

# Bufei huoxue capsules in the management of convalescent COVID-19 infection: study protocol for a multicenter, double-blind, and randomized controlled trial

Yuqin Chen<sup>1</sup>, Wenjun He<sup>1</sup> , Wenju Lu<sup>1</sup>, Yue Xing<sup>1</sup>, Jianling Bai<sup>2</sup>, Hao Yu<sup>2</sup>, Jiawei Zhou<sup>2</sup>, Jingyi Liang<sup>1</sup>, Jiyuan Chen<sup>1</sup>, Chi Hou<sup>1,3</sup>, Bihua Zhong<sup>1</sup>, Ting Wang<sup>4</sup>, Huazhuo Feng<sup>1</sup>, Xu Chen<sup>1</sup>, Tao Wang<sup>1</sup>, Kai Yang<sup>1</sup>, Nuofu Zhang<sup>1</sup>, Nanshan Zhong<sup>1</sup>, Chunli Liu<sup>1,\*</sup> and Jian Wang<sup>1,\*</sup>

<sup>1</sup>State Key Laboratory of Respiratory Disease, National Center for Respiratory Medicine, National Clinical Research Center for Respiratory Disease, Guangdong Key Laboratory of Vascular Disease, Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; <sup>2</sup>Department of Biostatistics, School of Public Health, Nanjing Medical University, Nanjing, China; <sup>3</sup>Department of Neurology, Guangzhou Women and Children's Medical Center, Guangzhou, China; <sup>4</sup>Department of Respiratory Children's Hospital of Chongqing Medical University, National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing, China

## Abstract

Up to 30 May 2021, the cumulative number of patients diagnosed with corona virus disease-19 (COVID-19) globally has exceeded 170 million, with more than 152 million patients recovered from COVID-19. However, the long-term effect of the virus infection on the human body's function is unknown for convalescent patients. It was reported that about 63% of COVID-19 patients had observable lung damage on CT scans after being released from the hospital. Bufei Huoxue (BFHX) capsules, including three active ingredients of traditional Chinese herbal medicine, has been used clinically to prevent and treat pulmonary heart diseases with Qi deficiency and blood stasis syndrome. Some small-scale clinical trials have found that BFHX can improve lung ventilation function, reduce blood viscosity, and improve cardiopulmonary function. However, the efficacy and safety of BFHX in the treatment of the recovery phase of COVID-19 are unknown. This study is a multicenter, double-blinded, randomized, controlled trial. Subjects with convalescent COVID-19 were randomized (1:1) into either a BFHX or control group and observed for three months concomitant with receiving routine treatment. The primary efficacy indicators are the evaluation results and changes of the St. George's Respiratory Questionnaire score, Fatigue Assessment Inventory, and 6-min walk distance. Based on the intention-to-treat principle, all randomly assigned participants will be included in the statistical analysis. The last visit's outcomes will be used as the final outcomes for participants who prematurely withdraw from the trial. Per protocol set will pick up from the full analysis set for analysis. Efficacy analysis will be performed on the intention-to-treat datasets and per-protocol datasets. This study and its protocol were approved by the Ethics Committee of our University. Prior to participation, all subjects provided written informed consent. Results will be disseminated at medical conferences and in journal publications. We aimed to determine the efficacy and safety of BFHX for the treatment of the convalescent COVID-19 patients.

Trial registration number: ChiCTR2000032573

## Keywords

Bufei Huoxue capsules, novel coronavirus 2019, recovery period, randomized controlled trial

Date received: 8 May 2021; accepted: 7 June 2021

Pulmonary Circulation 2021; 11(3) 1–9

DOI: 10.1177/20458940211032125

## Background

Since December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide. As of 30 May 2021, the number of coronavirus disease 2019 (COVID-19) cases continues to

The first four authors contributed equally to this work.

\*These authors contributed equally to this work and shared corresponding authorship.

Corresponding author:

Jian Wang, The First Affiliated Hospital of Guangzhou Medical University, No. 151 Yanjiang Road, Guangzhou, 510120, China.

Email: jiw037@ucsd.edu



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increase, with 170,689,914 confirmed cases, 3,550,093 deaths, and 152,678,258 recovered individuals across 220 countries and territories and indirectly affecting even more individuals through disruption of daily living.<sup>1</sup> It has been reported that about 63% of discharged patients still show lung damage on computed tomography (CT) scans six months after the onset of disease.<sup>2,3</sup> Emerging evidence suggests that COVID-19 adversely affects different human body systems. However, for these convalescent patients, the long-term human body's sequelae are yet unknown. Therefore, this issue deserves more attention. Chinese prevention and treatment guidelines recommend using traditional Chinese medicine for dialectical treatment for convalescent COVID-19 patients currently.

Bufei huoxue (BFHX) capsules are composed of three traditional Chinese medicines: astragalus, red peony, and psoralen.<sup>4</sup> It is reported that the astragalus possesses functions of strengthening the immune system, affecting interferon, enhancing the body's resistance to hypoxia and stress, promoting body metabolism, improving heart function, lowering blood pressure, protecting the liver, regulating blood sugar, antibacterial and inhibiting virus, hormone-like effect.<sup>5-8</sup> Modern medical research shows that astragalus contains various antibacterial active ingredients and can enhance the human body's immune function.<sup>9,10</sup> Thus, it can also be used to prevent the occurrence of certain infectious diseases. Astragalus is also effective in treating chronic appendicitis because it has the effect of supporting toxins and muscle growth.<sup>11</sup> Red peony can significantly improve the microcirculation state of the body, reduce the viscosity of serum and plasma, inhibit ADP-induced platelet aggregation, prolong prothrombin time, and activated partial thromboplastin time.<sup>12,13</sup> Psoralen can play well to strengthen the heart, realize the expansion of the coronary arteries, and promote the increasement of human blood flow.<sup>14-16</sup> The polysaccharides in the psoralen can also significantly enhance immunity.<sup>17</sup> Thus, the combined use of these three Chinese medicinal materials can improve lung function, microcirculation, anti-infection, anti-endotoxin, immunity, resistance to hypoxia, stress, and protect heart, lung, liver, and kidney functions.<sup>18-21</sup> However, it has not yet been reported whether BFHX has a therapeutic effect on convalescent COVID-19 patients. Therefore, we designed a three-month, randomized, double-blinded, placebo-controlled clinical trial to examine the efficacy and safety of BFHX for the treatment of convalescent COVID-19 patients.

## Methods

### Study design

This study incorporated a multicenter, randomized, double-blind, placebo-controlled clinical trial. It was developed according to the Standard Protocol Items: Recommendations for Interventional Trials Statement

(SPIRIT; the SPIRIT checklist is shown in supplementary file 1). Screening (Visit 0) is undertaken within two days prior to enrollment to assess eligibility and collect baseline data. Subjects who entered the primary screening were assessed for lung function, and those meeting all criteria will be randomly assigned (1:1) into the BFHX treatment group or control group. Subjects in both groups can take rehabilitation treatments such as oxygen inhalation, atomization inhalation, breathing training, exercise prescription, etc. According to the actual situation, they recheck viral nucleic acid at regular intervals relevant to Chinese government regulations. Patients were followed up at month 1 ( $30 \pm 1$  days) after randomization (Visit 1) and then followed up every one month until the end of treatment at 3rd month ( $90 \pm 3$  days). Data collected at Visit 0 included demographics (name, sex, age), medical history, vital signs, concomitant medications, laboratory, and auxiliary examinations, scale scores, and adverse events.

Additionally, medical history, medications, laboratory and auxiliary examinations, scale scores, and adverse events will be collected at each visit. Additional items will be evaluated at Visits 0 and 3. A schedule of assessments is shown in Table 1.

Basic medical history contains current medical history (symptoms and signs) and previous history.

Evaluation of cardiac and pulmonary function includes a Quality of Life scale (QOL), 6-min walk distance (6MWD), Fatigue Assessment Inventory (FAI); CRP: C-reactive protein.

### Sampling size

For patients with COVID-19 in the recovery period, assuming the 6MWD in the usual treatment group and combination with BFHX capsules of 411 and 461 m separately, we estimated that the sample size should be 120 cases (60 cases in each group) that has taken into account the drop-out rate not exceeding 15% with PASS (Version 11.0.7).<sup>22,23</sup>

### Study procedure

**Eligibility criteria.** The selection of participants will be based on the following inclusion and exclusion criteria.

#### **Inclusion criteria.**

1. Age  $\geq 18$  years old, male or female.
2. Patients who were diagnosed as COVID-19 according to the "The Diagnosis and Treatment Scheme of COVID-19 (The 7<sup>th</sup> Trial Edition)".
3. The condition meets the discharge standards stipulated in "The Diagnosis and Treatment Scheme of COVID-19 (The 7<sup>th</sup> Trial Edition)" after treatment.
4. The syndrome differentiations are the deficiency of lung and spleen Qi at the time of screening. According to the diagnostic criteria of "The Diagnosis and Treatment Scheme of COVID-19 (The 7<sup>th</sup> Trial Edition)".

**Table 1.** Study schedule of assessments.

Visit cycle evaluation projects	Screening stage	Visit 1	Visit 2	Visit 3
Time-window	Day-2 to 0	Month 1	Month 2	Month 3
Inclusion and exclusion criteria	●			
Informed consent	●			
Basic condition	●			
Basic medical history	●			
Complication	●			
Symptoms and signs	●	●		●
Blood routine test, urine routine	●			●
Liver, kidney function and CRP	●	●	●	●
Pregnancy tests (only for female)	●			
Sera specific antibodies	●			●
Chest CT	●			●
TCM Syndrome Score	●	●	●	●
Evaluation of cardiopulmonary function (QOL, 6MWD, FAI)	●	●	●	●
Adverse events	●	●	●	●
Drug combination	●	●	●	●
Distribution of test drugs	●	●	●	●
Withdrawal of test drug				●

CRP: C-reactive protein; TCM: Traditional Chinese medicine; FAI: Fatigue Assessment Inventory; QOL: Quality of Life scale; 6MWD: 6-min walk distance; ●: required.

5. The patient or his/her guardian agrees to participate in the study and provides written, informed consent for participation.

**Exclusion criteria.**

1. Known or suspected allergy to the components of BFHX.
2. Acute infections, along with other viruses or bacteria.
3. Abnormal liver and kidney function tests (ALT, AST, SCr  $\geq 1.5$  times the upper limit of normal).
4. Participating in other drug clinical trials.
5. Pregnant and lactating women; or those who cannot take effective contraceptive measures during the trial period.

6. Along with severe liver disease (such as liver tumors, various types of hepatitis, etc.) or a history of drug-induced liver injury or drugs that are currently used/expected to use potential liver damage during the study (immunosuppressive agents such as cyclosporine, tacrolimus, etc.; anti-tuberculosis drugs such as rifampicin, isoniazid, etc.; chemotherapy drugs such as cyclophosphamide, methotrexate, azathioprine, etc. and patients with liver damage restorative materials such as polygonum multiflorum, tusanqi, *Tripterygium wilfordii*).

7. Any other circumstances under which the investigator considers the patient to be unsuitable for participation in the study.

**Withdrawal criteria.**

1. Subjects' condition worsens or relapses during the administration period, and other treatment measures are required.

2. Subjects experience other complications or certain physiological changes, and it is not suitable to continue the trial during the clinical trial.

3. It should not continue to be tested for severe adverse events and some significant adverse events, etc.

4. Subjects do not meet the inclusion criteria and are mistakenly included in the trial or meet the trial's exclusion criteria.

5. Subjects having poor compliance with the dosing regimen.

6. Subjects are unwilling or impossible to continue the clinical trial and ask the investigator to withdraw from the trial.

7. Subjects do not propose to withdraw from the trial but no longer receive medication and testing and are lost to follow-up.

8. Subjects with incomplete vital data that may affect the statistical analysis.

**Discontinuation criteria.**

1. Subjects experiencing severe adverse reactions leading to suspension or termination of treatment during the trial.

2. Subjects whose condition deteriorates during the trial or subjects who withdraw consent or are unable to complete the trial because of other circumstances.

3. The sponsor requests suspension (such as funding reasons, management reasons, etc.).

4. Request to suspend the trial due to policy reasons.

5. Other circumstances that may cause the trial to be suspended.

**Recruitment and consent.** The informed consent document was presented to potentially eligible subjects to provide a

**Table 2.** Efficacy indicators.

Main efficacy indicators	Secondary efficacy measurements
Improvement of lung scan 6MWD	<ol style="list-style-type: none"> <li>1. SGRQ</li> <li>2. (1) Main syndrome in TCM (adynamia, dyspnea and anorexia)</li> <li>(2) Minor syndrome in TCM (ventosity, nausea /vomit and diarrhea)</li> <li>(3) Pale tongue and veins unapparent in TCM.</li> <li>3. Improvement of each symptoms</li> <li>4. Specific antibodies IgG of novel coronavirus in serum</li> </ol>

IgG: immunoglobulin G; SGRQ: St. George's Respiratory Questionnaire; 6MWD: 6-min walk distance.

comprehensive explanation of this study. Written consent was then obtained. This was explained to subjects by investigators at the time of obtaining consent.

**Interventions.** Subjects satisfying all criteria will be assigned (1:1) randomly into two groups as follows:

1. BFHX treatment group: BFHX 1.4 g three times daily in addition to routine recovery therapy.

2. Control group: placebo 1.4 g three times daily in addition to routine recovery therapy.

The routine recovery therapy is rehabilitation treatments such as oxygen inhalation, atomization inhalation, breathing training, and exercise prescription according to the subjects' actual situation. The virus nucleic acid should be reviewed at regular intervals according to relevant national regulations.

Test period: continuous observation for 90 days. During the baseline period, planned visits are conducted at the end of one month, two months, and three months after enrollment.

BFHX and placebo are uniformly manufactured by Guangdong Leiyunshang Pharmaceutical Co., Ltd (Yunfu, Guangdong Province, China), following the People's Republic of China's instructions Pharmacopoeia, which have an identical appearance and nearly similar taste.<sup>4</sup> Routine therapy will not differ between the two groups and will include rehabilitation treatments such as oxygen inhalation, atomization inhalation, breathing training, exercise prescription, etc. Where subjects have previously received recovery therapy for the treatment of COVID-19, the regimen will remain unchanged.

**Randomization and blinding.** A randomization scheme that generates a list of 160-case randomization sequence utilizing the stratified block randomization method by computer will be implemented by an independent statistician, which guarantees that enrolled patients will be evenly allocated to the BFHX group or the placebo group. Then, 60 participants in each group will be randomly selected. Concealment of allocation code relies on an opaque envelope. This trial requires that all participants and researchers involved in drug distribution, outcome evaluation, and data analysis are entirely blinded to allocation. The occurrence of severe adverse events or other unpredictable events allows unblinding under the principal investigator's (PI) permission.

## Outcome measurements

**Efficacy indicators.** The primary efficacy indicators are CT improvement rate of lung and the CT will be performed within two days prior to enrollment and three months later at the end of the clinical trial, FAI, and 6MWD. They will be performed and recorded at each time point (Table 2).

Clinical deterioration is defined as the need to increase medication or change the therapeutic regimen for the treatment of COVID-19, particularly experiencing severe adverse reactions leading to suspension or termination of treatment during the trial; or hospitalization caused by sequelae or relapse of COVID-19.

Other clinical symptoms and signs, biochemical indicators, and imaging indicators are recorded (Table 2) for comprehensive prognostic evaluation and risk assessment.

Secondary efficacy measurements include the following four indicators (Table 2):

(1) The evaluation results and changes of the St. George's Respiratory Questionnaire (SGRQ) score.

(2) According to the "Chinese Medicine Treatment" part of The Diagnosis and Treatment Plan (The 7<sup>th</sup> Trial Edition) and the "Recommendation on the Rehabilitation Guidance of Traditional Chinese Medicine for Coronavirus Disease in the Recovery Period (Trial)" summarized, the syndrome is generally based on the deficiency of the syndrome compatible with other symptoms.<sup>24,25</sup> The syndrome is at least one primary symptom combined with secondary symptoms judged by reference efficacy indicators (Table 2), and the symptoms will be performed and recorded at each time point.

(3) Improvement of individual symptoms will be performed and recorded at each time point.

(4) Serum new coronavirus specific antibody (IgG) will be performed within two days prior to enrollment and three months later at the end of the clinical trial.

**Safety evaluation.** Symptoms and signs, including the following four indicators:

(1) Vital signs (body temperature, heart rate, breathing, blood pressure) will be recorded at each visit.

(2) Laboratory tests will be performed within two days prior to enrollment and three months later at the end of clinical trial. They will include routine blood tests and urinalysis, liver function, and renal function.

(3) Adverse events will be assessed and recorded in the case report form (CRF).

**Evaluation of adverse events.** Adverse events, including symptoms, signs, and physical or laboratory examination abnormalities, will be carefully evaluated. All adverse events must be judged for their character, severity, and potential relationship to the study treatment. The correlation between adverse events and study treatment is divided into four levels: definite, probable, possible, and unrelated.

**Treatment allocation.** As the study is double-blinded, the participant will be unaware of which treatment they receive; those responsible for their care and evaluation (treating team and research team) will not know the allocation or coding of the treatment allocation. This blinding of the participant will be achieved by identical packaging and labeling of both the BFHX and matched placebo. A unique kit code will identify each container of BFHX/placebo. Randomized lists containing kit allocation will be computer-generated by the safety statistician and sent to the research investigator, who will produce the kits and allocation sequence. The safety statistician will manage the kit codes in the kit logistics application linked to the 24-h randomization system and maintain the back-up kit-code lists for each site.

**Data management and analysis.** Data collection and monitoring will be managed by a specialized data and safety monitoring board (DSMB). The DSMB is a clinical research expert committee composed of a statistician, a deputy chief physician in the respiratory department, and a junior Chinese medicine practitioner. They monitor the progress of the clinical trial and review safety and effectiveness data while the trial is ongoing. The DSMB will be free to investigate all participant information and has no prior competitive interest with other members of the experimental group. The project team members will collect and record the original subject data by the case report forms (CRFs), including a brief medical record, necessary information, treatment records, pre- and post-treatment evaluation data, follow-up data, adverse event records, etc. Any changes to these paper-based data forms will not be allowed without the investigation and authorization of the DSMB. Two team members blinded to the allocation will be responsible for logging information into a custom-designed and password-protected database, electronic data capture (EDC). Our data collection and management include CRF records and the EDC system. CRF records will be reviewed and checked weekly by the PIs. Electronic data collection and management can be carried out by the EDC system, providing a graphical user interface component for data entry, a validation component to check user data, and a reporting tool to analyze the collected data.

Missing data in clinical trials are inevitable, but it can be prevented as much as possible. Data management is the key

to ensure the quality of data. In the process of dealing with missing data, we will choose different processing methods according to the missing data mechanism from the judgment of data managers. For example, the last observation carried forward (LOCF), baseline observation carried forward, and worsts observation carried forward will be used to supplement the data. At the same time, it is necessary to make a sensitivity analysis of the test results. If the results of the sensitivity analysis are consistent with the results of the original analysis, it can be considered that conclusion has strong credibility; on the contrary, if there is a significant difference between the sensitivity analysis results and the initial analysis results, it is necessary to further analyze the missing data to find the source of the difference.

**Auditing.** The PIs will schedule a weekly meeting with all the study members to review eligibility of new participants enrolled in the study, consent forms, all CRFs, all assessment sheets filled during that week, adherence to trial interventions and policies, and reports of side effects. The PI will double check the entered data in terms of completeness, timeliness of entry, and correctness of the data. Random checks will also be done.

### **Clinical data analysis**

**General considerations.** Based on the intention-to-treat (ITT) principle, all randomly assigned participants will be included in the statistical analysis. The last visit's outcomes will be used as the final outcomes for participants who prematurely withdraw from the trial. Per protocol set will pick up from the full analysis set for analysis. Efficacy analysis will be performed on the ITT datasets and per-protocol datasets.

Descriptive statistics, including counts and percentages, means, and standard deviations, will be calculated for categorical outcomes and continuous outcomes, respectively. LOCF will impute the missing primary outcomes. For continuous outcomes, the two-tailed Student's t-test and Wilcoxon–Mann–Whitney test are used to test for differences between the group for normally distributed variables and non-normal distributed variables, respectively. Fisher's exact test is performed for categorical primary outcomes. The center effect will be considered by the generalized linear model. The significance level is 0.05 with the two-sided test. We do not consider type I error correction due to exploratory research. SAS version 9.4 (SAS Institute Inc.) will be used for all analyses. LOCF will be used to impute the missing primary outcomes. The methods that will be used to handle missing data are described for each analysis.

The methods that will be used to handle missing data are described for each analysis. As this is a double-blind clinical trial, statisticians will be blinded to group allocation throughout the study until the database has been locked and downloaded for final analysis. No one, including the safety statistician, supervising study statistician, back-up

safety statistician, or authorized individuals, will have access to the group allocations prior to the final analysis.

**Frequency of analyses.** Outcome data will be analyzed once only at the final analysis, although statistical monitoring of safety data will be conducted throughout the study and reported at agreed intervals. The final analysis will take place three months after the last patient is randomized.

**Endpoint analysis.** All analyses will be conducted using data from the ITT, defined as all patients who undergo randomization regardless of non-compliance with the intervention. The primary endpoint will also be analyzed in the per-protocol population to determine whether the results are sensitive to the exclusion of patients who violated the protocol (e.g., those who underwent randomization but were subsequently found to be ineligible). Primary and secondary analyses will be performed by a statistician who is unblinded to treatment allocation. Outcome measures will be analyzed by the Student's t-test, Wilcoxon–Mann–Whitney test, and Fisher's exact test appropriate for the data type. Such analyses will be adjusted for randomization minimization factors such as baseline values where applicable (such as age and sex). Baseline characteristics will be summarized for each randomized group.

**Safety analyses.** All patients who receive at least one dose of trial treatment will be included in the safety analysis set. The number of patients reporting a severe adverse event (up to 28 days after the last dose of medicine) and the details of all serious adverse events will be reported for each treatment group. The number of patients withdrawing from each treatment arm will be summarized, along with the reasons for withdrawal. The safety statistician will undertake all safety analyses performed prior to the final analysis.

**Subgroup analyses.** No subgroup analysis is planned.

**Adverse events.** An adverse event is defined as any untoward medical occurrence (including deterioration of a pre-existing medical condition) in a patient who has been administered a medicinal product; the event does not necessarily have a causal relationship with this product. The occurrence of adverse events will be recorded at Visits 1–3. At each visit, the research nurse will complete the adverse event checklist to determine whether the patient has experienced any expected adverse events. Only the occurrence and corresponding severity of adverse events will be recorded.

**Patient and public involvement.** Neither patients nor the public is involved in this study, including the planning, execution, analysis, and evaluation.

**Confidentiality.** All study related forms and information will be stored at the study site, where they are stored in cabinets

that can only be accessed by study members. All electronic databases will be password protected. Computers used during this study will also be password protected. Patients' personal information will be collected only upon recruitment and kept in the trial's regulatory binder, which will only be accessible via the PI upon valid request.

**Access to data.** The DSMB will have access to the data while the study is in progress. At conclusion of the study, PI and co-PI will have full access to the identified data.

**Dissemination policy.** All data and analysis will remain blinded until main outcomes are published. The study results will be communicated to the participants by email, letter by mail, or a phone call by the PI.

We will submit a de-identified dataset to an appropriate data archive after three years of study termination to share our data with the surgical community.

## Authorship

All authors should have contributed to this protocol reasonable and meaningful edits that culminated with this final protocol version. There is no intention to employ any professional writers.

## Discussion

The whole range of short- and long-term health effects associated with COVID-19 include fatigue, shortness of breath, cough, joint pain, chest pain, difficulty in thinking and concentration (sometimes referred to as "brain fog"), depression, muscle pain, headache, intermittent fever, and so on.<sup>26–30</sup> To date, most doctors and researchers are focusing on the treatment of critically COVID-19 patients and the development of vaccines. Still, less attention has been paid to the management and research of convalescent COVID-19 patients. However, there are numerous COVID-19 patients, of which more than 152 million are in the recovery period globally currently.<sup>1</sup> What is more, it is reported that 63% of COVID-19 patients had impaired lung function and pulmonary vessels.<sup>3</sup> Furthermore, we still know little about the long-term effects and damage of the SARS-COV-2 virus on humans. Therefore, it is necessary to perform some intervention on these convalescent COVID-19 patients.

According to the experience in the treatment of COVID-19, selecting TCM that can benefit and enhance immunity for convalescent COVID-19 patients under TCM theory's guidance has been incorporated into Chinese rehabilitation guidelines of COVID-19.<sup>24</sup> BFHX is composed of three main traditional Chinese medicine-astragalus, red peony root and psoralen, whose main components include psoralen, paeoniflorin, isopsoralen, verbasil glucoside, pentagalloyl glucose, verbasil isoflavones, tonic osteostatin.<sup>31–33</sup> Previous clinical studies have proved that BFHX has the effects on inhibiting cough and asthma, improving lung

function, pulmonary vascular hemodynamics, and the degree of inflammatory injury of lung.<sup>18</sup> It is reported that the core compounds contained in BFHX could act on targets such as IL6, MAPK8, PTGS2, PTGS1, and NCOA2, and regulate multiple signal pathways, thereby exerting a therapeutic effect on the recovery period of COVID-19 through a network pharmacology research.<sup>34</sup> Based upon our clinical experience and skills, we designed a multicenter randomized, double-blinded, placebo-controlled clinical trial to explore whether BFHX has a therapeutic effect on convalescent COVID-19 patients.

Before the COVID-19 vaccine is successfully developed and widely vaccinated, it is meaningful to explore the prevention and/or treatment strategies and clinical treatment of the COVID-19, including the medical intervention programs during the recovery period, which may make a contribution to save many lives and improve the quality of patients' life.<sup>35</sup> Therefore, this research has important implications. Moreover, Chinese patent medicine has the same dosage form as chemical medicine, it is very convenient for clinical application. Furthermore, the treatment has a fingerprint map based on the main medicinal ingredients, which guarantees the medicine quality's stability and brings convenience for later clinical promotion and application.<sup>31,36</sup> Thirdly, the evaluation of drugs for patients with COVID-19 needs to be scientifically and rigorously evaluated based on the existing efficacy evaluation system. This is also why the RCT study with the high-level evidence-based medical evidence was used in this study. Therefore, when we explore research drugs for clinical use of convalescent COVID-19 patients, we should not consider too much about the theoretical medical system on which these drugs are based, but on whether the drug has actual therapeutic efficacy after rigorous clinical research, which is also the value of this research lies on. It may be hard to apply TCM to treat COVID-19 patients in Western countries. However, this work can at least raise researchers' attention to the issue of COVID-19 patients in rehabilitation period. With a foundation for the application of TCM in some Asian countries, new therapeutic drugs and regimens can be provided for COVID-19 patients during the recovery period.<sup>37</sup> We expect that this clinical research can evaluate the efficacy and safety of BFHX in the treatment of COVID-19 patients in the recovery period.

#### **Declaration of conflicting interests**

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Jian Wang has received a research grant from Guangdong Leiyunshang Pharmaceutical Co., Ltd.

#### **Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was financially supported by Guangdong Leiyunshang

Pharmaceutical Co., Ltd. The role of the funders is to provide the funding and the interventional medications BFHX as well as providing/covering the cost of all examinations. The funder's role in the study is exclusive to providing the agreed upon research funding. The funder is not involved in this study, including the planning, execution, data management, statistical analysis, evaluation, or write-up. The funders have absolutely no role nor are they involved in study design or study conduct (the collection, management, analysis or interpretation of the data) or in writing the final manuscript/report or in the decision to submit the report for publication. This study was also financially supported by grants from the Guangzhou Institute of Respiratory Health for Key Research of Independent Project (Grant No. ZNSA-2020013).

#### **Provenance and peer review**

Not commissioned; externally peer-reviewed.

#### **Availability of data and materials**

Data sharing is not applicable to this article as no datasets are reported. Availability of datasets generated in the study will be included in papers reporting study outcomes. Access to the full protocol and model consent forms may be available from the author upon reasonable request.

#### **Ethics approval**

The present study is being conducted under the Declaration of Helsinki and relevant clinical study research regulations in China. The protocol was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. All sub-centers use the ethic of the lead institution to file in their own centers. The results of this study will be disseminated at medical conferences and in journal publications.

#### **Informed consent**

Prior to participation, all subjects must provide written informed consent.

#### **Trial registration**

The trial was pre-registered at the China Clinical Trials Registry on 3 May 2020 under the registration number ChiCTR2000032573. See <http://www.chictr.org.cn/edit.aspx>

#### **Modification of the protocol**

Any changes to the protocol may affect the process of the study, which will be agreed between the project leader and the supervisor, inform the sponsors and all members of the research group, and also need to be approved by the Ethics Committee; any deviations of the protocol will be fully documented using a breach report form.

#### **Trial status**

This article is based on protocol version 1.0 dated 17 April 2020. Recruitment has been completed. We are analyzing data at present. Any major protocol changes will be notified to the ethics committee and updated on the Chinese Clinical Trial Registry.

## Related articles

There are no any publications containing the results of this study have already been published or submitted to any journal.

## Authors' contributions

JW and CL were coordinators of the clinical trial, and WH wrote the first draft of the manuscript. YC and WL were critically involved as co-PIs in the planning and the conduct of the study (application for funding and trial design) and finalizing the manuscript. YX, NZ1, NZ2, and JZ were involved in critically revising the manuscript. CH, TW, and JC helped to finish the manuscript. XC and KY were investigators at the clinical site. JB, HY, and JZ were responsible for planning all statistical analyses. All authors read and approved the final manuscript.

## ORCID iD

Wenjun He  <https://orcid.org/0000-0003-1307-3455>

## References

1. Worldometer. COVID-19 coronavirus pandemic, <https://www.worldometers.info/coronavirus/> (2021, accessed 30 May 2021).
2. Shaw B, Daskareh M and Gholamrezaezhad A. The lingering manifestations of COVID-19 during and after convalescence: update on long-term pulmonary consequences of coronavirus disease 2019 (COVID-19). *Radiol Med*. Epub ahead of print 1 October 2020. DOI: 10.1007/s11547-020-01295-8
3. Sonnweber T, Sahanic S, Pizzini A, et al. Cardiopulmonary recovery after COVID-19 – an observational prospective multi-center trial. *Eur Respir J*. Print 2021 Apr. DOI: 10.1183/13993003.03481-2020
4. Lei Yun Shang Pharmaceutical Group Co., Ltd. The official production introduction of Bufei Huoxue Capsules, <http://www.lys.cn/productsandintroductions/info.aspx?itemid=55&Lcid=20> (2021, accessed 30 May 2021).
5. Li Y and Dongqing Y. Improving the body's immunity and delaying aging – on the new medicinal uses of *Ginkgo biloba*, berries, and astragalus. *Chin J Pract Tradit Chin West Med* 2003; 016: 1649.
6. Duanhong X, Xinyan J and Mei H. Effect of Astragalus polysaccharide on growth performance and immunity of weaned lamb. *China Feed* 2018; 12: 56–59. <http://dx.chinadoi.cn/10.15906/j.cnki.cn11-2975/s.20181212>
7. Yan H, Xiaohua L, Yali C, et al. Pharmacodynamical study about immunoenhancement effect of Radix Astragali on mice. *J Zhejiang Normal Univ (Nat Sci)* 2017; 2: 201–205 (in Chinese with English abstract).
8. Ziyang L, Degang Q, Yu S, et al. Activation of macrophage of phenylethanol glycosides extracted from *Cistanche tubulosa* and its synergistic effect with *Angelica sinensis* and *Astragalus propinquus* in regulating immunity. *Sci Technol Food Ind* 2020; 41: 311–316 (in Chinese with English abstract).
9. Tianren Y, Shuai W, Shuo H, et al. Comparative study on immunomodulatory effect of antimicrobial peptide sublancin and astragalus polysaccharide of mice. *Chin J Anim Nutr* 2018; 30: 256–265 (in Chinese).
10. Lijun S, Tianren Y, Haitao Y, et al. Immunomodulation effect of antimicrobial peptide sublancin and astragalus polysaccharides on immunosuppressed mice: a comparative study. *Acta Vet Zootech Sin* 2019; 50: 406–414 (in Chinese with English abstract).
11. Xin W. Observation on efficacy of radix scutellariae aluminum capsules in prevention of postoperative infection of appendicitis. *Evaluation and analysis of drug-use in hospitals of China* 2016; 16: 775–777 (in Chinese with English abstract).
12. Chao L, Jun W and Jun Y. Study on activating blood and eliminating stasis of total paeony glycoside (TPG). *J Chin Med Mater* 2000; 23: 557–560 (in Chinese Journal).
13. Huiping L, Jiakang L and Yang J. Effect of acupoint injecting with radix paeonia rubra injection on nail fold microcirculation. *China's Naturopathy* 2002; 10: 23 (in Chinese).
14. Zhoufeng Z. Psoralen increases white blood cells, improves myocardial ischemia, lowers blood lipids. *J Tradit Chin Med* 2002; 43: 413 (in Chinese).
15. Jingtian Q, Jialong W, Shiwei C, et al. Study on the vasodilatory effect mechanism of psoralen and bakuchiol. *China Pharm* 2019; 30: 3364–3368 (in Chinese Journal with English abstract).
16. Dongxuan Z, Jingtian Q, Yitian D, et al. Study on mechanism of vasodilatory effect of Isopsoralen. *Liaoning J Tradit Chin Med* 2020; 47: 189–192 (in Chinese with English abstract).
17. Xiaotian L and Zhongcheng S. Research progress on immune regulation of psoralen and its active ingredients. *Curr Immunol* 2017; 37: 80–83 (in Chinese).
18. Mei X, Yanni L, Na L, et al. Therapeutic effects of Bufei Huoxue capsule combined with Chuankezhi injection on chronic obstructive pulmonary disease at stable period. *Hebei Med J* 2019; 41: 981–984 (in Chinese with English abstract).
19. Zhigang M, Jie Y, Yi L, et al. The effects of invigorating lung and activating blood circulation capsule on inflammatory factors and immunologic function of patients with bronchial asthma at remission stage. *Lab Med Clinic* 2016; 13: 2746–2748 (in Chinese with English abstract).
20. Huan G and Haiwen Z. Clinical study of the herbal capsules of nourishing lung and activating blood circulation to treat chronic pulmonary cardiac disease. *Chin Gen Pract* 2007; 10: 667–668 (in Chinese with English abstract).
21. Bo Y, Linmin M, hao L, et al. A randomized and comparative control clinical study of the herbal capsules for nourishing lung and activating blood circulation for the treatment of chronic pulmonary cardiac disease. *Chin J New Drugs* 2005; 14: 1192–1195 (in Chinese with English abstract).
22. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.
23. Fujimoto Y, Oki Y, Kaneko M, et al. Usefulness of the desaturation-distance ratio from the six-minute walk test for patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 2669–2675.
24. Commission NH and Medicine SAoTC. New coronavirus pneumonia treatment plan (trial seventh edition). *Jiangsu J Tradit Chin Med* 2020; 52: 1–6 (in Chinese).
25. Recommendation on the Rehabilitation Guidance of Traditional Chinese Medicine for Coronavirus Disease in the Recovery Period (Trial), [http://www.gov.cn/zhengce/zhengceku/2020-02/24/content\\_5482544.htm](http://www.gov.cn/zhengce/zhengceku/2020-02/24/content_5482544.htm)
26. Robinson P. Long-term conditions and severe acute respiratory syndrome SARS-CoV-2 (COVID-19). *Br J Community Nurs* 2020; 25: 247–251.



27. Butler MJ and Barrientos RM. The impact of nutrition on COVID-19 susceptibility and long-term consequences. *Brain Behav Immun* 2020; 87: 53–54.
28. Iadecola C, Anrather J and Kamel H. Effects of COVID-19 on the nervous system. *Cell* 2020; 183: 16–27 e11.
29. Mitrani RD, Dabas N and Goldberger JJ. COVID-19 cardiac injury: implications for long-term surveillance and outcomes in survivors. *Heart Rhythm* 2020; 17: 1984–1990.
30. Wang F, Kream RM and Stefano GB. Long-term respiratory and neurological sequelae of COVID-19. *Med Sci Monit* 2020; 26: e928996.
31. Qing T, Xiaoxiao Z, Yuying Z, et al. HPLC fingerprint of Bufeï Huoxue capsules. *Central S Pharm* 2018; 16: 1200–1204 (in Chinese with English abstract).
32. Jing Y, Zhang H, Cai Z, et al. Bufeï huoxue capsule attenuates PM2.5-induced pulmonary inflammation in mice. evidence based complement *Altern Med* 2017; 2017: 1575793.
33. Li JS, Liu XF, Dong HR, et al. Effective-constituent compatibility-based analysis of Bufeï Yishen formula, a traditional herbal compound as an effective treatment for chronic obstructive pulmonary disease. *J Integr Med* 2020; 18: 351–362.
34. Sheng G, Wenxing W, Hong X, et al. Molecular mechanism of Bufeï Huoxue capsule on COVID-2019 based on network pharmacology and molecular docking. *Chin Tradit Herbal Drugs* 2020; 51: 2307–2316 (in Chinese with English abstract).
35. Mai F, Del Pinto R and Ferri C. COVID-19 and cardiovascular diseases. *J Cardiol* 2020; 76: 453–458.
36. Ting S and Xiangjie H. HPLC fingerprint of bufeïhuoxue capsules and simultaneous determination of multi-components. *China Pharm* 2019; 28: 19–23 (in Chinese with English abstract).
37. Svenson M and Bendtzen K. Effects of cyclic GMP-agonists on cyclosporin-induced suppression of human lymphokine production. *Allergy* 1985; 40: 529–534.