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# A multicenter randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of rhubarb in treating acute exacerbation of chronic obstructive pulmonary disease of the syndrome type phlegm-heat obstructing the lungs

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## KEYWORDS

Traditional Chinese medicine;  
COPD;  
Phlegm-heat obstructing the lung syndrome;  
Rhubarb;  
Randomized controlled trial

**Abstract** *Objective:* To observe the clinical efficacy and safety of oral administration of the traditional Chinese herb rhubarb to treat acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

*Method:* This was a multicenter randomized double-blinded placebo controlled study that took place in 7 provinces of China that enrolled 244 patients (aged 18–80 years) who had acute exacerbation of COPD with the traditional Chinese syndrome pattern of phlegm-heat obstructing lung. Participants were divided into experimental and control groups. The experimental group received 4.5 g of rhubarb granules twice daily and the control group received placebo granules. Both groups also received conventional Western therapy consisting of oxygen therapy, an antibiotic, expectorant, and a bronchodilator. Treatment lasted 10 days. Symptom scores for cough, sputum volume and color, wheezing and chest tightness before treatment and on days 3, 5, 7, and 10 during the treatment were recorded. Lung function, arterial blood gas and levels of serum inflammatory factors, interleukin-4 (IL-4), interleukin-8 (IL-8), and

*Abbreviations:* COPD, chronic obstructive pulmonary disease; TCM, traditional Chinese medicine; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; FEV<sub>1</sub>%, forced expiratory volume in 1 s/forced vital capacity ratio; FAS, full analysis set; PPS, per protocol set; CRP, C reactive protein; GOLD, global initiative for chronic obstructive lung disease; RT, routine test; ECG, electrocardiogram; ABG, arterial blood gas; TNF- $\alpha$ , tumor necrosis factor alpha; IL-4, interleukin 4.

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interleukin-10 (IL-10) and tumor necrosis factor-alpha (TNF- $\alpha$ ), before and after treatment were measured.

**Results:** The sample size of the full analysis set (FAS) was 244 participants, and the sample size of per protocol set (PPS) was 235. Following 10 days' treatment, symptom scores of the experimental group were markedly lower than those of the placebo group (FAS: mean difference  $-1.67$ , 95% CI:  $-2.66$  to  $-0.69$ ,  $P = 0.001$ ; PPS: mean difference  $-1.55$ , 95% CI:  $-2.56$  to  $-0.54$ ,  $P = 0.003$ ). Lung function in the experimental group was significantly higher than in the placebo group (FEV<sub>1</sub>, FAS: mean difference  $0.12$ , 95% CI:  $0.06$  to  $0.18$ ;  $P < 0.001$ ; PPS: mean difference  $0.12$ , 95% CI  $0.05$  to  $0.18$ ;  $P < 0.001$ . FVC: FAS: mean difference  $0.16$ , 95% CI:  $0.06$  to  $0.26$ ;  $P = 0.002$ ; PPS: mean difference  $0.16$ , 95% CI  $0.05$  to  $0.26$ ;  $P = 0.003$ . FEV<sub>1</sub>%, FAS: mean difference  $5.95$ , 95% CI:  $3.36$  to  $8.53$ ;  $P < 0.001$ ; PPS: mean difference  $5.92$ , 95% CI  $3.28$  to  $8.56$ ;  $P < 0.001$ ). PaO<sub>2</sub>, PaCO<sub>2</sub>, as well as serum inflammatory factors were also improved when compared to the placebo group. There were no significant differences in the incidence rate of adverse reaction between the two groups.

**Conclusions:** Compared with placebo, rhubarb granules significantly reduced symptom scores, improved blood oxygen level, controlled systemic inflammatory response, without significant adverse effects. Thus, rhubarb may be a beneficial adjuvant method for treating the phlegm-heat obstructing the lung syndrome pattern of AECOPD.

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## Introduction

Chronic obstructive pulmonary disease (COPD) is a worldwide chronic respiratory disease that seriously impairs health. The Global Burden of Disease Study projected that COPD, which ranked sixth as a cause of death in 1990, will become the third leading cause of death worldwide by 2020; a newer projection estimated COPD will be the fourth leading cause of death in 2030.<sup>1</sup> A 2010 large-scale epidemiologic survey showed that the prevalence of COPD in China is higher than that in developed countries, and this is likely to increase significantly.<sup>2</sup>

The hallmark symptoms of COPD are dyspnea, cough, and increased amounts of phlegm and/or purulent phlegm exceeding the daily variation that require a change in drug therapy. Patients with COPD will have acute exacerbations about 0.5–3.5 times annually.<sup>3,4</sup> Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) results in massive healthcare expenditures. Furthermore, morbidity and mortality from AECOPD is high. Rapid relief of symptoms, reducing the accelerating decline in lung function and quality of life caused by frequent attacks are the therapeutic targets for AECOPD.<sup>5–7</sup> Although symptoms in 50% of patients with AECOPD recover to baseline in 7 days, in 14% of patients, symptoms and reduced lung function can persist for 35 days, which typically induces or aggravates cardiovascular complications.<sup>8–10</sup>

Both drug and non-drug therapies are available for the treatment of AECOPD. Short-acting bronchodilators, corticosteroids, and antimicrobials among others are common agents. Non-drug approaches include reducing exposure to risk factors, home oxygen therapy, lung volume reduction surgery, and mechanical ventilation. However, these methods are only partially effective at controlling acute

exacerbations and continuing decline of lung function.<sup>11</sup> Therefore, preventing attacks and controlling symptoms of AECOPD are urgent areas of research.

Syndrome pattern differentiation is a unique feature of traditional Chinese medicine (TCM). Once a pattern of symptoms has been identified, treatment is instituted based on the pattern. One type of lung disorder pattern is called phlegm-heat. Its symptoms include cough, dyspnea, fever, and throat pain. The TCM etiology is accumulation of phlegm, which transforms into heat, resulting in phlegm-heat blockage of the lungs. Treatment principle is to use herbal prescriptions that have purging actions.

Clinical trials have validated that Chinese herbal compounds can relieve COPD symptoms, reduce frequency of AECOPD, and improve quality of life.<sup>12–14</sup> Our previously published randomized double-blind controlled study, of which this study was a part of, showed that the herbal formula Xuan Bai Cheng Qi formula can reduce the symptoms of phlegm-heat obstruction pattern of COPD, decrease AECOPD frequency, improve ventilatory disorders, and lower serum cytokine levels. Results indicated that based on the TCM theory the lung and the large intestine being interior-exteriorly related, treating the lung and large intestine simultaneously can effectively manage AECOPD.<sup>15</sup> In the formula, rhubarb (*Rheum palmatum* L.) is the main herbal ingredient whose action is to clear the stomach and intestines. In a study by Li et al, rhubarb and conventional Western medications were used at an early stage to treat AECOPD (phlegm-heat obstructing the lung syndrome) with apparent efficacy. However, their sample size was small and only a single case-control study test index was used.<sup>16</sup> Thus, we undertook this multicenter randomized double-blind, placebo-controlled trial to assess the efficacy and safety of rhubarb for phlegm-heat

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