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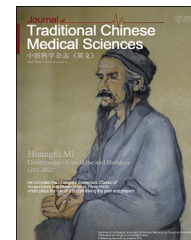
A multicenter randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of rhubarb in treating acute exacerbation of chronic obstructive pulmonary disease of the syndrome type phlegm-heat obstructing the lungs

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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

interleukin-10 (IL-10) and tumor necrosis factor-alpha (TNF-α), 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$_1$, 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$_1$%, 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$_2$, PaCO$_2$, 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.

Introduction

Chronic obstructive pulmonary disease (COPD) is a worldwide chronic respiratory disease that seriously impairs health. The Golbal 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.[1] 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.[2]

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.[3,4] 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.[5–7] 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.[8–10]

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.[11] 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.[12–14] 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.[15] 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.[16] Thus, we undertook this multicenter randomized double-blind, placebo-controlled trial to assess the efficacy and safety of rhubarb for phlegm-heat

obstructing the lung pattern of AECOPD to validate the TCM principle of treating the large intestine also treats the lungs.

Methods

Ethics and trial registration

This study was approved by ethical research committees of Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine (No. DZMSP20090302). This study was part of a larger trial registered with the Chinese Clinical Trial Registry Center (ChiCTR-TRC-09000533).

Study design and participants

This was a multicenter randomized double-blind, placebo-controlled clinical trial. Male and female patients aged 18—80 years with COPD, diagnosed from October 2009 to February 2013, were enrolled.

The sample size was calculated by the method of approximate sample size. Basing on comparable studies, suppose the effective rate of convertional medicine plus placebo was 75%, and the effective rate of convertional medicine combined with rhubarb was 90%.[16,17] The control group and trial group adoped 1:1 parallel design. With 5% one-side significance level and 90% statistical power, it was determined that 122 participants should be randomly assigned to each group, considering an approximate 10% drop-out rate. Overall, we studied 244 cases.

Randomization and blinding

SAS 8.0 software (SAS Institute, Cary, NC, USA) was used to generate 1—244 randomized numbers and a data table to randomize drug allocation and drug numbers. Patients who met the inclusion criteria and signed the informed consent form were randomly allocated to the treatment group or control group. Participants and investigators, including statisticians, were blinded to the identity of the experimental medicine and placebo. Unblinded envelopes were prepared at the same time to ensure physicians had access to the therapeutic measures administered to patients in case of an emergency.

Diagnostic criteria

Diagnoses of COPD and AECOPD were based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD; 2007)[18] criteria and on Chinese Society of Respiratory Diseases (2007) guidelines.[19]

Phlegm-heat obstructing the lung syndrome was diagnosed based on State Administration of Traditional Chinese Medicine guidelines[20] and criteria outline by Wang and Lu.[21]

Primary symptoms included cough and/or wheezing, yellow, sticky phlegm. Secondary symptoms included irritability, thirst with desire for cold liquids, fever without aversion to cold, yellow urine, hard stools, abdominal fullness, red tongue, yellow and greasy tongue coating, and slippery pulse and rapid pulse.

COPD was diagnosed if primary symptoms existed combined with any two or more of the secondary symptoms.

Inclusion and exclusion criteria

Patients were included if they met the diagnostic criteria of AECOPD; had GOLD levels 1 through 4 symptoms; had an acute attack of COPD within the past 5 days; were 18 through 80 years-old of either sex; were diagnosed with TCM syndrome pattern of phlegm-heat obstructing the lung; had not participated in other clinical trials within the past 1 month; and provided informed consent.

Patients were excluded if they had airway limitation caused by bronchiectasis, pulmonary cystic fibrosis, lung cancer, or other respiratory disease; had COPD and comorbidities such as heart failure, acute cerebral hemorrhage, digestive tract bleeding, aplastic anemia, acute renal failure, or other severe disease; COPD with unstable comorbidities such as hypertension, heart disease, diabetes; mental illness, severe neurologic deficit; severe diseases of the heart, liver, kidney, and hemopoietic system; recent use of immunosuppression agents; history of allergy or known allergy to rhubarb or drugs used in the trial; women who are pregnant or breastfeeding; and had diarrhea or bowel movements 3 or more times a day.

Withdrawal criteria

Withdrawal from the trial included the following situations: serious complications result from existing condition or process or rapid deterioration of existing condition; development of symptoms unrelated to existing condition that affect participant's completion of trial; poor adherence to trial protocol; participant unwilling to continue in trial.

Treatment

Conventional therapy
Both the experimental and control groups received conventional therapy, which was based on Chinese Society of Respiratory Diseases (2007) guidelines[19] and included infection control with oxygen therapy (1—3 L/min) and cefotaxime (2 g, intravenous gtt, Q12H); the expectorant ambroxol hydrochloride (60—180 mg/d, BID), and the bronchodilator aminophylline (200—300 mg/d, BID or TID).

Experimental and placebo treatments
The raw dried root and rhizome of rhubarb grown in Liangzhou District, Gansu Province in China, and obtained from Beijing Tong Ren Tang Pharmacy. The raw material was then manufactured into boil-free granules (lot number: 0905301-3) by Jiangyin Tianjiang Pharmaceutical Company (Jiangsu, China). This manufacturer also prepared the placebo granules, which consisted of cyclodextrin, a bittering agent, and food color. The rhubarb and placebo granules had were of similar color and taste and were administered at the same dosage: 9 g of granules (two

packets, 4.5 g/packet) dissolved in hot water, 30 min after breakfast and dinner, for 10 days. All participants were instructed not to use any other herbal medicines during the trial.

Outcome measures

Primary outcomes
The primary outcome measures were symptom scores, lung function, and safety index.

Symptom scores were determined based on a scale similar to the Likert scale[22] and on recommendations per Zheng.[23] Main symptoms of AECOPD, which are cough, sputum volume and color, severity of wheezing and chest tightness were scored on a scale of 0, 2, 4, and 6, which represented, respectively, symptomatic, mild, moderate, and severe,. Thus, the higher the score, the more severe the symptoms. Scoring was completed independently by investigators and participants before the trial started and on days 3, 5, 7, and 10 (final day).

Lung function changes in the form of forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and FEV_1 (% predicted) from baseline, measured on the day of randomization and 10 days after randomization. FEV_1 and FVC were measured using calibrated spirometry on the day of randomization before administration of the experimental medicine and placebo. On day 10 after randomization, FEV_1 and FVC were measured after the morning dose.

Safety parameters included changes in routine blood and urine test results, liver and kidney function test results, changes in electrocardiogram, and type, severity, and occurrence rate of adverse events.

Secondary outcomes
Secondary outcomes were arterial blood gas analysis and inflammatory factor expression.

Arterial blood gas analysis included partial pressure of carbon dioxide ($PaCO_2$) and partial pressure of oxygen (PaO_2). Inflammatory factors assayed were tumor necrosis factor alpha ($TNF\alpha$), the cytokines, interleukins 4, 8, and 10 (IL4, IL8, IL10).

Statistical analyses

Two researchers input the data using version 3.0 of Epidata (Epidata Association, Odense, Denmark) to set up a database. Analysis was performed against baseline information, therapeutic evaluation, and safety index. The per-protocol analysis set was used for participants who completed an interview survey but withdrew halfway through the study for various reasons. The last observation carried forward (LOCF) was applied to partial loss of data information.

The paired-sample t-test or analysis of covariance was used for continuous variable measurement data. The Huynh−Feldt (H−F) method was used for data that were measured repeatedly on the same observational index at different times. If H−F conditions were met, the data were then analyzed as for repeated measurements. The chi square test was used to test enumeration data. Therapeutic effects were tested with 95% confidence interval. A value of

$P < 0.05$ was considered significant. All data were analyzed with SPSS version 19.0.

Results

Study population

Participants were recruited from October 2009 to February 2013 from 8 medical centers: Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine (38 participants), Dongfang Hospital of Beijing University of Chinese Medicine (28 participants), Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine (38 participants), First Affiliated Hospital of Anhui University of Chinese Medicine (26 participants), Chinese Medicine Hospital of Hebei Province (40 participants), Affiliated Hospital of Gansu University of Chinese Medicine (16 participants), Affiliated Hospital of Liaoning University of Traditional Chinese Medicine (42 participants), and Chinese Medicine Hospital of Kaifeng City of Henan Province (16 participants).

At the outset, 285 patients were screened and evaluated, 41 patients were excluded, thus 244 participants were randomized (Fig. 1). Intention-to-treat analysis resulted in 122 allocated to the experimental group, and the remaining 122 participants in the placebo group. All 244 cases were included in the analysis. During the trial, 3 participants dropped out without explanation, 1 participant from the experimental group and participants from the placebo group. For participants who withdrew, data observed at the last time point was included in the analysis. All 244 participants completed baseline screening, and there was no statistical difference in demographic data (age, sex, height, and weight), vital signs (blood pressure and heart rate), disease duration, and symptom scores between groups ($P > 0.05$), indicating baseline data of the 2 groups were similar (Table 1).

Primary outcomes

There were no significant differences in main symptom (cough, expectoration, wheezing, and chest tightness) scores between the 2 groups at baseline before treatment (Table 2). On days 3, 5, 7, and 10 of treatment, main symptoms scores in the experimental group were significantly lower than those in the placebo group (Table 2).

There were no significant differences in FEV_1, FVC, and FEV_1% between the 2 groups at baseline before treatment (Table 3). After the end of treatment (on day 10), FEV_1, FEV, and FEV_1% were significantly higher in the experimental group compared with the placebo group (Table 3). Blood, urine RT, and liver and kidney function test results, as well as ECG assessments of the 2 groups were not significantly different before and after treatment (Table 4). Serious adverse reactions were not observed in either group. Two participants in the placebo group and seven participants in the experimental group developed diarrhea that was not statistically significant.
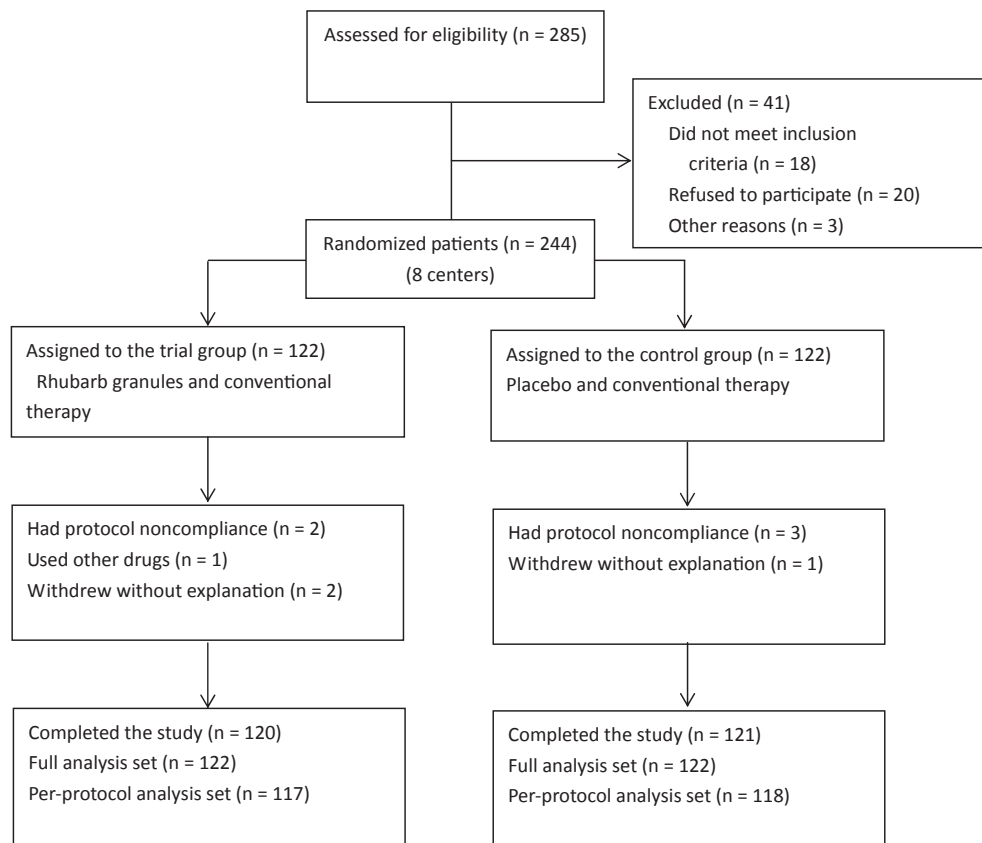
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                    ┌─────────────────────────────────┐
                    │ Assessed for eligibility (n = 285) │
                    └─────────────────────────────────┘
                                   │
                                   │        ┌──────────────────────────────────┐
                                   │───────▶│ Excluded (n = 41)                 │
                                   │        │   Did not meet inclusion          │
                                   │        │     criteria (n = 18)             │
                                   │        │   Refused to participate (n = 20) │
                                   │        │   Other reasons (n = 3)           │
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                    │ Randomized patients (n = 244)     │
                    │ (8 centers)                       │
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Fig. 1 Trial profile.

Boxes in the trial profile:

- Assigned to the trial group (n = 122) Rhubarb granules and conventional therapy
- Assigned to the control group (n = 122) Placebo and conventional therapy
- Had protocol noncompliance (n = 2) Used other drugs (n = 1) Withdrew without explanation (n = 2)
- Had protocol noncompliance (n = 3) Withdrew without explanation (n = 1)
- Completed the study (n = 120) Full analysis set (n = 122) Per-protocol analysis set (n = 117)
- Completed the study (n = 121) Full analysis set (n = 122) Per-protocol analysis set (n = 118)

Secondary outcomes

$PaCO_2$ and PaO_2 did not differ significantly between the 2 groups at baseline before treatment (Table 5). However, at the end of treatment on day 10, $PaCO_2$ in the experimental group was significantly lower than that in the placebo group (Table 5), and PaO_2 was significantly higher than that in the placebo group. When attempting to collect blood samples for inflammatory factor analyses, only 20 serum samples were collected from the treatment group, and 17 were collected from the placebo group. At baseline, there were no significant differences in the levels of TNF-α, IL4, IL8, and IL10 between the 2 groups (Table 6). At the end of treatment on day 10, levels of TNF-α, IL8, and IL-4 were significantly lower in the experimental group than in the placebo group. However, IL10 levels were significantly higher in the experimental group than in the placebo group (Table 6).

Discussion

TCM theory holds that the lung and the large intestine are interior-exteriorly related. The lung and large intestine are connected through their channels, and the two organs are thus physiologically interrelated, and affect one another pathologically. For example, patients with allergic rhinitis (upper respiratory system) and asthma (lungs) had more lower gastrointestinal symptoms compared with patients with diabetes, osteoarthritis, rheumatoid arthritis.[24]

Digestive system manifestations, such as gastroesophageal reflux, gastrointestinal mucosal barrier dysfunction, slow gastrointestinal motility, abdominal distension, constipation, among other symptoms are usually during AECOPD.[25,26] Our previous study showed that symptoms of the lower digestive tract, such as constipation and abdominal distension, can have a negative impact on pulmonary symptoms, induce AECOPD, and reduce quality of life.[27] Therefore, in treating COPD, it is important to ensure the intestinal tract remains unobstructed in patients with lower digestive tract symptoms of constipation and abdominal distension. Maintaining an unobstructed gut is a common TCM treatment for constipation of excess heat pattern. In China, Major Order the Qi Decoction (da cheng qi tang), a representative prescription for clearing the gut, is often modified for treatment of the phlegm-heat obstructing the lung pattern of COPD. A systematic review reported that treating patients who have frequent AECOPD with modifications of this formula appears to improve $FEV_1\%$, reduce arterial PCO_2, and shorten duration of mechanical ventilation. However, large-sample RCTs validating these findings are lacking.[28]

Rhubarb is a Chinese herb that has been used for centuries to treat intestinal obstruction. The active chemical compounds in this herb are emodin, chrysophanic acid, rhein, and anthraquinone glycoside.[29–33] These compounds have antipyretic, anti-inflammatory, anti-aging, antioxidant, and immune regulatory effects, and are thus used clinically for acute intestinal obstruction, chronic nephrosis, acute pancreatitis among other disorders. The

Table 1 Baseline characteristics of participants.

Characteristics	Trial group (n = 122)	Control group (n = 122)	$t/X^2/Z$	P
Age (SD), years	69.9 ± 10.3	70.7 ± 9.8	0.621	0.54
Body mass index (SD), kg/m^2	23.2 ± 3.4	22.8 ± 3.1	−1.09	0.28
Sex				
Male, (n) %	84 (69%)	82 (67%)	0.08	0.78
Female, (n) %	38 (31%)	40 (33%)		
Body temperature (°C)	36.6 ± 0.6	36.7 ± 0.6	0.444	0.66
Exacerbation				
Frequency (times)	2.5 ± 1.2	2.6 ± 1.2	0.575	0.57
Currently exacerbation	3.5 ± 1.3	3.5 ± 1.3	0.000	1
Smoking status				
Currently smoking, n (%)	21 (17%)	16 (13%)	0.74	0.39
Never smoked, n (%)	47 (38%)	52 (42%)		
Ever smoked, n (%)	54 (44%)	54 (44%)		
No. of packs/years	326.3 ± 210.9	337.9 ± 192.6	0.07	0.95
FEV1/FVC	55.5 ± 9.8	56.9 ± 9.6	1.163	0.25
GOLD classification				
GOLD 1, n (%)	9 (7%)	9 (7%)	1.37	0.24
GOLD 2, n (%)	62 (51%)	58 (48%)		
GOLD 3, n (%)	37 (30%)	45 (37%)		
GOLD 4, n (%)	14 (12%)	10 (8%)		

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SD, standard deviation.

Table 2 Cumulative symptom scores in rhubarb and control groups during 10-day treatment.

Cumulative symptom scores	Full analysis set			Per-protocol analysis set		
	Rhubarb group[a] (n = 122)	Control group[a] (n = 122)	Treatment effect[b] (95% CI; P)	RR Rhubarb group[a] (n = 117)	Control group[a] (n = 118)	Treatment effect[b] (95% CI; P-value)
Day1 (Baseline)	19.3 (4.5)	20.1 (4.3)	−0.77 (−1.88, 0.33; 0.17)	19.4 (4.5)	20.1 (4.3)	−0.70 (−1.84, 0.44; 0.23)
Day 3	14.3 (4.2)	16.5 (4.1)	−2.16 (−3.20, −1.11; <0.001)	14.3 (4.2)	16.4 (4.0)	−2.09 (−3.14, −1.04; <0.001)
Day 5	10.5 (3.6)	13.2 (4.2)	−2.71 (−3.68, −1.73; <0.001)	10.5 (3.6)	13.1 (4.1)	−2.59 (−3.58, −1.60; <0.001)
Day 7	8.0 (3.8)	9.6 (3.7)	−1.67 (−2.62, −0.73; 0.001)	8.1 (3.8)	9.5 (3.7)	−1.46 (−2.41, −0.50; 0.003)
Day 10 (End)	5.3 (4.1)	7.0 (3.7)	−1.67 (−2.66, −0.69; 0.001)	5.4 (4.1)	6.9 (3.7)	−1.55 (−2.56, −0.54; 0.003)

Abbreviation: CI, confidence interval.
Mauchly's test of sphericity was applied: W = 0.534, $P < 0.001$.
[a] Data presented as mean (SD).
[b] Repeated measures analysis of variance (ANOVA) for estimating with 95% confidence interval for difference.

TCM action of rhubarb takes place primarily in the large intestine, but by virtue of the relatedness of the large intestine and lung, symptoms of the lung, such as AECOPD, can also be alleviated by rhubarb. Although these effects are well-known in TCM and reported in the literature, there are still no persuasive large-scale, evidence-based studies of its safety and efficacy.

Our study was a randomized double-blinded placebo controlled study that took place in 8 medical centers in 7 cities in China. By day 3 of receiving rhubarb and conventional medicine, symptoms, including cough, amount of sputum, wheezing, and chest tightness began to improve. Arterial blood gas values also improved. The safety parameters measured in this study as well as the fact that no adverse reactions occurred in either group, indicated that rhubarb plus conventional therapy appears to be a safe therapy.

COPD leads to systemic inflammatory responses including oxidative stress, activation of inflammatory cells in the peripheral blood and early generation of inflammatory cytokines.[34] Levels of IL4, IL8, TNF-α, and other inflammatory factors are higher in patients with AECOPD than

Table 3 Lung function measurements in rhubarb and control groups before and after 10-day treatment.

Lung function	Full analysis set			Per-protocol analysis set		
	Rhubarb group[a] (n = 122)	Control group[a] (n = 122)	Treatment effect[c] (95% CI; P)	Rhubarb group[a] (n = 117)	Control group[a] (n = 118)	Treatment effect[c] (95% CI; P)
FEV_1 (liters)						
Day 1 (Baseline)	1.19 (0.38)[b]	1.19 (0.40)	0.00 −(−0.10, 0.10; 0.97)	1.19 (0.38)	1.19 (0.39)	0.00 −(−0.09, 0.10; 0.93)
Day 10 (End)	1.41 (0.39)	1.29 (0.47)	0.12 (0.01, 0.23; 0.03)	1.42 (0.38)	1.29 (0.47)	0.12 (0.01, 0.23; 0.03)
Mean D[b]	0.22 (0.19)	0.10 (0.30)	0.12 (0.06, 0.18; <0.001)	0.22 (0.19)	0.10 (0.32)	0.12 (0.05, 0.18; <0.001)
FVC (liters)						
Day 1 (Baseline)	2.18 (0.65)	2.10 (0.58)	0.08 −(−0.08, 0.23; 0.31)	2.19 (0.65)	2.11 (0.57)	0.08 −(−0.07, 0.24; 0.30)
Day 10 (End)	2.39 (0.53)	2.17 (0.62)	0.21 (0.07, 0.36; 0.004)	2.40 (0.51)	2.19 (0.60)	0.21 (0.07, 0.35; 0.005)
Mean D[b]	0.21 (0.42)	0.08 (0.48)	0.16 (0.06, 0.26; 0.002)	−0.21 (0.42)	−0.08 (0.48)	0.16 (0.05, 0.26; 0.003)
FEV_1% Perd						
Day 1 (Baseline)	53.48 (18.98)	52.13 (19.17)	1.35(−3.46, 6.16; 0.58)	54.01 (18.84)	52.17 (19.27)	1.84 (−3.06, 6.74; 0.46)
Day 10 (End)	62.49 (18.90)	55.35 (20.59)	7.14 (2.16, 12.12; 0.005)	63.10 (18.59)	55.56 (20.68)	7.54 (2.48, 12.59; 0.004)
Mean D[b]	9.01 (10.39)	3.22 (10.53)	5.95 (3.36. 8.53; <0.001)	9.09 (10.46)	3.39 (10.50)	5.92 (3.28, 8.56; <0.001)

Abbreviations: CI, confidence interval; FEV_1%pred, FEV_1 percentage of predicted value; FVC, forced vital capacity; Mean D, mean difference.
  [a] Data presented as mean (SD).
  [b] $P < 0.01$: Change between pre-treatment and post-treatment (within group difference by paired t test).
  [c] Covariance analysis estimate with 95% confidence interval (CI) for differences.

in patients with stable COPD.[35,36] Pathophysiology of COPD involves interaction of numerous inflammatory cell types leads to an imbalance of cellular immunity, promotes appearance and development of COPD airway inflammation and eventually leads to structural remodeling of the airways and progressive airflow limitation.[37−39] Our study found significantly reduced levels of TNF-α and IL8 and increased levels of IL10 in the experimental group compared with the placebo group, indicating that rhubarb may have helped regulate inflammatory cells and thus control airway inflammation.

However, there are some limitations to this study. First, the duration of the study is only 10 days. Changes of patients' quality of life and the frequency of acute exacerbations of COPD were not observable. In addition, it is difficult to get blood samples, so the comparison between levels of TNF-α, IL4, IL8, and IL10 are not from all enrolled patients, which may therefore be biased. Further studies should be performed to evaluate the long-term efficacy of rhubarb formula as an adjuvant treatment for phlegm-heat obstructing the lung syndrome pattern of AECOPD, and

Table 4 Safety profile.

Variables[a]	Rhubarb group[b] (n = 122)		Control group[b] (n = 122)		P[a]
	Day 1 (Baseline)	Day 10 (End)	Day 1 (Baseline)	Day 10 (End)	
WBC (10^9/L)	9.1 (4.7)	7.6 (3.2)	9.4 (8.0)	7.5 (3.1)	0.78
HB (g/L)	143.0 (29.2)	136.2 (26.8)	136.3 (28.1)	134.3 (28.1)	0.52
RBC (10^{12}/L)	4.4 (0.7)	4.5 (1.1)	4.3 (0.6)	4.3 (0.6)	0.28
PLT (10^9/L)	212.4 (63.6)	210.9 (62.5)	209.4 (76.9)	207.5 (68.4)	0.80
NEUT (%)	66.5 (15.2)	61.8 (15.6)	68.9 (14.9)	62.1 (13.4)	0.44
ALT (U/L)	20.8 (13.5)	23.8 (11.6)	21.9 (16.3)	22.5 (14.1)	0.22
BUN (mmol/L)	6.1 (1.6)	5.8 (2.4)	6.1 (2.8)	5.8 (2.8)	0.90
Cr (umol/L)	79.5 (24.5)	77.1 (20.6)	85.2 (46.5)	80.3 (35.9)	0.99

Abbreviations: ALT, alanine aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; HB, hemoglobin; NEUT, neutrophilic granulocytes; PLT, platelets; RBC, red blood cells; WBC, white blood cells.
  [a] Covariance analysis for between group after treatment.
  [b] Data presented as mean (SD).

Table 5 Arterial blood gas analysis in rhubarb and control groups before and after 10-day treatment.

Variables	Full analysis set			Per-protocol analysis set		
	Rhubarb group[a] (n = 122)	Control group[a] (n = 122)	Treatment effect[c] (95% CI; P)	Rhubarb group[a] (n = 117)	Control group[a] (n = 118)	Treatment effect[c] (95% CI; P)
PaO_2						
Day 1 (Baseline)	70.6 (20.3)	71.5 (18.9)	−0.86 (−5.80, 4.08; 0.73)	70.3 (20.1)	71.3 (19.1)	−0.93 (−5.97, 4.11; 0.72)
Day 10 (End)	84.7 (20.4)	80.5 (15.9)	4.25 (−0.36, 8.86; 0.07)	85.3 (20.6)	80.8 (16.0)	4.56 (−0.16, 9.30; 0.06)
Improvement from baseline	14.6 (24.2)	9.0 (17.5)	4.55 (0.26, 8.84; 0.04)	15.5 (23.8)	9.5 (17.3)	4.91 (0.55, 9.27; 0.03)
$PaCO_2$						
Day 1 (Baseline)	44.44 (9.9)[b]	46.2 (12.1)	−1.77 (−4.55, 1.01; 0.21)	44.0 (9.7)	45. 9 (11.8)	−1.88 (−4.66, 0.89; 0.18)
Day 10 (End)	38.2 (8.6)	41.5 (8.3)	−3.26 (−5.39, −1.13; 0.003)	38.0 (8.4)	41.4 (8.4)	−3.39 (−5.55, −1.23; 0.002)
Mean D[b]	−6.3 (12.0)	−4.8 (9.0)	−2.67 (−4.60, −0.74; 0.007)	6.0 (12.1)	4.5 (8.8)	−2.78 (−4.75, −0.80; 0.006)

Abbreviations:CI, confidence interval; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial carbon dioxide pressure; Mean D, mean. difference.
  [a] Data presented as mean (SD).
  [b] $P < 0.01$: Change between pre-treatment and post-treatment (within group difference by paired t test).
  [c] Covariance analysis estimate with 95% confidence interval (CI) for differences.

Table 6 Pro-inflammatory cytokine levels in rhubarb and control groups before and after 10-day treatment.

Biomarkers	Rhubarb group[a]			Control group[a]			Treatment effect[d] (95% CI; P-value)
	Day 1 (Baseline)	Day 10 (End)	Mean D[c]	Day 1 (Baseline)	Day 10 (End)	Mean D	
TNFα (pg/mL)19 16	20.5 (3.4)	5.1 (1.9)	−15.49 (4.39)	18.9 (3.6)	6.5 (1.6)	−12.43 (3.28)[c]	−1.41 (−2.69, −0.14; 0.03)
IL−4 (pg/mL)19 17	6.0 (1.8)	2.8 (1.4)	−3.61 (1.78)	6.2 (1.4)	3.4 (1.3)	−2.77 (1.70)[c]	−0.98 (−1.71, −0.24; 0.01)
IL−8 (pg/mL)20 17	17.7 (3.3)	12.1 (3.1)	−5.62 (4.31)	18.0 (4.2)	14.9 (3.9)	−3.08 (5.36)[b]	−2.81 (−5.15, −0.46; 0.02)
IL−10 (pg/mL)20 17	3.6 (0.8)	4.5 (1.1)	0.91 (1.22)	3.5 (0.7)	3.7 (1.0)	0.12 (1.21)	0.85 (0.12, 1,58; 0.02)

Abbreviations: CI, confidence interval; TNFα, tumor necrosis factor alpha; IL, interleukin; Mean D, mean difference.
  [a] Data presented as mean (SD).
  [b] $P < 0.05$.
  [c] $P < 0.01$: Change between pre-treatment and post-treatment (within group difference by paired t test).
  [d] Covariance analysis estimate with 95% confidence interval for differences.

verify the inflammatory mechanism of rhubarb in the treatment of AECOPD.

Conclusion

We showed that oral administration of the granule form of the Chinese herb rhubarb along with conventional therapy helped treat phlegm-heat obstructing the lung syndrome pattern of AECOPD and no significant side effects were observed. The therapeutic mechanism of rhubarb may be related to its ability to attenuate inflammation but further studies are required to verify this.

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Author contributions

The design and implementation of the study is the responsibility of Yuhang Li, Fengjie Zheng and Miao Liu performed statistical analysis of data and wrote the report. Yueqi Wang, Xianggen Zhong, and Yan Sun were responsible

for the preparation and quality control of drugs. Ruohan Wu, Jinchao Zhang, Kuo Gao, and Yuchao Liu were responsible for clinical data entry and review. All authors have approved the publication of the final manuscript. All authors declare there are no conflicts of interest among them.

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