

# Effects of the Chinese herbal formula San-Huang Gu-Ben Zhi-Ke treatment on Stable Chronic Obstructive Pulmonary disease:study protocol of a randomized, double-blind, placebo-controlled trial

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## Method Article

**Keywords:** Chronic obstructive pulmonary disease; traditional Chinese medicine; Chinese herbal formula San-Huang Gu-Ben Zhi-Ke; clinical trials; clinical protocols

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## Abstract

**Background:** Due to the large number of patients, high mortality rate as well as high social costs and economic burden, Chronic obstructive pulmonary disease (COPD) has become one of the most important health problem around the world, which has attracted people's attention. Currently, Chinese herbs have been widely used as alternative medicine (CAM) for COPD patients. Chinese herbal formula San-Huang Gu-Ben Zhi-Ke (SHGBZK) have shown good clinical efficacy in COPD in preclinical studies. Animal experiments have enhanced that it has mucosal immune barrier function, it can maintain airway wall integrity, reduce inflammatory cell infiltration, promote inflammatory damage repair, and relieve airway narrow conditions.

**Methods/design:** The study is a randomized, double-blind, placebo-controlled trial. A total of 100 COPD patients at stable stage that diagnosed with syndrome of deficiency of lung qi and spleen qi will be recruited and randomly assigned to one of the two treatments group, with 50 in each group. One hundred COPD patients were randomly assigned to two treatment groups (SHGBZK treatment, N=50; placebo treatment, N=50). The two groups will receive basic treatment for COPD according to the 2017 GOLD Guidelines for Chronic Obstructive Pulmonary Disease. Patients will stick to the treatment they used to take as much as possible, and will be given present general treatment when AECOPD occurs during the study. Both groups will receive an 24-weeks intervention, and patient status was assessed at 24 weeks later and 28 weeks after treatment. After the 24-weeks treatment, another 28 weeks will be followed up. The outcome measures including the frequency and duration of acute exacerbation, lung function, TCM symptom score, exercise capacity, and quality of life will be assessed.

**Discussion:** It is hypothesized that SHGBZK will have beneficial effects in reducing the frequency and duration of acute exacerbation, improving exercise capacity function of COPD patients at stable stage that diagnosed with syndrome of deficiency of lung qi and spleen qi. This study may establish a new method for COPD patients, and thus differentiation from other drugs used for similar clinical indications in clinical use.

**Trial registration:** Chinese Clinical Trial Registry, ID: ChiCTR1800016349. Registered on 26 May 2018.

**Keywords:** Chronic obstructive pulmonary disease; traditional Chinese medicine; Chinese herbal formula San-Huang Gu-Ben Zhi-Ke; clinical trials; clinical protocols.

## Background

COPD is characterized by persistent and limited airflow, which can be progressively aggravated. The repeated acute exacerbation of COPD (AECOPD) can lead to a variety of complications, which cause the overall situation of disease getting worse [i]. Its reductions are a major goal of COPD management and an important indicator for evaluating the treatments. According to statistics, [ii]the incidence of COPD is about 10% in the global population. It is expected that the fatality rate of COPD will rise to the third place in the world [iii], and the economic burden will rank the fifth in the world by 2020. In China, the prevalence

of COPD in people over 40 years old is 8.2%[[iv]], the number of deaths due to COPD exceeds 1 million each year, and the number of disabled people over 5 million. In addition to pulmonary symptoms, studies[[v]] have shown that the most common complications of COPD patients are cardiovascular disease, diabetes, asthma and anemia. Most patients have one or two complications, which increase the social and economic burden. And most patients have mental anxiety symptoms[[vi]], which affects the working ability and quality of life[[vii]] of patients seriously. As COPD can be prevented, effective preventive measures will help to delay the recurrence and progressive aggravation of the disease.

Current treatments for COPD include inhaled corticosteroids and bronchodilators[[viii]]. Although effective at alleviating symptoms, these treatment methods do not alter disease progression. There is a pressing need searching a better treatment[[ix]], which could have a certain effect in improving the clinical symptoms, lower lung function decline, reduce mortality and shorten the hospitalization time. Traditional Chinese medicine has a great advantage in reducing the risk for severe exacerbation, improving lung function, positively impacting quality of life, and improving exercise capacity in stabilized patients with COPD, which can supplement the deficiency of modern medical treatment[[x]].

SHGBZK Chinese medicine is a Chinese herbal formula developed by Professor Chao Enxiang, a great doctor of Chinese medicine, who has more than 50 years of clinical experience. Preliminary clinical data demonstrated that it has good clinical efficacy in COPD and no obvious side effects[[xi]]. Animal experiments have enhanced that it has mucosal immune barrier function, it can maintain airway wall integrity, reduce inflammatory cell infiltration, promote inflammatory damage repair, and relieve airway narrow conditions. This study aims to evaluate the efficacy and safety of SHGBZK Chinese medicine for further research, in order to form a new safe and effective method in the treatment of stable COPD.

**Study objectives:** This study will evaluate the safety and efficacy of the Chinese herbal formula SHGBZK Chinese medicine as a treatment for COPD patients at stable stage that diagnosed with syndrome of deficiency of lung qi and spleen qi.

**Design and Setting:** One hundred patients with stable COPD were randomly assigned to two treatment groups—SHGBZK Chinese medicine treatment, N=50; placebo treatment, N=50. The two groups will receive basic treatment for COPD according to the 2017 GOLD Guidelines for Chronic Obstructive Pulmonary Disease. Both groups will receive an 24-weeks intervention, and patient status was assessed at 24 weeks later and 28 weeks after treatment.

**Main Outcome Measures:** The primary outcome is frequency of acute exacerbation of COPD. The secondary outcomes are duration of acute exacerbation of COPD, TCM symptom score, lung function, CAT score, MMRC grade, BODE score and 6-minute walking distance.

## Methods

### Study design

We will conduct a A randomized, double-blind, placebo-controlled trial. A flowchart of the study protocol is shown in Figure 1.

## Ethics and recruitment

All patients will sign the informed consent before inclusion. The study has been approved by the Ethical Research Committees of the China-Japanese Friendship Hospital with identifier 2018-57-K41-1. Any revisions of the study protocol will be submitted to the ethics committee.

COPD patients will be recruited from either the out-patient department or open recruitment. Recruitment began from November 2018 until a sample of 100 patients are enrolled.

## Inclusion criteria

The inclusion criteria are outlined below:

- The diagnostic criteria of COPD reference to Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease 2013 Revision [i] will be adopted as inclusion criteria for this trial;
- Patients with stable symptoms such as cough, sputum production or breathlessness for
- 4 weeks with no AE;
- The risk assessment of AECOPD is high risk (in the past 1 year, the number of AE is  $\geq$  2 times or being hospitalized is  $\geq$  1 time due to AE);
- the TCM syndrome pattern of lung qi and spleen qi deficiency, reference to Guidelines for TCM Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease 2011 edition [ii];
- aged between 40 and 80 years;
- with informed signed consent and participate voluntarily in the study.

## Exclusion criteria

Exclusion criteria include the following:

- confirmed diagnosis of Pneumonia and/or moderate to severe AECOPD in the past 4 weeks;
- Accepted Pneumonectomy in the past or Lung volume reduction surgery in 12 months before screening;
- Accepted long-term oxygen therapy (time > 15h / d) or mechanical aerator;

- Patients with a history of asthma, active tuberculosis, lung cancer, bronchiectasis, pulmonary embolism, pulmonary heart disease, interstitial lung disease or other active diseases;
- Patients with lower extremity activity limitation are unable to complete the six-minute walk test;
- Patients were diagnosed with serious hypertension, diabetes, tumors, primary heart, liver, kidney or blood system disease;
- Scr exceeds the upper limit of the reference value by 1.5 times, or AST, ALT  $\geq$  2 times the upper limit of the reference value;
- Patients with congenital or acquired immunodeficiency disease;
- Patients who are known or suspected of a history of alcohol or drug abuse;
- Patients with confusion, dementia or any kind of mental illness;
- Pregnant or breast-feeding women;
- Allergic to the used medicine;
- Frequent use of glucocorticosteroids orally;
- Patients were enrolled in other clinical trials during the previous three months;
- Researchers believe that who is not appropriate to participate in clinical trials.

## **Withdrawal, dropout and discontinuation**

Participants are free to withdraw at any time during the trial. Participants who wish to withdraw will be offered the option to cease trial medication but continue attending scheduled visits for outcome measurement. Participants who withdraw will be followed to investigate the reason for withdrawal. Participants may be advised to discontinue the treatment if there is a product-related adverse event of a serious nature or if the participant was not compliant with the study requirements. Discontinuers will not be replaced by new participants. Intention-to-treat analysis will be performed on missing data from discontinuers with the last observation carried forward method.

## **Sample size**

A total of 100 patients will be enrolled into this study with 50 in each group, respectively. The frequency of acute exacerbation of COPD is considered as the primary outcome. According to a previous study [[iii]] [[iv]], the number of the exacerbation frequency was 1.17 times every year by treatment of conventional medicine, and that was 0.97 times every year by treatment of TCM, and that was 0.68 times every year by treatment of both conventional medicine and TCM. Assume that there would be promotional value only when the exacerbation frequency decreased at least once for one patient every six months. The standard deviation $\pm$ SD $\pm$ value is 1 .25 times per year $\pm$ the two-sided  $\alpha$  is 0. 05 $\pm$ and  $\beta$  is 0. 10. Based on the formula (Due to technical limitations, the formula has been placed in the supplementary files section) of the

comparison between the means of the two samples, the sample size in each group is 40. Considering a 20% dropout rate over the course of the study, 50 patients will be enrolled in each group and the total sample size will be 100.

## Randomization and masking

**Randomization** The block randomization method was used. Select the appropriate length of the segment, and use the SAS9.4 (SAS Institute Inc., Cary, NC, USA) to generate a randomization sequence for 100 subjects (test group, control group) according to a 1:1 ratio, and list the treatment allocation corresponding to the serial number 001-100 (That is a random coding table). The placebo is made of SHGBZK Chinese medicine (5% and dextrin 95%) to insure the mimic appearance, smell, and taste. Both researchers and participants will not know the assignment. The randomization sequence table will be kept in a file. The method, process, group setting, and grouping result of the randomization sequence will be recorded either, so as to be checked when necessary. The information on intervention assignments will be kept in the third consulting center of biomedical statistics.

**Blind** Blind Design: In this study, the two stage blind was used. The first stage blind was represented by groups A and B. The second stage blind was respectively designated with the corresponding test drugs and placebo; The blind management and preservation: The blinding is carried out by the statistical unit. The clinical trial unit and the statistical analysis unit are respectively deposited in accordance with the relevant regulations after the blind sealed. The process of drug coding will be written by the blinder and saved; Emergency unblinding: if adverse event occurs during the study, the main investigator can decide whether to unblind according to the subject. The investigator needs to record the time, location and cause of the unblinding, and record in the medical record and CRF (the group information after unblinding should not be recorded in the CRF).

## Intervention measures

The two groups will receive basic treatment for COPD according to the 2017 GOLD Guidelines for Chronic Obstructive Pulmonary Disease. Patients will stick to the treatment they used to take as much as possible, and will be given present general treatment when AECOPD occurs during the study. Patients in the experimental group will take SHGBZK, while the control group will take SHGBZK placebo. The TCM granules are compound preparations of Chinese herbs and its main components are shown in Table 1. Each bag of SHGBZK granule (batch number: 180606) contains 3 g. The components of the TCM granules are produced and packed by An Hui Ji Ren Pharmaceutical Co. Ltd. with the authentication quality of Goods Manufacturing Practice (Approval Number: AH20160363), Anhui, PR China. The test results of drug quality were consistent with the required quality standards. Each type of granule will be given orally, four bags each time, three times a day for 24 weeks.

Patients need to take medication as directed by the doctor from us. The use of glucocorticoids, antibiotics, mucolytic agents and antitussive agents was prohibited during the study except there is AECOPD, and oral or external Chinese medicine preparations with the effect of tonifying spleen and lung were prohibited during the trial period.

## Outcome measure

### Primary outcome measure

The frequency of AECOPD is the primary outcome measure. AECOPD is characterized by increased respiratory symptoms, which is beyond daily routine variation, and requires a change in regular medication. Its reductions are a major goal of COPD management and an important indicator for evaluating the treatments. If at least 2 major symptoms or 1 major symptom plus more than 1 minor symptoms occur:

- ☒ Major symptoms: increased difficulty in breathing, increased sputum volume, purulent sputum;
- ☒ Minor symptoms: upper respiratory tract infection, unexplained fever, and wheezing.

If the interval between two onsets of acute exacerbation is within 1 week, and the acute exacerbation last for at least 2 days, it is counted as one number acute exacerbation. The number of frequency and duration of AECOPD occurred each time during the 24-week treatment period and 7-month follow-up, and then count the total number and average number of frequency and duration.

### The secondary outcome measures

**AECOPD situation** Time of first AECOPD occurs, the interval between two onsets of acute exacerbation, the duration of AECOPD and the severity of AECOPD after the treatment.

**TCM symptom score** TCM symptom of COPD patients at stable stage that diagnosed with syndrome of deficiency of lung qi and spleen qi will be adopted. The TCM symptom score scale is scored from 0 (normal) to 22 (severe). TCM symptom score is shown in Table 2.

**Lung function** The indicators of forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), forced expiratory volume in 1 second (FEV1% pred) and (FEV1/FVC); maximum expiratory mid-flow (MMEF) and peak expiratory flow (PEF) will be tested. A positive change from baseline in them will indicate the improvement in lung function.

**Dyspnea** The Modified Medical Research Council (MMRC) by the American Thoracic Society [19] will be assessed to evaluate the level of dyspnea. The MMRC scale is a simple grading system that scored from 0 (less severe) to 4 (severe).

**Quality of life** The COPD Assessment Test (CAT) will be adopted. The CAT is the self-complete questionnaires with eight items, each formatted as a semantic six-point ranging from 0 to 5. Range of CAT scores from 0 to 40. Higher scores denote a more severe impact of patient's quality of life. The patients will be invited to complete the questionnaires through face-to-face survey. The patients can answer each question and check the most appropriate opinion (a specific score) in their standards, hopes, pleasures, and concerns. Meanwhile, an investigator in each center will be assigned in the office to help the patients, and to check through each completed questionnaire to ensure that the patients answer all the questions.

**The 6-minute walking distance (6MWD)** This is to evaluate the distance a person can walk on a flat surface in 6 min to assess the exercise capacity.

**BODE index** will be adopted. BODE stands for Body mass index, airflow Obstruction, Dyspnea and Exercise capacity. Range of BODE scores from 0 to 40. The BODE score was further quartilized as follows: quartile 1 (a score of 0 to 2 points), quartile 2 (a score of 3 to 4 points), quartile 3 (a score of 5 to 6 points), and quartile 4 (a score of 7 to 10 points). The higher the level, the worse the patient's condition.

**Concomitant medication status.** Drug therapy that used to treat COPD during the study will be recorded.

**Mortality** All-cause mortality and COPD mortality will be calculated for the subjects during the study.

**Safety** The routine blood, urine, and stool tests, liver and kidney function tests, and an electrocardiogram are performed. Adverse events will be recorded at any time during the treatment period and follow-up period.

**Screening and run-in, baseline, treatment periods and endpoint**

The Adverse event, Physical examination, AECOPD situation, MMRC, CAT and TCM symptom score will be recorded at baseline (week 0), in every 4 weeks during the study period. The 6MWD and BODE will be recorded at weeks 0, 4, 12, 24, 32 and 52. The lung function will be observed at weeks 0, 24, and 52. Safety will be measured at weeks 0, 12 and 24, except Adverse event and Physical examination. The schedule of the assessment and interventions is depicted in Figure 2.

## Statistical analysis

All data will be analyzed by an independent statistician using SAS 9.4. For all analyses,  $P < 0.05$  is considered statistically significant. Measurement data will be presented as number of cases, mean, standard deviation, minimum, median, maximum, upper quartile (Q1), lower quartile (Q3), 95% confidence interval (95% CI) data. The paired-sample t test or signed rank sum test will be used to compare the difference between the two groups or pretreatment and posttreatment within one group. The analysis of covariance will be used to compare the differences of center effector other confounding factors.

## Discussion

Syndrome differentiation is the basic principle of Chinese medicine to recognize and treat diseases. It is held that the efficacy of TCM is most obviously observed in alleviating or improving the characteristic symptoms of patients diagnosed with the corresponding TCM syndrome. Professor Chao Enxiang, a great doctor of Chinese medicine, attaches great importance to the position and role of the body's vital energy in the pathogenesis of COPD. He emphasizes that "positive Qi exists in the body, thus evil Qi cannot invade". He believes that deficiency of lung and spleen and obstruction of phlegm and turbidity are the main pathogenesis characteristics of COPD in stable period. SHGBZK was developed for Tonifying the lung and strengthening the spleen, resolving phlegm and relieving cough.

According to the previous clinical studies, SHGBZK Chinese medicine has a good clinical effect on improving the effective rate of cough and cough in patients with 100%, improving wheezing efficiency by 85.71%. The total effective rate of SHGBZK is 96.67%, and no obvious toxicity or side effects is found. In our study, we will conduct a randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of the Chinese herbal formula SHGBZK Chinese medicine for stable COPD patients that diagnosed with syndrome of deficiency of lung qi and spleen qi. This study may establish a new method for COPD patients at stable stage, and thus differentiation from other drugs used for similar clinical indications in clinical use.

In our study, the frequency of acute AECOPD has been chosen as the primary outcome. We also employ validated and objective tools, such as the ACT score and FEV1 as outcome measurements. These measurements improve the reliability and generalizability of the results. Measures will be taken to strengthen quality control. To avoid the bias from the researchers' in the procedure of this study, an investigator separate from all of the clinical researchers will be hired as the contact person who preserve

and record the randomization information. Therefore, the clinical researchers do not have any effect on enrollment or randomization. Meanwhile outcome assessments will be made by an independent clinical statistician blinded to group allocation and uninvolved in providing intervention or management. Otherwise, we built a TCM symptom score table to evaluate the TCM symptom of COPD patients at stable stage that diagnosed with syndrome of deficiency of lung qi and spleen qi. However, there are some limitations of the study. The 6-month treatment period and 7-month follow-up duration is a little short, and the sample size is a little small to observe the changes in lung function and then show the effect of SHGBZK treatment.

The study has been developed according to the Consolidated Standards of Reporting Trials<sup>®</sup>CONSORT<sup>®</sup> [i]Statement.

## Declarations

### Acknowledgements

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### Funding

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### Availability of data and materials

Not applicable.

### Authors' contributions

YQZ, XL and DML are co-first authors of this manuscript, contributing equally to the design, conduct of the trials and drafting the manuscript. All authors participated in the design of the study. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

The Ethical Committee of the China-Japanese Friendship Hospital approved this study on 16 May 2018 (2018-57-K41). Written informed consent was obtained from all volunteers, and the study conformed to the ethical principles set forth by the Declaration of Helsinki.

### Ethics approval and consent to participate

The study has been approved by the Ethical Research Committees of the China-Japanese Friendship Hospital with identifier 2018-57-K41-1. Any revisions of the study protocol will be submitted to the ethics committee.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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## Tables

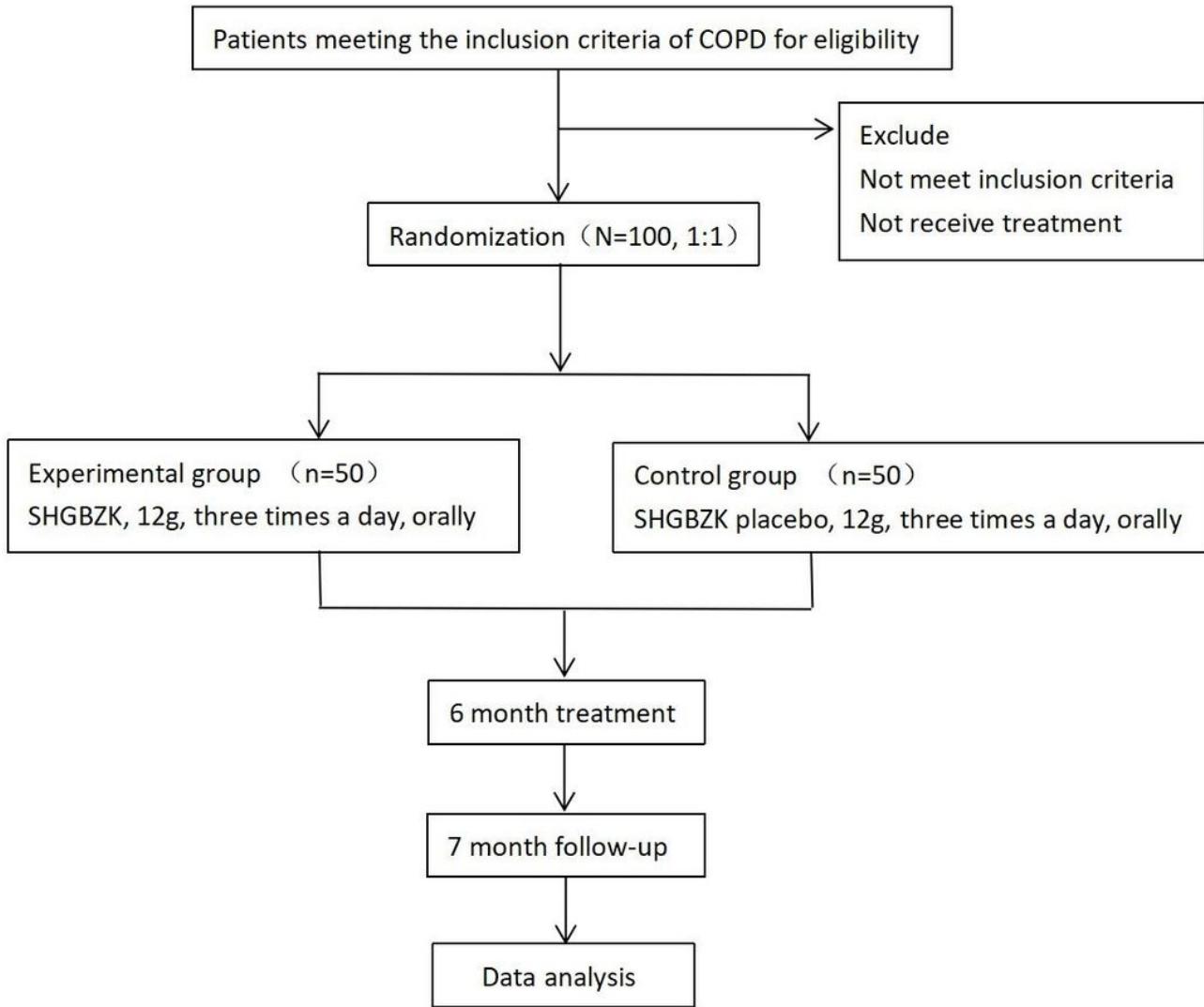
**Table 1 - Main components of traditional Chinese medicine treatment**

Chinese name	Latin name	Amount (g)
Chinese herbal formula San-Huang Gu-Ben Zhi-Ke		
Huang Qi	Astragalus propinquus	15
Huang Jing	Polygonatum sibiricum	12
Chen Pi	Pericarpium citri reticulatae	10
Bai Bu	Stemona japonica	10
Wu Wei Zi	Schisandra chinensis	8
Chi Shao	Paeonia lactiflora Pall	10
Huang Qin	Scutellaria baicalensis Georgi	8

**Table 2 - TCM symptom score**

Main symptom [score]	Normal [0]	Light[2]	Medium[4]	Severe[6]
Cough	No	Intermittent cough during the day	Cough in day and night without affecting work and sleep	Cough frequently in day and night, which affect work and sleep
Sputum	No	A small amount of sputum	Sputum and wheezy phlegm	A large amount of sputum and loud wheezy phlegm
Shortness of breath	No	Shortness of breath after work	Fatigue and shortness of breath	Be short of breath when quiet
Secondary symptoms	Normal [0]	Light[1]	Medium[2]	Severe[3]
Spontaneous perspiration	No	Sweat while eating	Intermittent sweat	Sweat soaks clothes, sweat more after work
Loss of appetite	No	Loss of appetite, but eat as usual	Eat less but not than 1/3 of usual	Eat less than 1/3 of usual
Weak	No	Can do light physical work	Can't do physical work	General fatigue, intend to stay in bed
Abdominal distention and Loose stool	No	Light Abdominal distention, and the stool is not forming	Abdominal distention is obvious and Loose stool	Abdominal distention is obvious and water-like stool

## Figures



**Figure 1**

Flow chart of the study - A randomized, double-blind, placebo-controlled trial is adopted. A total of 100 patients will be recruited and randomly assigned to one of the two treatments group, with 50 in each group. One hundred COPD patients were randomly assigned to two treatment groups (SHGBZK treatment, N=50; placebo treatment, N=50). The two groups will receive basic treatment for COPD according to the 2017 GOLD Guidelines for Chronic Obstructive Pulmonary Disease. Patients will stick to the treatment they used to take as much as possible, and will be given present general treatment when AECOPD occurs during the study. Both groups will receive an 24-weeks intervention, and patient status was assessed at 24 weeks later and 28 weeks after treatment. After the 24-weeks treatment, another 28 weeks will be followed up. The outcome measures including the frequency and duration of acute exacerbation, lung function, TCM symptom score, exercise capacity, and quality of life will be assessed. Patients need to take medication as directed by the doctor from us. The use of glucocorticoids, antibiotics, mucolytic

agents and antitussive agents was prohibited during the study except there is AECOPD, and oral or external Chinese medicine preparations with the effect of tonifying spleen and lung were prohibited during the trial period.

	Study period										
	Enrollment		Allocation						Follow up		
Time point	-1 week	Week4	Week8	Week12	Week16	Week20	Week24	Week32	Week40	Week52	
<b>Enrollment</b>											
Informed consent	×										
General information	×										
Medical history	×										
Eligibility screen	×										
Concomitant edication	×	×	×	×	×	×	×	×	×	×	
Allocation	×										
<b>Intervention</b>											
SHGBZK		◆					◆				
SHGBZK Placebo		◆					◆				
<b>Assessment</b>											
AECOPD situation	×	×	×	×	×	×	×	×	×	×	
Lung function	×						×			×	
CAT	×	×	×	×	×	×	×	×	×	×	
MMRC	×	×	×	×	×	×	×	×	×	×	
6MWD	×	×		×			×	×		×	
BODE	×	×		×			×	×		×	
TCM symptom score	×	×	×	×	×	×	×	×	×	×	
<b>Safety</b>											
Adverse event	×	×	×	×	×	×	×	×	×	×	
Physical examination	×	×	×	×	×	×	×	×	×	×	
Blood routine	×			×			×				
Urine routine	×			×			×				
Kidney and liver function	×			×			×				
12-lead electrocardiogram	×			×			×				
<b>Compliance assessments</b>		×	×	×	×	×	×	×	×	×	

**Figure 2**

Schedule of enrollment, intervention and assessments - The Adverse event, Physical examination, AECOPD situation, MMRC, CAT and TCM symptom score/TCM symptom of COPD patients at stable

stage that diagnosed with syndrome of efficiency of lung qi and spleen qi will be adopted. will be recorded at baseline week 0, in the every 4 weeks during the study period. The 6MWD and BODE will be recorded at weeks 0, 4, 12, 24, 32 and 52. The lung function will be observed at weeks 0, 24, and 52. Safety will be measured at weeks 0, 12 and 24, except Adverse event and Physical examination.

## Supplementary Files

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