

Fucoidan attenuates airway remodeling in asthmatic mice

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Abstract. Airway remodeling is a pathological hallmark of asthma that is difficult to reverse and effective therapeutic interventions remain limited. The present study investigated whether fucoidan, a natural sulfated polysaccharide derived from seaweed, attenuates airway remodeling in ovalbumin (OVA)-induced asthmatic mice. In total, 40 female Kunming mice were randomly assigned to four groups (n=10/group): Asthma, budesonide, fucoidan and control. Asthma was induced by OVA sensitization and challenge. Budesonide was administered via nebulization, while fucoidan was given by oral gavage prior to OVA challenge. Bronchoalveolar lavage fluid was collected for total and differential cell count and levels of interleukin-21, thymic stromal lymphopoietin, α -smooth muscle actin and collagen I in the lavage fluid were measured by ELISA. Lung sections were evaluated by hematoxylin and eosin staining for histopathological changes and immunohistochemistry for protein expression. Fucoidan significantly alleviated asthma-like behavior, including scratching, shortness of breath and restlessness, and reduced total cells, neutrophils, lymphocytes and eosinophils in bronchoalveolar lavage fluid compared with the OVA group ($P<0.05$). Fucoidan decreased the elevated levels of interleukin-21, thymic stromal lymphopoietin, α -smooth muscle actin and collagen I ($P<0.05$), with effects comparable with those of budesonide ($P>0.05$). Histological examination revealed that fucoidan attenuated

peribronchial inflammatory infiltration, bronchial wall thickening and luminal narrowing. Immunohistochemical analysis confirmed that fucoidan suppressed the expression of IL-21, thymic stromal lymphopoietin, α -smooth muscle actin and collagen I in lung tissue, as reflected by significantly decreased integrated optical density values relative to the model group ($P<0.05$). Collectively, these findings indicated that fucoidan attenuates airway remodeling in asthmatic mice, which may be associated with downregulation of interleukin-21 and thymic stromal lymphopoietin. Although the underlying mechanisms and clinical applicability require validation, the present results suggest that fucoidan merits investigation as a potential candidate for asthma therapy.

Introduction

Asthma is a heterogeneous disease with chronic airway inflammation as its key pathology, characterized primarily by recurrent cough and wheezing, and accompanied by variable airflow limitation (1). Airway remodeling refers to structural changes resulting from chronic airway inflammation, including epithelial injury, smooth muscle hyperplasia and hypertrophy, abnormal extracellular matrix (ECM) deposition, subepithelial fibrosis and angiogenesis (2-4). These structural alterations can lead to irreversible airflow limitation and are key drivers of asthma progression from controllable symptoms to refractory and severe forms associated with long-term complications such as chronic obstructive pulmonary disease (5). Therefore, elucidating its pathogenesis and preventing airway remodeling are key objectives in asthma management.

Previous studies have shown that asthma airway remodeling results from persistent inflammatory injury and repair responses (6-8). The pathological processes primarily involve imbalance between abnormal ECM deposition and degradation, as well as proliferation and phenotypic changes in airway smooth muscle (ASM). IL-21 and thymic stromal lymphopoietin (TSLP) are key cytokines that drive chronic airway inflammation and promote ECM deposition, ASM proliferation and hypertrophy (9,10). The expression levels of α -smooth muscle actin (SMA) and collagen (Col)-I are important markers for evaluating ASM activation and ECM deposition (11). Thus, targeting these molecules and investigating their regulatory mechanisms provide a valid approach for studying anti-remodeling strategies.

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Fucoidan, a natural sulfated polysaccharide extracted from brown algae, has attracted attention due to its broad spectrum of biological activities, including anti-inflammatory, immunomodulatory, antitumor and antifibrotic effects (12,13). Studies indicate that fucoidan modulates immune cell function and inhibits the production of inflammatory mediators (14–16). These properties align with the hyperactivated immune-inflammatory state and fibrotic processes in asthma pathology. Based on this, it was hypothesized that fucoidan may alleviate airway remodeling in asthma by regulating key remodeling-associated factors such as IL-21, TSLP, α -SMA and Col-I.

Previous studies on fucoidan in asthma have primarily focused on inflammatory modulation (17–19), leaving its effects on structural airway remodeling, particularly via IL-21/TSLP pathway, largely unexplored. Budesonide is a first-line inhaled corticosteroid for asthma with established efficacy in mitigating airway remodeling. To the best of our knowledge, however, a direct comparison between fucoidan and budesonide for remodeling outcomes under identical experimental conditions has not been reported.

In the present study, an asthmatic mouse model was established by OVA (ovalbumin) sensitization and challenge. Behavioral changes, lung histopathology, ELISA and immunohistochemistry (IHC) were used to systematically evaluate the effects of fucoidan on asthma symptoms, airway structural remodeling and the expression levels of IL-21, TSLP, α -SMA and Col-I in bronchoalveolar lavage fluid (BALF) and lung tissue. The aim was to verify the role of fucoidan in airway remodeling in asthmatic mice and explore its potential mechanisms, providing experimental evidence for the development of potential asthma therapeutic strategies.

Materials and methods

Animals. Specific pathogen-free (SPF) female Kunming (KM) mice (age, 6–8 weeks; weight, 19–24 g) were purchased from the Shandong Qingdao Experimental Animal Center and housed under standard SPF conditions (temperature, 22–24°C; relative humidity, 50–60%; 12-h light/dark cycle) in the Science and Education Building, West Coast Campus of the Affiliated Hospital of Qingdao University, Qingdao, Shandong, China [certificate no. scxk (Lu) 20130010]. This outbred strain was selected for its use in OVA-induced asthma models (20), genetic heterogeneity approximating human diversity and practical advantages including ready availability, cost-effectiveness, strong disease resistance, good adaptability and high reproductive and survival rates (21). The animal experiments were approved by the Experimental Animal Ethics Committee of the Affiliated Hospital of Qingdao University (approval no. AHQU-MAL20150101QYL). All procedures adhered to relevant Chinese national regulations on laboratory animal welfare and ethics and complied with the American Veterinary Medical Association Guidelines for the Euthanasia of Animals (22,23). Every effort was undertaken to minimize animal suffering and decrease the number of animals used.

Asthmatic mouse model. In total, 40 mice were randomly divided into four groups ($n=10$ /group): Asthma model (OVA), budesonide treatment group (OVA + budesonide), fucoidan (OVA + fucoidan) and control group. Mice were housed in a

specific pathogen-free environment with free access to food and water. An asthma model was induced by intraperitoneal OVA (Sigma-Aldrich; Merck KGaA) sensitization and nebulized OVA challenge, as previously described (24). Briefly, mice in the OVA, OVA + budesonide and OVA + fucoidan groups were intraperitoneally injected with a sensitization solution containing 10 μ g OVA and 1.6 mg aluminum hydroxide in 0.1 ml PBS on days 1, 8 and 15. On day 22 to 35, mice in the OVA group were nebulized with 1% OVA solution for 30 min daily. Mice in the OVA + budesonide (AstraZeneca, UK) group received budesonide nebulization (200 μ g in 3.6 ml saline) 1 h before each OVA challenge. Based on previous studies (25–27), mice in the OVA + fucoidan group were administered fucoidan (50 mg/kg; Sigma-Aldrich; Merck KGaA) by gavage 1 h before each challenge. Control mice received saline instead of OVA during both sensitization and challenge phases. All mice survived the experimental period. All mice were euthanized 24–48 h after the last challenge for sample collection.

Collection and analysis of bronchoalveolar lavage fluid (BALF). Prior to sample collection, all mice were anesthetized with intraperitoneal pentobarbital sodium (50 mg/kg). The depth of anesthesia was confirmed by the absence of pedal withdrawal reflex. Euthanasia was performed by exsanguination via cardiac puncture and ~1 ml blood was collected. This was followed by cervical dislocation to ensure death. The cessation of respiration and heartbeat, along with the absence of pain reflex, was used to confirm death.

BALF was collected immediately. Briefly, tracheal intubation was performed and the lungs were lavaged with 0.8 ml ice-cold PBS. The lavage process was repeated three times and the fluid was recovered. The pooled BALF was centrifuged at 500 $\times$ g for 10 min at 4°C. The supernatant was separated and stored at -80°C for subsequent analysis. The cell pellet was resuspended in PBS and cytospin smears were prepared using a Cytospin centrifuge at 32 $\times$ g for 4 min at room temperature. The smears were air-dried and stained with Wright-Giemsa stain at room temperature for 1–2 min, followed by the addition of an equal volume of phosphate buffer (pH 6.4–6.8) for 3–5 min. The slides were rinsed with distilled water, air-dried. Total cell and differential counts of eosinophils, lymphocytes and neutrophils were performed using a hemocytometer under a light microscope. The levels of IL-21, TSLP, α -SMA and Col-I in the BALF supernatant were measured using ELISA kits (R&D Systems) according to the manufacturer's instructions. Although α -SMA is primarily an intracellular protein and Col-I is an insoluble ECM component, their detection in BALF supernatant has been reported previously (11). During remodeling, activated myofibroblasts expressing α -SMA shed into the airway lumen, releasing this protein into BALF (28), while Col-I undergoes dynamic turnover generating soluble fragments detectable in airway fluid (29).

Lung histopathology. The right lung tissue was fixed in 4% paraformaldehyde at 4°C for 24 h, embedded in paraffin and sectioned (4 μ m thickness). For each animal, three non-consecutive sections (distance, ≥ 50 μ m) were selected for hematoxylin and eosin (H&E) staining and IHC to avoid sampling bias. For H&E staining, sections were deparaffinized in xylene, rehydrated through a descending ethanol series,

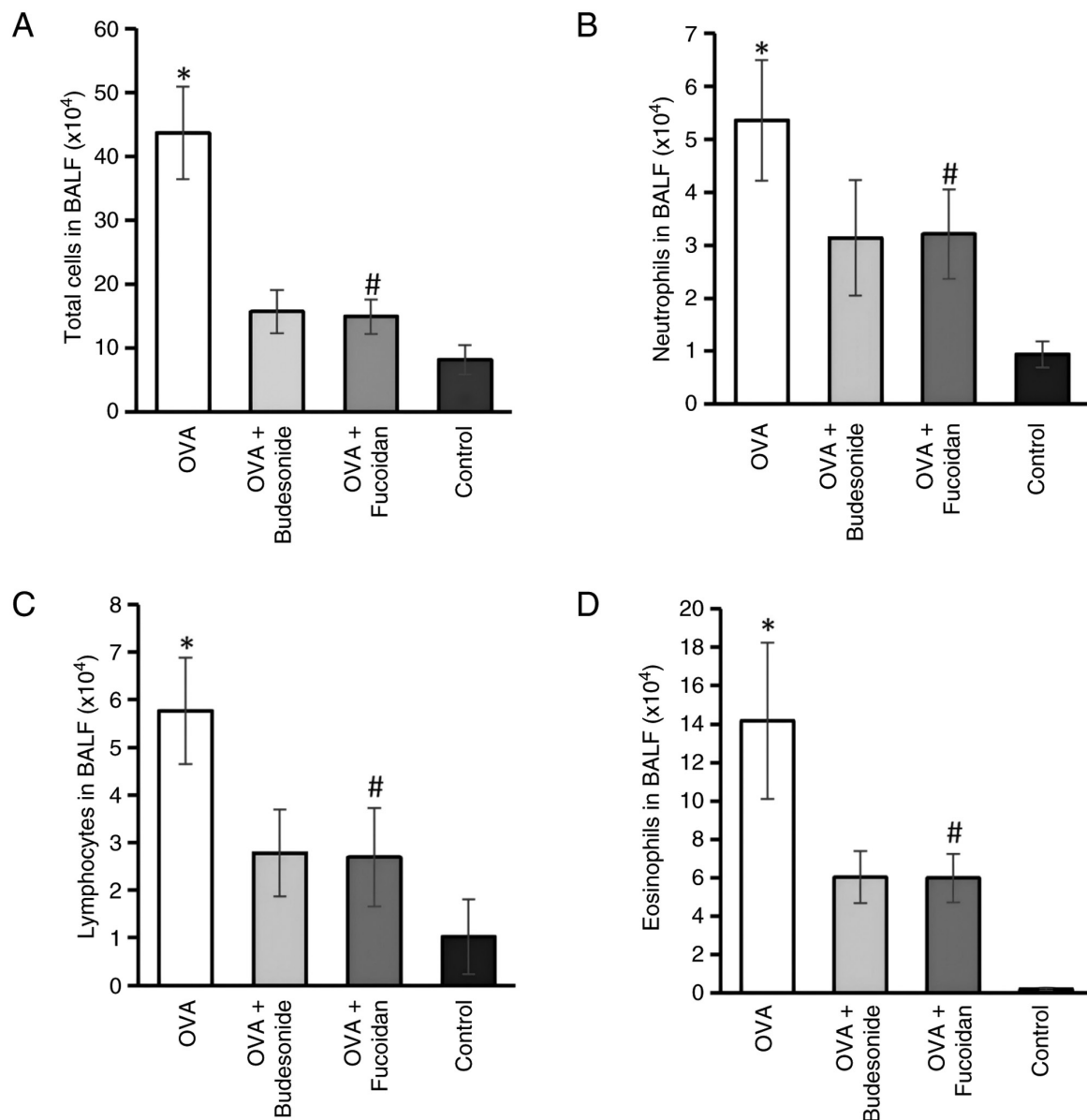


Figure 1. Inflammatory cell counts in BALF of asthmatic mice following fucoidan treatment. (A) Total cells, (B) neutrophils, (C) lymphocytes and (D) eosinophils in BALF of mice. * $P < 0.05$ vs. Control; # $P < 0.05$ vs. OVA. BALF, bronchoalveolar lavage fluid; OVA, ovalbumin.

stained with hematoxylin for 10 min at room temperature, differentiated, counterstained with eosin for 1 min at room temperature, dehydrated, cleared and mounted. Sections were stained with H&E to observe general pathological changes such as inflammatory cell infiltration around airways and vessels, airway wall thickness and lumen narrowing. For airway wall thickness quantification, five randomly selected bronchioles per section were imaged at x400 magnification. The airway wall area (Wat) and the perimeter of the basement membrane (Pbm) were measured using Image-Pro Plus software (version 6.0; Media Cybernetics, Inc.). Airway wall thickness was expressed as the ratio of Wat to Pbm. All measurements were performed using a uniform protocol. Sections were examined under a light microscope (Olympus, Japan). IHC was performed to detect the expression of IL-21, TSLP, α -SMA and Col-I in lung tissues. After deparaffinization in xylene, rehydration through a graded ethanol series and antigen retrieval was performed in citrate buffer

(pH 6.0) at 92–96°C for 15 min, endogenous peroxidase was blocked with 3% hydrogen peroxide at room temperature for 10 min, followed by blocking with goat serum (ZSGB-BIO) at room temperature for 15 min. Sections were incubated overnight at 4°C with the following primary antibodies: Rabbit anti-IL-21 polyclonal antibody (Bioss, bs-2621R; 1:200 dilution), rabbit anti-TSLP polyclonal antibody (Bioss, bs-0449R; 1:200 dilution), rabbit anti- α -SMA polyclonal antibody (Bioss, bs-10196R; 1:200 dilution), and rabbit anti-Col-I polyclonal antibody (Bioss, bs-10423R; 1:500). The next day, sections were incubated with a biotin-labeled goat anti-rabbit IgG working solution (ZSGB-BIO, ZB-2010; 1:200 dilution) at room temperature for 15 min, followed by incubation with a horseradish peroxidase-labeled streptavidin working solution (ZSGB-BIO, Beijing, China) at room temperature for 15 min. Color development was performed with a DAB kit (ZSGB-BIO, Beijing, China) and counterstaining with hematoxylin at room temperature for 2 min. For integrated optical density (IOD)

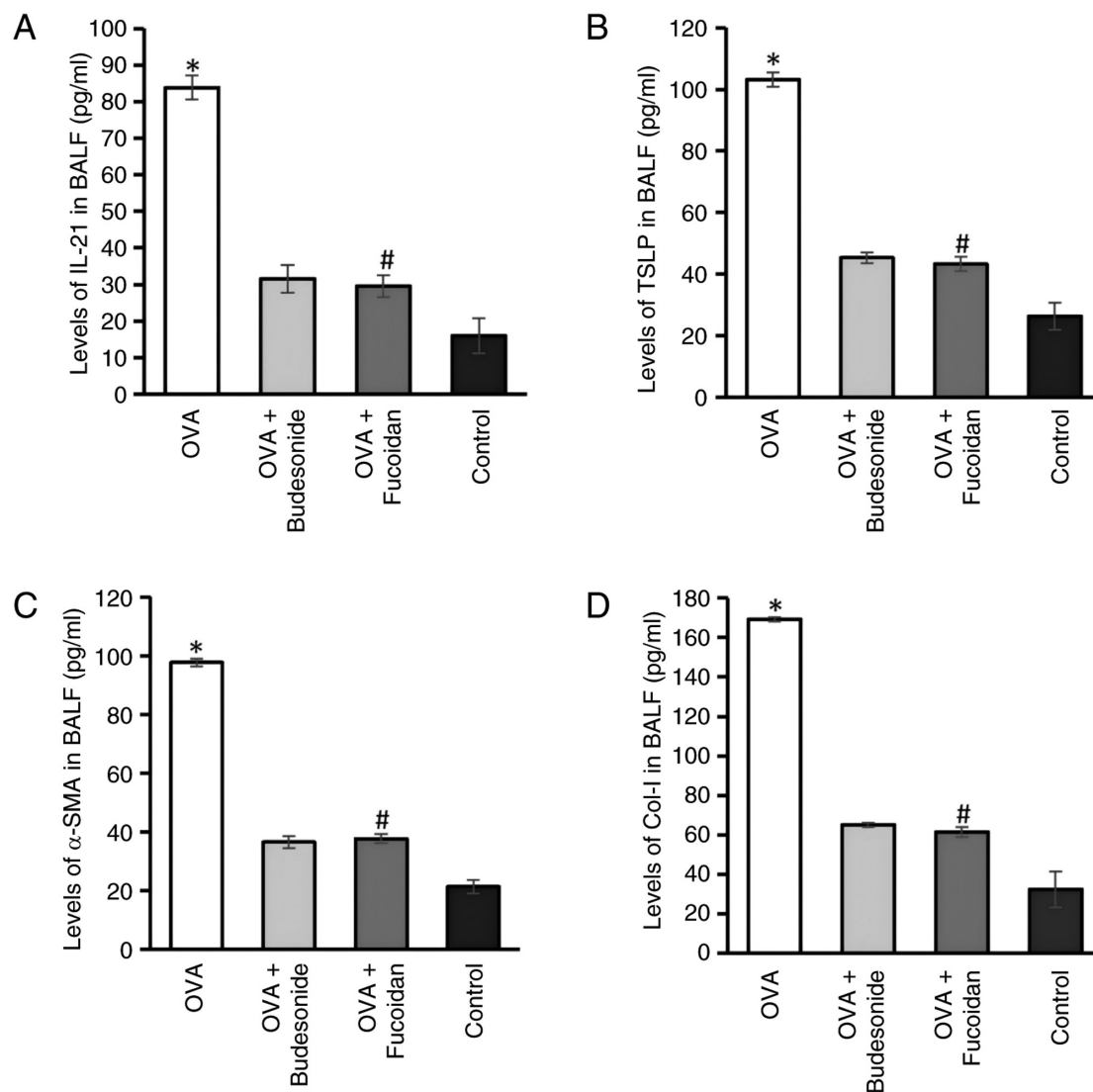


Figure 2. Levels of remodeling-associated factors in BALF of asthmatic mice after fucoidan treatment. The levels of (A) IL-21, (B) TSLP, (C) α -SMA and (D) Col-I in BALF were assayed by ELISA. * $P < 0.05$ vs. Control; # $P < 0.05$ vs. OVA group. BALF, bronchoalveolar lavage fluid; OVA, ovalbumin; TSLP, thymic stromal lymphopoietin; SMA, smooth muscle actin; Col, collagen.

quantification, five random high-power fields (magnification, x200) were captured under light microscopy. The IOD of positively stained areas (yellowish-brown) was measured using Image-Pro Plus (version 6.0; Media Cybernetics, Inc.) with a uniform threshold applied to all images. The mean IOD/unit area was calculated for each sample.

Statistical analysis. Normality was assessed using the Shapiro-Wilk test and homogeneity of variance was assessed using Levene's test. Data are presented as the mean $\pm$ SD from 10 independent biological replicates/group. All analyses were performed using SPSS 22.0 (IBM Corp.). For multiple group comparisons, one-way ANOVA was used when data met the assumptions of normality and homogeneity of variance, followed by Tukey's honestly significant difference post hoc test for pairwise comparisons. When variances were unequal, the Games-Howell post hoc test was applied. For non-normally distributed data, the Kruskal-Wallis test was used, followed by pairwise comparisons using the Mann-Whitney U test with

Bonferroni correction. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Fucoidan ameliorates asthma-like symptoms in mice. OVA-challenged mice exhibited typical asthma-like symptoms such as scratching, shortness of breath and restlessness (data not shown). Control mice showed no notable behavioral or respiratory changes. Mice in the OVA + fucoidan group exhibited markedly alleviated behavioral symptoms compared with the OVA group, with an extent of improvement similar to that observed in the OVA + budesonide group.

Fucoidan decreases inflammatory cell counts in BALF. Cell count analysis of BALF (Fig. 1) revealed that the total cell number in the OVA group was $43.67 \pm 7.26 \times 10^4/\text{ml}$, which was significantly higher than that in the control group ($8.18 \pm 2.28 \times 10^4/\text{ml}$; $P < 0.05$). Neutrophils, lymphocytes and eosinophils were also markedly elevated in the OVA group

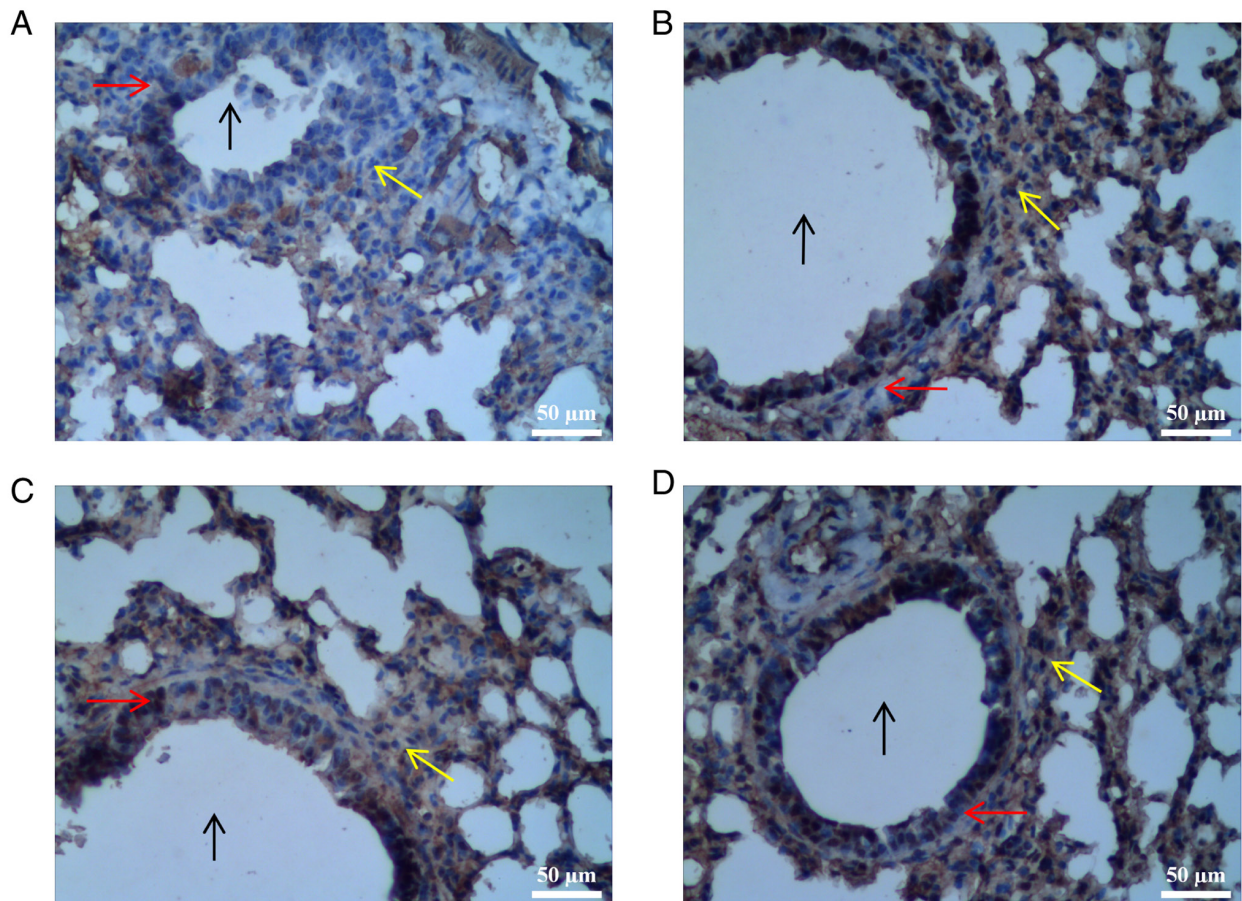


Figure 3. Effect of fucoidan on pathological changes in lung tissue of asthmatic mice. Representative hematoxylin and eosin-stained lung sections from (A) OVA, (B) OVA + budesonide, (C) OVA + fucoidan and (D) control groups. Magnification, x400. Red arrows indicate bronchial wall thickening; black arrow, luminal narrowing; yellow arrows indicate inflammatory cell infiltration. Scale bar, 50 μ m. OVA, ovalbumin.

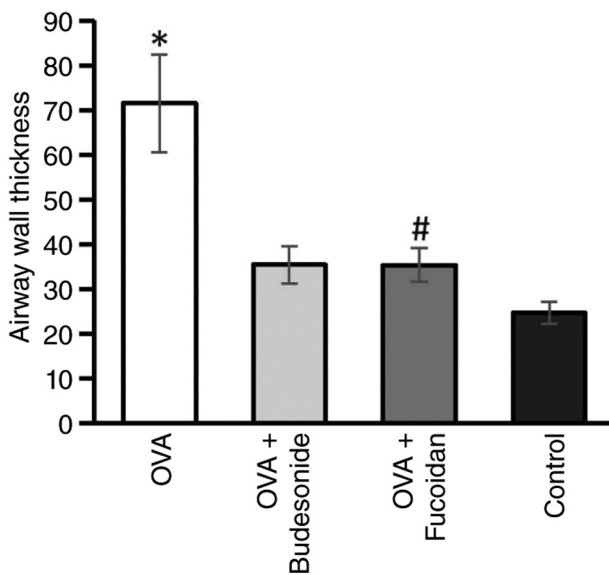


Figure 4. Quantitative analysis of airway wall thickness. The thickness is expressed as the ratio of airway wall area to basement membrane perimeter. * $P < 0.05$ vs. Control; # $P < 0.05$ vs. OVA. OVA, ovalbumin.

(5.36 ± 1.14 , 5.77 ± 1.12 and $14.18 \pm 4.07 \times 10^4/\text{ml}$, respectively; $P < 0.05$ vs. control). Following fucoidan intervention, the total cell count decreased to $14.96 \pm 2.69 \times 10^4/\text{ml}$, with significant

reductions also observed in each inflammatory cell subtype (neutrophils, 3.21 ± 0.85 ; lymphocytes, 2.69 ± 1.03 and eosinophils, $5.98 \pm 1.26 \times 10^4/\text{ml}$; all $P < 0.05$ compared with the OVA group). The effect of fucoidan was comparable with that of the OVA + budesonide group (total cells, 15.72 ± 3.43 ; neutrophils, 3.14 ± 1.09 ; lymphocytes, 2.78 ± 0.92 ; eosinophils, $6.02 \pm 1.35 \times 10^4/\text{ml}$; all $P > 0.05$). These results indicated that fucoidan can reduce the levels of inflammation and fibrosis-related factors.

Fucoidan downregulates the levels of remodeling-associated inflammatory factors in BALF. ELISA (Fig. 2) showed that the concentrations of IL21, TSLP, α SMA and ColI in BALF of the OVA group were 83.79 ± 3.32 , 103.15 ± 2.42 , 97.67 ± 1.35 and 169.24 ± 1.25 pg/ml, respectively, all significantly higher than those in the control group (15.95 ± 4.73 , 26.31 ± 4.32 , 21.35 ± 2.21 and 32.21 ± 9.07 pg/ml, respectively; $P < 0.05$). Levels of these factors in the OVA + fucoidan group decreased to 29.47 ± 2.94 , 43.24 ± 2.31 , 37.69 ± 1.59 and 61.32 ± 2.56 pg/ml, respectively, which were significantly lower than those in the OVA group ($P < 0.05$). The decrease was comparable with that in the OVA + budesonide group ($P > 0.05$). These results suggest an association between fucoidan and reduced levels of these factors, which may contribute to the observed attenuation of airway remodeling.

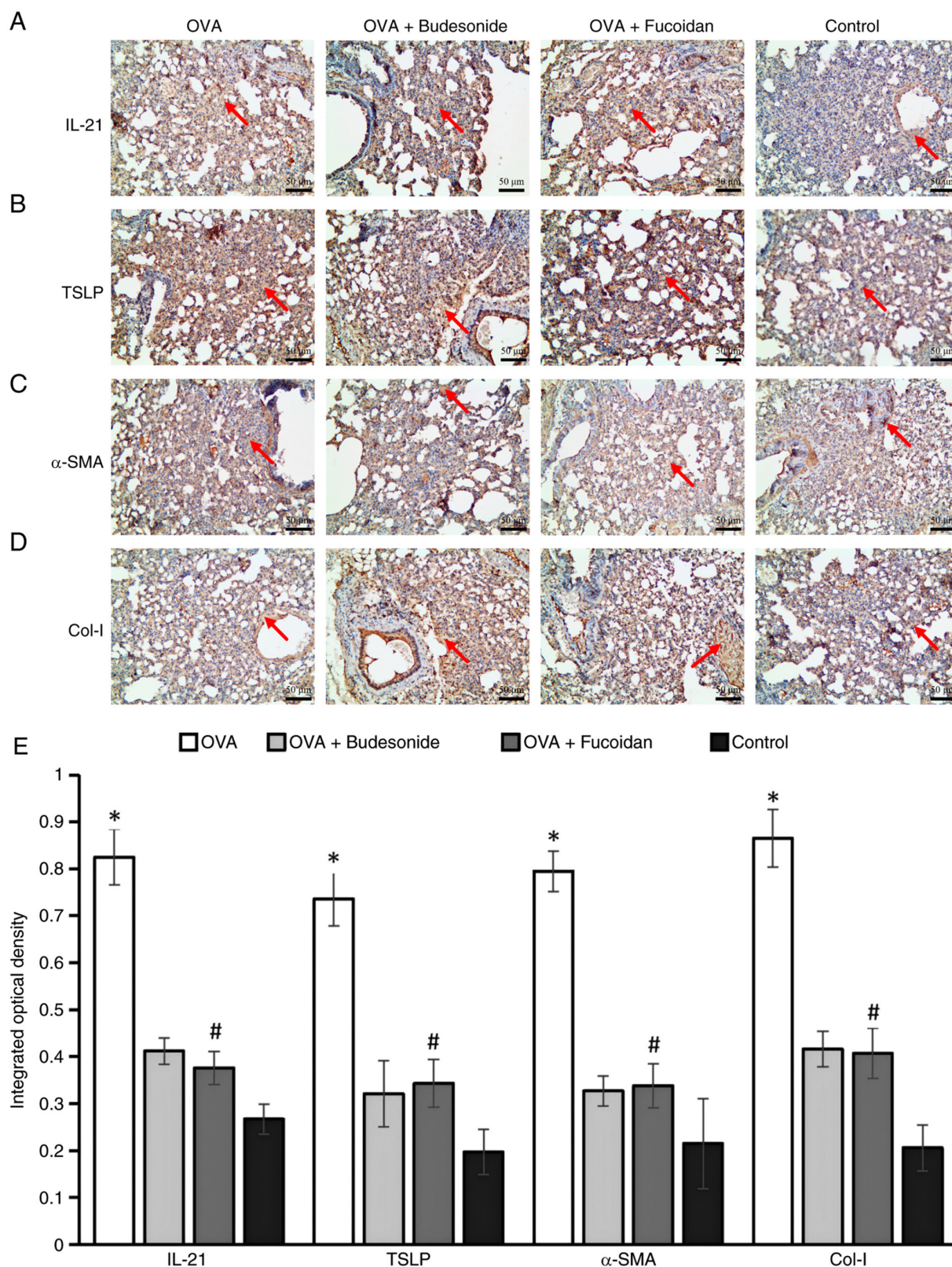


Figure 5. Immunohistochemical analysis of remodeling-associated proteins in lung tissue. Representative immunohistochemical staining for (A) IL-21, (B) TSLP, (C) α -SMA and (D) Col-I in lung sections. Magnification, $\times 200$. Arrows indicate positive staining (yellowish-brown). Scale bar, 50 μ m. (E) Quantification of protein expression levels. *P<0.05 vs. control; #P<0.05 vs. OVA. OVA, ovalbumin; TSLP, thymic stromal lymphopoietin; SMA, smooth muscle actin; Col, collagen.

Fucoidan attenuates pathological changes of airway remodeling in lung tissue. H&E staining of lung tissue (Fig. 3) revealed notable inflammatory cell infiltration, predominantly

eosinophils and lymphocytes, around airways and blood vessels in the OVA group, along with marked thickening of the bronchial wall and obvious luminal narrowing. OVA + fucoidan

group showed a significant decrease in peribronchial inflammatory cell infiltration and wall thickening, with pathological improvement comparable with that of the OVA + budesonide group. In control mice, the bronchial epithelium remained intact, the airway lumen was smooth without evident folds or narrowing, the wall showed no obvious thickening and no notable inflammatory cell infiltration was observed around airways or vessels.

Quantitative analysis of airway wall thickness (Fig. 4) was performed by measuring the airway wall area (Wat) and the perimeter of the basement membrane (Pbm, μm), with Wat/Pbm representing airway wall thickness. The wall thickness in the OVA group was $71.56 \pm 10.87 \mu\text{m}^2/\mu\text{m}$, significantly higher than that in the control group ($24.68 \pm 2.51 \mu\text{m}^2/\mu\text{m}$; $P < 0.05$). Wall thickness decreased to $35.37 \pm 3.78 \mu\text{m}^2/\mu\text{m}$ in the OVA + fucoidan and $35.42 \pm 4.25 \mu\text{m}^2/\mu\text{m}$ in the OVA + budesonide group. Both treatment groups exhibited a significant decrease compared with the OVA group ($P < 0.05$), with no statistical difference between them ($P > 0.05$). These results indicate that fucoidan significantly suppressed asthma-induced structural thickening of the airway wall, with an effect similar to that of the inhaled corticosteroid budesonide.

Fucoidan suppresses the expression of remodeling-associated proteins in lung tissue. Representative immunohistochemical staining for IL21, TSLP, αSMA , and ColI in lung tissue is shown in Fig. 5A-D. Compared with the control group, the expression of all four factors was significantly enhanced in the OVA group, with yellowishbrown positive signals primarily distributed around alveolar epithelium, lung interstitium, bronchi and accompanying blood vessels. Quantitative analysis was performed using ImagePro Plus software by calculating the IOD/unit area. The IOD values for IL21, TSLP, αSMA and ColI in the OVA group were 0.825 ± 0.059 , 0.726 ± 0.057 , 0.795 ± 0.043 and 0.865 ± 0.061 , respectively, all significantly higher than those in the control group (0.267 ± 0.032 , 0.197 ± 0.048 , 0.215 ± 0.096 and 0.206 ± 0.049 , respectively; $P < 0.05$). Following fucoidan intervention, the IOD values decreased to 0.376 ± 0.035 , 0.343 ± 0.051 , 0.338 ± 0.047 and 0.407 ± 0.053 , respectively, showing a significant decrease compared with the OVA group (all $P < 0.05$). The inhibitory effect of fucoidan was comparable with that of the budesonide group ($P > 0.05$; Fig. 5E).

Discussion

Childhood asthma is a major global health concern. Although the global age-standardized prevalence of childhood asthma has declined since 1990, the absolute number of affected children remains high, and upward trends have re-emerged in certain high-income and industrialized regions (30,31). Airway remodeling can begin early in life, even before clinical diagnosis, and early structural changes are associated with permanent loss of lung function (32). However, the disease remains poorly controlled, imposing notable burdens and adverse impacts on families and society (33). Airway remodeling refers to irreversible structural alterations in the airway resulting from persistent chronic inflammation (34). Traditionally regarded as an end-stage outcome of prolonged

airway inflammation that emerges only in advanced, poorly controlled asthma (35), growing evidence indicates that airway remodeling can occur early in the disease course (36,37). Airway remodeling and inflammation may coexist, progress in parallel and exhibit a mutually reinforcing, causal relationship (38). Remodeling is associated with asthma severity, difficulty of treatment and long-term prognosis (39). Therefore, exploring the mechanisms underlying airway remodeling and developing novel therapeutic strategies are key for improving asthma control and patient outcomes (40).

Increased deposition of ECM proteins, predominantly collagen, in the reticular basement membrane region, lamina propria or submucosa is a core feature of airway remodeling (41). This altered deposition pattern serves as a distinguishing marker between asthmatic and healthy airways (42). MMPs are key enzymes in ECM metabolism (43). The homeostasis of ECM turnover is primarily regulated by the dynamic balance between MMPs and their tissue inhibitors (TIMPs) (44,45). The equilibrium between MMPs and TIMPs is the central mechanism for maintaining normal ECM renewal and structural integrity. Hyperplasia and hypertrophy of ASM are a common manifestation of asthmatic airway remodeling (46). The increase in ASM mass may originate from bronchial epithelial cells activating signaling pathways such as Wnt/ β -catenin, which drive the proliferation and migration of ASM cells (ASMCs) (47,48).

IL-21, a pleiotropic cytokine primarily produced by activated CD4^+ T cells, plays a key role in immune-associated and allergic disease (49). IL-21 has been demonstrated to drive abnormal ECM deposition, leading to tissue fibrosis and remodeling, by modulating the balance between TIMPs and MMPs (50). The present findings show that fucoidan significantly decreased IL-21 levels in both BALF and lung tissue of asthmatic mice, accompanied by attenuated airway remodeling. This suggests a possible association between decreased IL-21 levels and the anti-remodeling effect of fucoidan. However, the present data do not establish a direct mechanistic link between fucoidan treatment and IL-21 signaling and further mechanistic studies are required to establish causality.

TSLP, primarily expressed and secreted by epithelial cells, is a key initiator of allergic inflammatory responses and is notably upregulated in the airways of patients with asthma (51,52). Beyond driving T helper cell 2-type inflammation, TSLP can directly act on lung fibroblasts to upregulate $\alpha\text{-SMA}$ and Col-I through STAT3 signaling, thereby promoting ASM hyperplasia and ECM deposition (10,53). Intervention with anti-TSLP antibodies decreases airway wall thickening in experimental mice (54). Consistently, the present study demonstrates that fucoidan significantly reduces TSLP levels and attenuated airway remodeling, which suggests a potential association between TSLP modulation and the anti-remodeling effects of fucoidan. However, the present findings do not establish a direct mechanistic link between fucoidan and TSLP signaling and direct experimental confirmation is needed.

In asthmatic airway remodeling, the expression of αSMA and ColI is typically markedly upregulated. αSMA is a key marker protein for the activation, proliferation and transition of ASMCs toward a myofibroblast phenotype (55); its

upregulation directly reflects increased ASM mass, enhanced contractile function and phenotypic alteration. ColI is the predominant collagen type deposited during airway remodeling and its excessive accumulation leads to bronchial wall thickening, stiffening and fibrosis (56,57). Therefore, both are regarded as key indicators for assessing the severity of airway remodeling. The present results demonstrate that the expression of α SMA and ColI was significantly elevated in lung tissue of the asthmatic model group, whereas fucoidan markedly suppressed the expression of both proteins, confirming the attenuating effect of fucoidan on asthmatic airway remodeling. Taken together with its inhibitory effects on IL-21 and TSLP, fucoidan may exert anti-remodeling effects through multiple pathways, potentially involving IL-21 and TSLP. However, the causal association remain to be established and the present findings do not establish a direct mechanistic link between fucoidan and IL-21/TSLP signaling.

Inhaled corticosteroids (ICSs), particularly budesonide, are well-established as effective anti-inflammatory drugs for asthma, controlling symptoms, improving lung function and reducing airway inflammation and hyper-responsiveness (58,59). Upon reaching the lung, ICSs bind to glucocorticoid receptors and modulate the transcription of inflammatory genes, thereby attenuating airway remodeling (60,61). ICSs suppress the increase in ASM mass linked to remodeling (62). In the present study, the budesonide-treated group showed alleviated asthma symptoms, diminished inflammatory infiltration, milder structural changes and significantly lower levels of remodeling-associated indicators compared with the asthma model group, corroborating the role of ICSs in controlling asthma and mitigating airway remodeling.

However, concerns regarding the longterm side effects of ICS remain prevalent, driving ongoing efforts to identify alternative therapeutic agents for asthma (63). Fucoidan, a natural sulfated polysaccharide derived from seaweed and other marine plants, exhibits a molecular framework similar to that of heparin and possesses a range of biological functions, including immunomodulatory, antiinflammatory, antiviral, antioxidant, anticoagulant and antitumor activities (60,64). In the present OVA-induced asthmatic mouse model, oral administration of fucoidan demonstrated effects comparable with those of budesonide nebulization in improving asthma symptoms, decreasing airway inflammatory cell infiltration, decreasing airway wall thickness and downregulating the expression of IL21, TSLP, α SMA and ColI in lung tissue. These findings suggested fucoidan may exert antiinflammatory and antiremodeling effects similar to those of ICSs, likely through a multitarget mechanism.

In recent years, marine-derived sulfated polysaccharides have garnered increasing attention due to their broad anti-inflammatory and anti-fibrotic activity (65-67). For example, fucoidan extracted from *Gracilaria lemaneiformis* mitigates allergic responses by modulating transcription factors within T cell subsets (68). Chen *et al* (69) demonstrated that fucoidan from *Cladosiphon okamuranus* alleviates symptoms of atopic dermatitis. Beyond its direct anti-inflammatory effects, emerging evidence suggests fucoidan may attenuate airway remodeling via inhibition of epithelial-mesenchymal transition (EMT) (70). EMT is a critical early event in asthmatic

airway remodeling (71), during which airway epithelial cells acquire a myofibroblast-like phenotype and contribute to excessive ECM deposition and subepithelial fibrosis (72). In pulmonary fibrosis models (73,74), low-molecular weight fucoidan from *Laminaria japonica* inhibits TGF- β 1-induced EMT through concurrent downregulation of both TGF- β /Smad and PI3K/AKT signaling pathways (75). Similarly, fucoidan from *Costaria costata* decreases TGF- β 1-induced EMT in A549 cells by inhibiting the TGF- β /Smad and PI3K/AKT/mTOR pathways (70). As these signaling cascades are pivotal drivers of EMT in the asthmatic airway epithelium, decreased α -SMA and Col-I expression in the present study may partly reflect fucoidan-mediated suppression of EMT. This hypothesis is supported by reports that fucoidan inhibits EMT through Wnt/ β -catenin and ERK pathways in other disease models (76-78), including renal fibrosis (via inhibition of heparanase and MMP-9), hemangioma (via the Wnt/ β -catenin pathway), and breast cancer under hypoxia (via the HIF-1 α pathway). Collectively, these findings suggest that, in addition to its anti-inflammatory actions, fucoidan may exert anti-remodeling effects partially through EMT inhibition. To the best of our knowledge, however, direct evidence in asthma is lacking and future studies incorporating *in vitro* EMT assays and pathway-specific inhibitors are warranted to confirm this mechanism.

Several limitations of the present should be acknowledged. First, the present data demonstrate associations rather than causation between fucoidan and the reduction of IL-21, TSLP, α -SMA and Col-I. No loss- or gain-of-function experiments (cytokine neutralization, gene knockout or specific pathway inhibitors) were performed to confirm that fucoidan directly targets these molecules or their downstream signaling cascades. Therefore, while the present findings suggest an association between fucoidan and the downregulation of these remodeling-related factors, the present data do not establish a direct mechanistic link between fucoidan and IL-21/TSLP signaling. The precise molecular mechanisms remain to be established. Future studies incorporating *in vitro* assays with recombinant cytokines or pathway-specific inhibitors are warranted to validate causality. Additionally, while the present study measured α -SMA and Col-I in BALF supernatant using validated commercial ELISA kits, these proteins are primarily tissue-bound; their presence in BALF reflects soluble fragments released during active remodeling rather than total tissue content. Future studies incorporating tissue western blotting or immunohistochemical quantification may corroborate these findings. Second, only one dose of fucoidan (50 mg/kg) was tested. Although this dose was selected based on previous reports demonstrating efficacy in OVA-induced allergic airway inflammation models (25-27), dose-response associations and alternative routes (such as inhalation) remain unexplored. Future studies incorporating multiple doses are needed to define the optimal therapeutic regimen. Third, lung function and airway hyperresponsiveness were not assessed, limiting the ability to identify associations between histological improvements with functional respiratory outcomes. The present study did not include plethysmography or invasive pulmonary resistance measurements due to equipment and resource constraints. While histopathological and biochemical data

indicated that fucoidan attenuated structural remodeling, the functional value of these changes remains to be confirmed. Future studies using forced oscillation technique or invasive airway resistance measurements are warranted to evaluate whether the histological benefits translate into improved lung function. Fourth, the present study used only female KM mice over a 35-day period; whether effects are sex-, strain- or time-dependent is unclear. Although KM mice are an outbred strain that may better reflect human genetic diversity than inbred strains, their inherent variability, along with the exclusive use of female mice, limits the generalizability of the present findings. Future studies using male and female animals and additional inbred strains are warranted to confirm the reproducibility of the present results. Fifth, systematic toxicity was not assessed. Although no mortality or notable adverse effects were observed and body weight was monitored daily, liver and kidney function were not evaluated. Future safety studies are warranted. Sixth, the histological and immunohistochemical assessments were not performed under blinded conditions. The investigators who conducted image acquisition, scoring and IOD quantification were aware of the group allocation, which may introduce assessment bias. Although random field selection and a uniform threshold were applied to minimize subjectivity, future studies should incorporate strict blinding to ensure objective evaluation. Assessment of asthma-like behaviors was descriptive and qualitative, based on daily observation rather than a standardized scoring system or objective monitoring. This may have introduced observer bias. Future studies should incorporate validated behavioral scoring criteria or video-based tracking to quantify symptom severity. Finally, the present study did not examine the reversibility or long-term sustainability of the anti-remodeling effects. Addressing these gaps is necessary before clinical translation.

In conclusion, the present study demonstrates that oral administration of fucoidan decreased airway inflammatory cell infiltration and expression of IL-21, TSLP, α -SMA and Col-I and attenuates airway wall thickening in an OVA-induced mouse model of asthma. These effects were comparable with those of budesonide. However, the present findings did not establish a direct mechanistic link between fucoidan treatment and IL-21/TSLP signaling and the underlying molecular mechanisms have not been fully established. The limitations preclude direct clinical extrapolation. Further mechanistic studies, dose-response evaluation and alternative route-of-administration assessments are necessary to determine whether fucoidan may serve as a complementary or alternative approach to existing asthma therapies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XW and JG wrote the manuscript and analyzed data. YQ and JG performed experiments. YH and LH interpreted data. SZ analyzed data. YH, SZ and LH constructed figures. RG and YQ designed the study and confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

All procedures involving animals were approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (approval no. AHQU-MAL20150101QYL; Qingdao, Shandong, China) and conformed to guidelines for the Care and Use of Laboratory Animals of the Ministry of Health, China.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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