibit the above manifestations by clearing ROS generation *in vivo* and *in vitro*. Additionally, this effect might be achieved by binding of sesamin to PINK1 and Parkin. Overall, sesamin may alleviate airway inflammation in asthma by inhibiting mitophagy and mitochondrial apoptosis.

glutathione peroxidase, CAT, and the markers of oxidative stress, such as thiobarbituric acid responsive substances and MDA. Consistently, we found that sesamin up-regulated SOD and CAT but decreased MDA in CRE-induced asthma. Moreover, sesamin also up-regulated Nrf2 and HO-1 expression. Research suggested that Nrf2 and HO-1 can regulate oxidative stress and has a non-negligible role in asthma development. Deficiency of Nrf2 can cause asthma exacerbation.²⁶ Nrf2 initiates downstream HO-1 expression, which is considered as an important endogenous antioxidant and cytoprotective enzyme. Thus, sesamin could inhibit asthma inflammation through inducing antioxidative enzymes, thereby inhibiting oxidative stress and tissue damage. In addition, sesamin has been reported to protect human colon adenocarcinoma cell line from oxidative stress damage and inflammation by inhibiting ROS generation in ulcerative colitis and enhancing the activation of Nrf2 and AKT/ERK.¹³ As we all know, ROS mainly come from mitochondria.⁴ Therefore, reducing the level of mtROS may be an effective strategy to suppress airway inflammation. Our data suggested that sesamin could attenuate ROS in lung tissues and mtROS production in TNF- α /IL-4 stimulated BEAS-2B cells. On the basis of the above findings, we hypothesize that the sesamin may reduce airway inflammation and oxidative stress through inhibiting ROS.

Mitochondrial dysfunction regulated by ROS can trigger the mitochondrial apoptosis pathway.⁴ Excessive production of ROS can cause serious damages including affecting the mitochondrial membrane potential.⁴ MMP decrease is the initial event in the apoptotic cascade, which is followed by the release of cytochrome c and sensitization of the caspase proteins.²⁷ In addition, inhibiting ROS production can up-regulate mitochondrial membrane potential and prevent apoptosis induced by Th2 cytokines.²⁸ The antiapoptotic effects of sesamin have been widely reported.^{15,16} Consistently, our data showed that sesamin inhibited TNF- α /IL-4-stimulated MMP in BEAS-2B cells, indicating the inhibitory role of sesamin on the mitochondrial apoptosis. Furthermore, we found that sesamin attenuated cell apoptosis, including the expression of Bax and cleaved caspase-3, while enhanced the expression of Bcl-2 both *in vivo* and *in vitro*. Therefore, we suppose that sesamin might reduce airway inflammation partly through the regulation of mitochondrial apoptotic pathway. Recently, it has been shown that NLRP3 activation has extensive and tight interactions with mitochondrial damage and apoptosis.²⁹ ATP/purinergic receptor-7 (P2 $\times$ 7)/NLRP3 inflammasome activation aggravates airway inflammation in asthma.³⁰ Some natural compounds, including sesamin, could exert therapeutic effects on cardiac injury through the SIRT1/NLRP3 signaling pathway.³¹ However, the effect of sesamin on

NLRP3 activation in asthma is unknown and needs further investigation.

Mitophagy is characterized as a process by which mitochondria are degraded by autophagy to maintain cellular homeostasis,³² which often occurs in airway inflammation and remodeling mediated by environmental pollutants and allergens.³³ However, dysregulated mitophagy in turn induces an inflammatory response, leading to chronic inflammation.⁴ Tsubouchi et al.³⁴ revealed that PINK1-mediated enhancement of mitophagy associated with the pathogenesis of chronic obstructive pulmonary disease. In addition, Jin et al.³⁵ demonstrated that excessive activation of mitophagy may be detrimental to immune cell homeostasis. Therefore, the intervention of mitophagy may help alleviate the development of asthma. Indeed, 3-MA and Ca²⁺/ox-CaMKII inhibitor could attenuate allergic asthma *in vivo* and *in vitro*.⁴ Mitophagy is mainly mediated by PINK1/Parkin.³⁵ Under normal conditions, the PINK1 could translocate into the inner membrane of mitochondria and then is cleaved by the peptidases and proteases of mitochondria. However, under stress conditions, PINK1 accumulates on the outer membrane mitochondria and subsequently promotes the recruitment of Parkin and its ubiquitination.⁶ Lazarou et al.³⁶ showed that the recruitment of PINK1 and Parkin promoted the transfer of autophagy receptors to the mitochondria, and subsequently initiated mitophagy by recruiting ULK1. Recently, Dimasuay et al.³⁷ confirmed that Parkin could promote the release of mitochondrial DNA and aggravate airway inflammation in asthma. Parkin can also inhibit p53 and activate NF- κ B to enhance lung injury stimulated by lipopolysaccharide³⁸ and rheumatoid arthritis.³⁹ We learned that sesamin efficiently inhibited the PINK1 and mitochondrial Parkin expression in the lungs of asthmatic mice and the translocation in BEAS-2B cells exposed to TNF- α /IL-4. The translocation was further inhibited by sesamin after siPINK1 or siParkin transfection. These results reveal that sesamin might alleviate asthmatic airway inflammation through inhibiting PINK1/Parkin-mediated mitophagy. At present, the debate between mitophagy and apoptotic cell death still exists.⁴⁰ It is known that mitophagy was up-regulated in asthma.⁴ The mitochondrial ox-CaMKII inhibitors can inhibit mitophagy, thereby reducing asthma development.⁴ The production of mtROS can trigger apoptosis in asthma, while inhibition of apoptosis can also alleviate asthma.²⁸ However, the direct action of mitophagy mediated by PINK1/Parkin to apoptotic cascade in asthma still needs to be further explored. In addition, we analyzed the binding of sesamin with PINK1 and Parkin with molecular docking, which is an important method for learning how chemical compounds interact with their molecular targets in the drug development area.⁴¹ The results may provide supporting evidence that sesamin could bind to PINK1 and Parkin protein. Together, based on the animal and cellular experiments, we believe that sesamin may exert its biological effects partially as an inhibitor by targeting PINK1 or Parkin.

Our results indicate that sesamin may reduce airway inflammation by inhibiting mtROS, PINK1/Parkin-mediated mitophagy, and mitochondrial apoptosis both *in vivo* and *in vitro* (Figure 7). Moreover, there is a lack of data on the bioavailability of sesamin in humans, which is worthy of an in-depth discussion. Sesamin may serve as a novel inflammation inhibitor of asthma.

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Notes

The authors declare no competing financial interest.

ABBREVIATIONS USED

CRE, cockroach extract; ROS, reactive oxygen species; BALF, bronchoalveolar lavage fluid; mtROS, mitochondrial ROS; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; PINK1, PTEN-induced putative kinase 1; Nrf2, nuclear factor erythroid 2 related factor 2; HO-1, heme oxygenase 1; SOD, superoxide dismutase; Bcl-2, B-cell lymphoma-2; Bax, BCL-2-associated X; mLN, mediastinal lymph nodes; MDA, malondialdehyde; CAT, catalase; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide

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