

# A Randomized Controlled Study on the Therapeutic Effects of Doxofylline Combined with Erchen Decoction in COPD Model Rats and Its Impact on Serum IL-6 Levels

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**Abstract** [Objectives] To explore the therapeutic effects of doxofylline combined with Erchen decoction in chronic obstructive pulmonary disease (COPD) model rats and its impact on serum IL-6 levels. [Methods] Rats were divided into seven groups: blank, model, Erchen decoction, doxofylline, and combined medication groups at low, medium, and high doses. After successful modeling, they were administered intragastrically at the respective doses for 4 weeks. [Results] Compared to the control group, serum IL-6 levels in the Erchen decoction group and the combined medication groups at low and medium doses were significantly decreased ( $P < 0.05$ ). Additionally, the body weight of rats after treatment was significantly increased compared to before treatment ( $P < 0.05$ ). [Conclusions] Doxofylline combined with Erchen decoction can reduce serum IL-6 levels in COPD rats, improve their body weight, and exert a therapeutic effect on COPD.

**Key words** Erchen decoction, Doxofylline, Compatibility, Chronic obstructive pulmonary disease (COPD), IL-6, Changes in body weight

## 1 Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airway inflammation and reduced lung function. Traditional treatments, such as bronchodilators, have limited efficacy and notable side effects<sup>[1]</sup>. Doxofylline, a novel theophylline derivative, dilates the bronchi by inhibiting phosphodiesterase. Compared to traditional theophylline drugs, doxofylline exhibits a stronger bronchodilatory effect and a lower incidence of side effects, and possesses antitussive properties<sup>[2]</sup>. Erchen decoction is an expectorant with effects that include regulating qi, harmonizing the energizer, drying dampness, and resolving phlegm. In traditional Chinese medicine theory, COPD is classified as "lung distension". Its typical symptoms—aggravated coughing, increased phlegm, wheezing, and shortness of breath—correspond to the clinical manifestations of the syndrome characterized by obstruction of the lung by phlegm. Erchen decoction is a traditional Chinese medicine formula renowned for its expectorant properties. It functions by drying dampness, dissolving phlegm, reducing inflammation, and alleviating symptoms associated with COPD<sup>[3]</sup>. This study evaluated the effect of combined interventions on COPD by measuring IL-6 levels and changes in body weight.

## 2 Materials and methods

**2.1 Experimental animals** Forty-two SPF-grade Sprague-Dawley (SD) male rats (Changsha Tianqin Biotechnology Co., Ltd., License No.: scxk[X]2014-0010 and scxk[X]2014-0011) were used.

**2.2 Main reagents and instruments** The main reagents and instruments used in this study included Hongtashan cigarettes (Hongta Tobacco Group Co., Ltd., barcode 6901028315425); doxofylline tablets (Zhejiang Anglikang Pharmaceutical Co., Ltd., SFDA approval No.: H20000011); TNF- $\alpha$  kit (Wuhan Boster Bioengineering Co., Ltd.); chloral hydrate solution (Chengdu Kelong Chemicals Co., Ltd.); lipopolysaccharide (Beijing Solarbao Technology Co., Ltd.); gentamicin sulfate injection (Ruiyang Pharmaceutical Co., Ltd., SFDA approval No.: H37021929); sodium chloride injection (Chenxin Pharmaceutical Co., Ltd., SFDA approval No.: H37022337); water bath constant temperature shaker (Model ZD-85, Changzhou Jintan Liangyou Instrument Co., Ltd.); Infinite F50 microplate reader (Beijing Changheng Rongchuang Technology Co., Ltd.); electronic analytical balance (Model E200YB-C, Changshu Shuangjie Testing Instrument Factory); and centrifuge (Model TGL-16, Hunan Xiangyi Laboratory Instrument Development Co., Ltd.).

**2.3 Animal grouping and administration** Using 5% bitter acid and the random number table method for labeling, a total of seven experimental groups were established: the model control group (Group A), the blank control group (normal saline group) (Group B), the doxofylline group (Group C), the Erchen decoction group (Group D), the low-dose doxofylline combined with Erchen decoction group (combined medication group at low dose, Group E), the medium-dose doxofylline combined with Erchen decoction group (combined medication group at medium dose,

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Group F), and the high-dose doxofylline combined with Erchen decoction group (combined medication group at high dose, Group G), with six rats in each group.

Group A was administered 0.2 mL of normal saline via intratracheal injection on days 1 and 14. These rats were maintained in the same environment but were not exposed to smoke. Beginning on day 15, Group B received intragastric administration of normal saline twice daily; Group C received doxofylline via intragastric administration at a dose of 17.3 mg/kg twice daily; Group D received Erchen decoction at 10 g/kg once daily; Group E was treated with doxofylline at 17.3 mg/kg twice daily combined with a low dose of Erchen decoction at 5 g/kg once daily; Group F received doxofylline at 17.3 mg/kg twice daily combined with a medium dose of Erchen decoction at 10 g/kg once daily; and Group G was administered doxofylline at 17.3 mg/kg twice daily combined with a high dose of Erchen decoction at 20 g/kg once daily. Every Sunday at 10:00 in the morning, the rats were weighed and received intragastric administration. The total dose was adjusted weekly according to changes in their body weight over a period of 4 consecutive weeks.

**2.4 Modeling methods** The COPD rat model was developed through exposure to cigarette smoke in combination with airway infusion of lipopolysaccharide<sup>[4]</sup>. A total of 42 SPF SD rats were selected. All rats underwent a 3 d acclimation period and were fasted for 6 h prior to the commencement of the experiment. Except for Group A, the other groups received intratracheal injections of 0.2 mL of 1 mg/mL lipopolysaccharide on the 1<sup>st</sup> and 14<sup>th</sup> d. From the 2<sup>nd</sup> to the 13<sup>th</sup> d and from the 15<sup>th</sup> to the 28<sup>th</sup> d, the rats were placed in a transparent, sealed fumigation chamber measuring

38 cm × 46 cm × 63 cm for exposure to Hongtashan cigarette smoke (20 min/time, 2 times/d, 20 cigarettes/time). After all animals were maintained for 4 weeks, the subsequent experiments were conducted.

**2.5 Observation indicators and detection methods** Prior to the sacrifice of the rats, blood samples were obtained from the cardiac vertex, and the serum was subsequently isolated for further analysis. The IL-6 levels in the serum of each group of rats were measured using an enzyme-linked immunosorbent assay (ELISA).

**2.6 Statistical analysis** Statistical analyses were conducted using SPSS 27.0. Comparisons between two groups were performed using the *t*-test for continuous variables, while analysis of variance (ANOVA) was employed for comparisons among multiple groups. Data were presented as mean ± standard deviation ( $\bar{x} \pm s$ ), and a *P*-value of less than 0.05 was considered statistically significant.

### 3 Results and analysis

**3.1 Comparison of IL-6 levels across various groups** Compared to the control group, IL-6 levels were significantly reduced in all other groups. Notably, the pure traditional Chinese medicine group and the combined medication groups at low and medium doses exhibited significant decreases in IL-6 levels ( $P < 0.05$ ). Furthermore, IL-6 levels in the combined medication groups at low and medium doses were significantly higher than those in the pure traditional Chinese medicine group ( $P < 0.05$ ). Additionally, the combined medication group at medium dose demonstrated significantly higher IL-6 levels than the combined medication group at low dose ( $P < 0.05$ , Table 1).

**Table 1 Comparison of IL-6 levels across various groups**

Group	Dose//g/kg	IL-6 level//mmol/L
Blank control	10	89.99 ± 18.14
Model control	10	143.75 ± 71.69
Erchen decoction	10	138.94 ± 28.66
Doxofylline	17.3	122.81 ± 41.81
Combined medication group at low dose	17.3 (Doxofylline), 5 (Erchen decoction)	125.36 ± 30.26
Combined medication group at medium dose	17.3 (Doxofylline), 10 (Erchen decoction)	115.88 ± 23.43
Combined medication group at high dose	17.3 (Doxofylline), 20 (Erchen decoction)	106.62 ± 57.83

**3.2 Changes in body weight of rats** The study found that treatment regimens capable of effectively reducing IL-6 levels—specifically, the Erchen decoction group and the combined medication groups at low and medium doses—significantly promoted

weight gain in rats. Notably, the body weight after treatment was significantly greater than before treatment, and it continued to increase throughout the treatment period ( $P < 0.05$ ). Detailed data are presented in Table 2.

**Table 2 Changes in body weight of rats before and after treatment**

Group	Before treatment	After treatment
Erchen decoction	184.67 ± 21.61	218.83 ± 32.43
Combined medication group at low dose	209.80 ± 26.86	239.60 ± 29.46
Combined medication group at medium dose	192.33 ± 27.78	217.33 ± 14.58

## 4 Discussion

Currently, Western medical treatment for COPD primarily focuses

on anti-inflammatory therapy and bronchodilation, supplemented by symptomatic treatments including antitussives, expectorants,

and oxygen therapy. Nevertheless, challenges persist, such as significant pulmonary damage and a high rate of disease recurrence. Consequently, strategies aimed at reducing lung injury and minimizing the likelihood of recurrence are critical components of effective COPD management<sup>[5]</sup>. The combination of doxofylline and Erchen decoction represents a therapeutic approach that integrates traditional Chinese medicine with Western medicine. This strategy can produce synergistic effects through complementary mechanisms, reduce side effects, enhance patient tolerance, and holds considerable clinical potential. Interleukin-6 (IL-6) is a multifunctional cytokine that plays a crucial role in various biological processes, including inflammatory responses, immune regulation, and hematopoiesis<sup>[6]</sup>. It serves as a valuable biomarker for assessing the severity of inflammatory responses in patients with COPD<sup>[7]</sup>. COPD is characterized as a chronic wasting condition that frequently results in weight loss among patients. Research indicates that 24% of individuals with stable COPD exhibit low body weight, with this proportion increasing to between 54% and 60% during periods of acute exacerbation. Body weight serves not only as an independent prognostic factor but also demonstrates a progressively stronger association with prognosis as the severity of lung function decline worsens<sup>[8–9]</sup>. Several studies have reported that an increase in body mass index (BMI) is significantly associated with an increase in the FEV1/FVC ratio, demonstrating a strong positive correlation. Additionally, the inflammatory cytokine IL-6 has been shown to promote protein catabolism and accelerate muscle atrophy. These findings suggest that body weight is a critical factor in assessing the therapeutic outcomes of COPD. Therefore, this study focused on evaluating changes in body weight and IL-6 levels in a COPD rat model before and after treatment to investigate the disease model.

Doxofylline inhibits the synthesis and release of adenine nucleotides, promotes the relaxation of airway smooth muscle, and stimulates the secretion of metabolite-activated proteins, thereby significantly enhancing ciliary clearance. Additionally, it effectively antagonizes adenosine receptors, resulting in the alleviation of airway spasms and bronchodilation<sup>[10]</sup>. Erchen decoction originates from the *Taiping Huimin Heji Ju Fang (Prescriptions of the Bureau of Taiping People's Welfare Pharmacy)* and consists of traditional Chinese medicinal ingredients, including *Pinellia ternata*, *Citri Reticulatae Pericarpium*, *Poria cocos*, and *Glycyrrhiza uralensis*. In the formulation, *P. ternata* serves as the principal ingredient and contains alkaloids, volatile oils, and other constituents that contribute to drying dampness and resolving phlegm. *Citri Reticulatae Pericarpium* functions as a ministerial drug, rich in volatile oils and flavonoids. It not only regulates the ascending and descending movement of qi within the spleen and lungs to harmonize qi and the middle energizer but also dries dampness, regulates qi, and warms to transform phlegm and turbidity. The *Essentials of Materia Medica* states that *Citri Reticulatae Pericarpium* possesses properties that enable it to dry and disperse, nourish and purge, as well as to ascend and descend. It is particularly effective in treating qi stagnation within the middle energizer when accompanied by cold syndrome, addressing both the symptoms and the underlying cause simultaneously. *P. cocos* is commonly employed as an

adjuvant herb; its primary constituents, polysaccharides and triterpenoids, contribute to strengthening the spleen and eliminating dampness. *G. uralensis*, a conductant drug, contains glycyrrhizic acid, glycyrrhizin, and other compounds that serve to harmonize the effects of various herbs.

This study demonstrated that the combination of doxofylline and Erchen decoction more effectively reduced the inflammatory cytokine IL-6 in the serum of COPD models. Additionally, the body weight of COPD rat models increased following treatment, indicating that this combination exerts a therapeutic effect on COPD in these models. When used in combination, the therapeutic effect of reducing serum IL-6 levels demonstrates a positive correlation with dose, but this relationship is not strictly linear. Further investigation is required to elucidate the mechanisms underlying the enhanced therapeutic efficacy of the combination and to clarify the relationship between therapeutic effect and drug dose.

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