Postprint: Study on the Intervention Effect of Bufei Yishen Component Formula III Component Compatibility on Airway Remodeling in Rats with Chronic Obstructive Pulmonary Disease

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Abstract

Background Chronic obstructive pulmonary disease (COPD) is a major chronic disease, and airway remodeling is an important pathological mechanism. Bufei Yishen Formula demonstrates good therapeutic efficacy on COPD, and its effective component formula Bufei Yishen Component Formula III (ECC-BYF III) demonstrates equivalent efficacy, which can significantly improve airway remodeling in COPD model rats, but the compatibility law of its components remains to be elucidated.

Objective To evaluate the intervention effects of ECC-BYF III and its component compatibility on airway remodeling in COPD based on a COPD rat model.

Methods The components of ECC-BYF III were divided into four categories: Qi-supplementing, kidney-tonifying, phlegm-resolving, and blood-activating, and were grouped into different component compatibility groups using mathematical permutation and combination methods. Animal experiments were conducted from May to September 2018. Two hundred and sixteen SD rats were randomly divided into normal, model, ECC-BYF III, different component compatibility, and aminophylline groups, totaling 18 groups with 12 rats in each group. During weeks 1-8, a stable COPD rat model was established using cigarette smoke exposure combined with repeated bacterial infection (except for the normal group); during weeks 9-16, corresponding drug interventions were administered. Hematoxylin-eosin (HE) staining was used to observe changes in airway wall and airway smooth muscle; enzyme-linked immunosorbent assay (ELISA) was used to detect serum levels of matrix metalloproteinase-12 (MMP-12), basic fibroblast

growth factor (bFGF), and levels of airway remodeling-related indicators such as collagen (COL)-1, COL-3, and MMP-12 in bronchoalveolar lavage fluid (BALF). Region (R) values were used to comprehensively evaluate the intervention effects of each component compatibility on airway remodeling in COPD rats.

Results Compared with the model group, airway wall thickness was reduced in the ECC-BYF III and its component compatibility groups and the aminophylline group, and the average number of airway smooth muscle cells was decreased in the ECC-BYF III group, Qi-supplementing and phlegm-resolving group, strengthening body resistance and phlegm-resolving group, strengthening body resistance and blood-activating group, Qi-supplementing and pathogen-eliminating group, and aminophylline group ($P<0.05$). Compared with the model group, serum bFGF levels were decreased in the ECC-BYF III group, kidney-tonifying group, Qi-supplementing and phlegm-resolving group, Qi-supplementing and blood-activating group, kidney-tonifying and phlegm-resolving group, and kidney-tonifying and blood-activating group; serum MMP-12 levels were decreased in the ECC-BYF III group and strengthening body resistance group; BALF MMP-12 and BALF COL-1 levels were decreased in the ECC-BYF III and its component compatibility groups and the aminophylline group; BALF COL-3 levels were decreased in the ECC-BYF III group, kidney-tonifying group, phlegm-resolving group, blood-activating group, strengthening body resistance group, Qi-supplementing and phlegm-resolving group, Qi-supplementing and blood-activating group, kidney-tonifying and blood-activating group, strengthening body resistance and phlegm-resolving group, Qi-supplementing and pathogen-eliminating group, kidney-tonifying and pathogen-eliminating group, and aminophylline group ($P<0.05$). Comprehensive evaluation using R values for airway wall thickness, airway smooth muscle hyperplasia, and all airway remodeling-related indicators in serum and BALF showed that, except for the phlegm-resolving and pathogen-eliminating component compatibility, ECC-BYF III and other component compatibility groups and the aminophylline group could all improve airway remodeling in COPD rats ($P<0.05$), with the Qi-supplementing and pathogen-eliminating, strengthening body resistance and phlegm-resolving, and Qi-supplementing and blood-activating component compatibility demonstrating better effects on improving airway remodeling in COPD rats.

Conclusion ECC-BYF III and its component compatibility can intervene in airway remodeling in COPD rats to varying degrees, among which the Qi-supplementing and pathogen-eliminating, strengthening body resistance and phlegm-resolving, and Qi-supplementing and blood-activating component compatibility (all containing Qi-supplementing components: ginsenoside Rh1 and astragaloside) demonstrated more significant effects.

Full Text

The Evaluation of Effective-Component Compatibility of Bufei Yishen Formula III and Components Compatibility in Treating Airway Remodeling of COPD

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a major chronic disease, and airway remodeling is an important pathological mechanism. Bufei Yishen formula demonstrates good efficacy for COPD, and its effective-component compatibility, Bufei Yishen Component Formula III (ECC-BYF III), shows equivalent therapeutic effects by significantly improving airway remodeling in COPD model rats. However, the component compatibility pattern remains to be elucidated.

Objective: To evaluate the intervention effects of ECC-BYF III and its component compatibility on airway remodeling in COPD rats.

Methods: The components of ECC-BYF III were divided into four categories: Qi-supplementing, Kidney-tonifying, Phlegm-resolving, and Blood-activating. Using mathematical permutation and combination methods, these were divided into different component compatibility groups. Animal experiments were conducted from May to September 2018. Two hundred sixteen SD rats were randomly divided into 18 groups (n=12 each): normal, model, ECC-BYF III, different component compatibility groups, and aminophylline group. From weeks 1–8, a COPD stable-phase rat model was established using cigarette smoke exposure combined with repeated bacterial infections (except for the normal group). From weeks 9–16, corresponding drug interventions were administered. Hematoxylin-eosin (HE) staining was used to observe airway wall and smooth muscle changes. Enzyme-linked immunosorbent assay (ELISA) detected serum levels of matrix metalloproteinase-12 (MMP-12) and basic fibroblast growth factor (bFGF), and bronchoalveolar lavage fluid (BALF) levels of collagen (COL)-1,

COL-3, and MMP-12. Region (R) value comprehensive evaluation was used to assess the intervention effects of each component compatibility on airway remodeling in COPD rats.

Results: Compared with the model group, ECC-BYF III and its component compatibility groups, as well as the aminophylline group, showed reduced airway wall thickness. The ECC-BYF III group, Qi-supplementing Phlegm-resolving group, Fuzheng Phlegm-resolving group, Fuzheng Blood-activating group, Qi-supplementing Quxie group, and aminophylline group demonstrated significantly decreased mean airway smooth muscle cell counts ($P<0.05$). Serum bFGF levels were reduced in the ECC-BYF III, Kidney-tonifying, Qi-supplementing Phlegm-resolving, Qi-supplementing Blood-activating, Kidney-tonifying Phlegm-resolving, and Kidney-tonifying Blood-activating groups. Serum MMP-12 levels decreased in the ECC-BYF III and Fuzheng groups. BALF MMP-12 and COL-1 levels were reduced in all ECC-BYF III component compatibility groups and the aminophylline group. BALF COL-3 levels decreased in the ECC-BYF III, Kidney-tonifying, Phlegm-resolving, Blood-activating, Fuzheng, Qi-supplementing Phlegm-resolving, Qi-supplementing Blood-activating, Kidney-tonifying Blood-activating, Fuzheng Phlegm-resolving, Qi-supplementing Quxie, Kidney-tonifying Quxie, and aminophylline groups ($P<0.05$). R-value comprehensive evaluation of airway wall thickness, smooth muscle hyperplasia, and all airway remodeling-related indicators in serum and BALF showed that, except for Phlegm-resolving and Quxie component compatibility, ECC-BYF III and other component compatibility groups, as well as aminophylline, improved airway remodeling in COPD rats ($P<0.05$). The Qi-supplementing Quxie, Fuzheng Phlegm-resolving, and Qi-supplementing Blood-activating component compatibility groups showed better effects.

Conclusion: ECC-BYF III and its component compatibility can intervene in airway remodeling in COPD rats to varying degrees, with Qi-supplementing Quxie, Fuzheng Phlegm-resolving, and Qi-supplementing Blood-activating (all containing Qi-supplementing components: ginsenoside Rh1 and astragaloside) showing particularly significant effects.

Keywords: Pulmonary disease, chronic obstructive; ECC-BYF III; Airway remodeling; Components compatibility; Rats

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by incompletely reversible airflow limitation. Airway remodeling represents a crucial pathological mechanism in COPD, closely associated with airway narrowing and irreversible airflow limitation. Primarily occurring in small airways, airway remodeling is a process of structural changes and repeated repair of airway walls following injury, characterized by thickened

airway walls and narrowed lumens. The mechanisms remain incompletely understood but are believed to involve inflammatory responses, oxidative stress, protease/anti-protease imbalance, and extracellular matrix deposition. Airway remodeling-induced luminal narrowing increases airflow resistance and causes persistent airflow limitation, representing a critical stage in COPD progression. Therefore, effective intervention for airway remodeling constitutes an important therapeutic strategy for COPD.

Bufei Yishen formula is an effective clinical prescription for COPD that can alleviate symptoms, reduce acute exacerbation frequency, and improve quality of life. Component formulas composed of effective component compatibility represent a new model for modern Chinese medicine research, facilitating drug quality control and mechanism elucidation. Our research group previously used systems pharmacology combined with in vivo and in vitro experiments to optimize Bufei Yishen Component Formula I and II, resulting in ECC-BYF III, which comprises ginsenoside Rh1, astragaloside, icariin, nobiletin, and paeonol. Previous studies demonstrated that ECC-BYF III effectively improves lung function, inhibits inflammatory responses, and alleviates airway remodeling in COPD rats. However, the specific component compatibility patterns underlying its effects on airway remodeling require further investigation.

Guided by traditional Chinese medicine (TCM) theory and based on the original single herbs' functions, we categorized ECC-BYF III components into four classes: Qi-supplementing (ginsenoside Rh1 and astragaloside), Kidney-tonifying (icariin), Phlegm-resolving (nobiletin), and Blood-activating (paeonol). Using different component compatibility combinations, we evaluated their intervention characteristics on COPD airway remodeling in a cigarette smoke exposure and repeated bacterial infection-induced COPD stable-phase rat model.

1. Materials and Methods

1.1 Experimental Materials

1.1.1 Animals: Two hundred sixteen SPF-grade SD rats (weight 200$±$20 g, half male and half female) were purchased from Henan Experimental Animal Center (SCXK[Yu]2017-0001). All experiments were approved by the Animal Welfare Ethics Committee of the First Affiliated Hospital of Henan University of Chinese Medicine (Approval No. YFYDW2019031).

1.1.2 Cigarettes and Bacteria: Hongqiqu filter cigarettes (hard gold red, produced by Henan China Tobacco Industry Co., Ltd., flue-cured type, tar 11 mg, nicotine 0.9 mg, carbon monoxide 11 mg) and *Klebsiella pneumoniae* (strain No. 46117) from the China Medical Bacterial Collection Center of the National Institutes for Food and Drug Control were used.

1.1.3 Drugs and Reagents: Ginsenoside Rh1 (CHB180608) was purchased from Chengdu Chroma-Biotechnology Co., Ltd.; astragaloside (MUST-

17022804), icariin (MUST-16111710), and paeonol (MUST-16071405) from Chengdu Mansite Biotechnology Co., Ltd.; nobiletin (HL-20170312) from Xi' an Huilin Biotechnology Co., Ltd.; and aminophylline tablets (100 mg/tablet $×$100 tablets) from Shandong Xinhua Pharmaceutical Co., Ltd. Hematoxylin staining solution (H9627) was from Sigma-Aldrich (USA). ELISA kits for rat MMP-12 (E-EL-R0044c), bFGF (E-EL-R0091c), COL-1 (E-EL-R0233c), and COL-3 (E-EL-R0233c) were purchased from Wuhan Elabscience Biotechnology Co., Ltd.

1.2 Experimental Methods

Animal experiments were conducted from May to September 2018. Rats were housed under controlled conditions: temperature $(25\$\pm 2)°C, relative humidity(50\pm\$10)\%$, with sterile water and feed. After one week of acclimatization, rats were randomly divided into 18 groups (n=12 each, half male and half female). From weeks 1-8, a COPD stable-phase rat model was established using cigarette smoke exposure combined with repeated bacterial infections (except for the normal group). Lung function was measured every 4 weeks to evaluate model success. From weeks 9-16, corresponding drug interventions were administered.

Drug dosages were calculated using the equivalent dose coefficient conversion formula: D_{rat} = D_{human} × (HI_{rat}/HI_{human}) × (W_{rat}/W_{human})^(2/3), where D represents dose, HI represents body shape coefficient, and W represents body weight. Specific group assignments and drug interventions are detailed in Table 1 .

1.2.3 Histopathology: The left lung was perfused with 4% paraformaldehyde, embedded in paraffin, and sectioned at 4 m for routine HE staining. Airways with diameters of 200-400 m and regular shape were selected under microscopy to measure internal and external diameters. Airway wall thickness (m) = external diameter - internal diameter. Airway perimeter and smooth muscle cell counts were measured to calculate mean airway smooth muscle cell number (cells/mm) = (total cell count)/(external perimeter - internal perimeter).

1.2.4 ELISA: Serum bFGF and MMP-12 levels, and BALF MMP-12, COL-1, and COL-3 levels were measured by ELISA.

1.3 Comprehensive Evaluation Using Region (R) Value

The R-value comprehensive evaluation method (Copyright Registration No.: National Registration 2013-A-00096833) was used to evaluate airway remodeling-related indicators in serum and BALF, as well as overall indicators. This method calculates drug correction intensity based on disease impact on indicators and drug corrective effects, providing comprehensive assessment of multiple indicators.

1.4 Statistical Analysis

Data were analyzed using IBM SPSS 22.0 software. Measurement data with homogenous variance were analyzed using least significant difference (LSD) method, expressed as ($\bar{x}\pm s$). One-way ANOVA was used for inter-group comparisons with significance level α=0.05.

2. Results

2.1 Effects on Airway Wall Thickness and Smooth Muscle Cell Count

Significant differences were observed among the 18 groups in airway wall thickness and mean airway smooth muscle cell count ($P<0.05$). Compared with the normal group, the model group showed significantly increased airway wall thickness and smooth muscle cell count ($P<0.05$). Compared with the model group, ECC-BYF III and its component compatibility groups, as well as the aminophylline group, demonstrated reduced airway wall thickness. The ECC-BYF III group, Qi-supplementing Phlegm-resolving group, Fuzheng Phlegm-resolving group, Fuzheng Blood-activating group, Qi-supplementing Quxie group, and aminophylline group showed significantly decreased mean airway smooth muscle cell counts ($P<0.05$). Results are shown in Table 2 and Figure 1 [Figure 1: see original paper].

2.2 Effects on Airway Remodeling Markers in Serum and BALF

Significant differences were found among groups in serum bFGF, serum MMP-12, BALF MMP-12, BALF COL-1, and BALF COL-3 levels ($P<0.05$). The model group exhibited significantly elevated levels of all markers compared with the normal group ($P<0.05$). Compared with the model group, serum bFGF decreased in the ECC-BYF III, Kidney-tonifying, Qi-supplementing Phlegm-resolving, Qi-supplementing Blood-activating, Kidney-tonifying Phlegm-resolving, and Kidney-tonifying Blood-activating groups. Serum MMP-12 decreased in the ECC-BYF III and Fuzheng groups. BALF MMP-12 and COL-1 levels decreased in all ECC-BYF III component compatibility groups and the aminophylline group. BALF COL-3 levels decreased in the ECC-BYF III, Kidney-tonifying, Phlegm-resolving, Blood-activating, Fuzheng, Qi-supplementing Phlegm-resolving, Qi-supplementing Blood-activating, Kidney-tonifying Blood-activating, Fuzheng Phlegm-resolving, Qi-supplementing Quxie, Kidney-tonifying Quxie, and aminophylline groups ($P<0.05$). Results are shown in Table 3 .

2.3 Comprehensive Evaluation of Intervention Effects

Due to varying effects of different component compatibility groups on individual indicators, R-value comprehensive evaluation was employed. Evaluation of airway remodeling-related indicators in serum and BALF showed that, except for Phlegm-resolving, Quxie, Kidney-tonifying Phlegm-resolving, and

Fuzheng Blood-activating groups, ECC-BYF III and other component compatibility groups, as well as aminophylline, could correct airway remodeling indicator secretion to varying degrees ($P<0.05$), with Qi-supplementing Quxie, Qi-supplementing Blood-activating, and Fuzheng Phlegm-resolving showing the best effects.

Comprehensive evaluation of all indicators (airway wall thickness, smooth muscle hyperplasia, and all airway remodeling-related indicators in serum and BALF) showed that, except for Phlegm-resolving and Quxie component compatibility, ECC-BYF III and other component compatibility groups, as well as aminophylline, significantly improved airway remodeling in COPD rats ($P<0.05$). The Qi-supplementing Quxie, Fuzheng Phlegm-resolving, and Qi-supplementing Blood-activating component compatibility groups demonstrated superior effects, as shown in Table 4 .

3. Discussion

In TCM, COPD belongs to the categories of "Feizhang" (lung distension) and "Chuanbing" (panting disease), most closely resembling Feizhang. Pathogenic factors affecting the lungs, if untreated, lead to retained phlegm and blood stasis that damage vital Qi, resulting in deficiency of lung, spleen, and kidney with compromised defense, making patients susceptible to repeated external pathogen attacks. The main pathogenesis is "deficiency with accumulation," complicated by phlegm and blood stasis obstruction. Deficiency manifests as lung-kidney Qi deficiency, Yang deficiency, or Yin-Yang dual deficiency, with lung deficiency as the onset and kidney deficiency as the foundation, and Qi deficiency as the root. Accumulation refers to phlegm and blood stasis forming masses that progressively damage vital Qi, making deficiency difficult to restore. As Zhu Danxi stated in *Danxi' s Methods of Treatment*: "Feizhang with cough, unable to lie on either side, is caused by phlegm with blood stasis obstructing Qi." This indicates Feizhang results from phlegm-blood stasis intermingling and obstructing lung Qi. Chronic deficiency of lung, spleen, and kidney with phlegm-blood stasis blocking airways causes airway stagnation, obstructing lung Qi which becomes distended and fails to descend properly. This mechanism aligns with COPD airway remodeling causing airway narrowing and obstruction, leading to airflow limitation. Therefore, COPD airway remodeling can be understood as chronic deficiency of vital Qi with phlegm-blood stasis obstructing airways. Lung-kidney Qi deficiency with phlegm-blood stasis is the main pattern in stable COPD, with treatment focusing on supplementing lung and kidney while resolving phlegm and activating blood.

ECC-BYF III was optimized from Bufei Yishen formula. Our previous animal studies demonstrated that ECC-BYF III significantly improves lung function, inhibits inflammatory responses, and alleviates airway remodeling in COPD rats. This study aimed to explore the component compatibility patterns underlying its intervention in COPD airway remodeling.

Airway remodeling, characterized by irreversible structural changes and airflow limitation, represents the primary pathological basis for airflow obstruction in COPD. COPD patients show thickened and deformed airway walls, most notably with smooth muscle thickening, causing luminal narrowing and increased airflow resistance. Airway remodeling manifests as airway wall thickening, smooth muscle cell proliferation, and extracellular matrix deposition. In COPD, small airway smooth muscle cells show prominent hyperplasia and hypertrophy. Our results confirmed that the cigarette smoke and bacterial infection model induced significant airway wall thickening and smooth muscle cell proliferation. ECC-BYF III intervention significantly reduced these pathological changes, indicating substantial corrective effects on airway remodeling.

Airway remodeling involves complex damage/repair mechanisms with multiple factors. Basic fibroblast growth factor (bFGF) is a potent mitogenic peptide that promotes growth, proliferation, and differentiation of smooth muscle cells, fibroblasts, and vascular endothelial cells, recruiting them for tissue reconstruction. bFGF also activates fibroblasts to increase collagen synthesis and deposition in airway walls. Serum bFGF expression correlates closely with airway obstruction severity in COPD acute exacerbations. Matrix metalloproteinases (MMPs) degrade extracellular matrix and basement membrane components, participating in airway remodeling. Under cigarette smoke and bacterial stimulation, increased MMPs degrade collagen, promote extracellular matrix deposition, and accelerate remodeling. Our study showed significantly elevated serum bFGF and MMP-12, and increased BALF MMP-12, COL-1, and COL-3 in COPD rats, likely due to bFGF-promoted collagen synthesis. ECC-BYF III significantly reduced these levels, suggesting its mechanism may involve regulating bFGF and MMP-12 secretion and reducing extracellular matrix deposition.

To explore component compatibility patterns, we examined different combinations' effects on remodeling markers. R-value evaluation revealed that, except for Phlegm-resolving, Quxie, Kidney-tonifying Phlegm-resolving, and Fuzheng Blood-activating groups, all other ECC-BYF III component compatibility groups corrected airway remodeling indicators in serum and BALF, with Qi-supplementing Quxie, Qi-supplementing Blood-activating, and Fuzheng Phlegm-resolving showing optimal effects. Comprehensive evaluation of all indicators showed that, except for Phlegm-resolving and Quxie groups, all other component compatibility groups significantly improved airway remodeling, with Qi-supplementing Quxie, Fuzheng Phlegm-resolving, and Qi-supplementing Blood-activating demonstrating superior efficacy. Notably, these three optimal combinations all contained Qi-supplementing components (ginsenoside Rh1 and astragaloside), suggesting that component compatibility containing these Qi-supplementing agents provides better corrective effects on COPD airway remodeling, though the mechanisms require further investigation.

This study, based on ECC-BYF III' s established efficacy, evaluated different component compatibility patterns for intervening in COPD airway remodeling, providing insights for component formula compatibility and optimization

of treatment principles. However, given the complex mechanisms of COPD airway remodeling, this study only evaluated ECC-BYF III component compatibility patterns in vivo. Future studies should employ in vitro models to further evaluate efficacy characteristics, explore mechanisms in depth, and provide foundations for clinical application and new drug development of Bufei Yishen component formulas.

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Author Contributions

LI Jiansheng conceptualized the "component compatibility" research approach and designed the study. QIN Yanqin and DONG Haoran performed animal husbandry, drug interventions, lung function testing, and airway remodeling measurements. YANG Jingfan and LI Haibo conducted lung histopathology examinations. QIN Yanqin and YANG Jingfan collected and analyzed experimental data. QIN Yanqin drafted the manuscript. ZHAO Peng and LI Jiansheng revised the manuscript. QIN Yanqin and LI Jiansheng finalized the manuscript and are responsible for the final version.

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Conflict of Interest

The authors declare no conflict of interest.

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