

Treating patients infected with the SARS-CoV-2 Omicron variant with a traditional Chinese medicine, Shufeng Jiedu capsule

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SUMMARY Patients infected with the Omicron variant of SARS-CoV-2 mainly develop mild COVID-19, manifesting as upper respiratory symptoms, fatigue, and fever. Shufeng Jiedu capsule (SFJDC), a traditional Chinese medicine indicated for treatment of upper respiratory infections in China, was tested for its efficacy and safety in treatment of an Omicron infection at a mobile cabin hospital in response to an outbreak of COVID-19 in Shanghai, China in April 2022. In this open-label, randomized controlled trial, patients in the control group received best supportive care, while those in the test group received additional SFJDC therapy for 7 days. SFJDC markedly alleviated patients' symptoms including a sore throat, coughing, fatigue, and a fever after 7 days of treatment. The virus negative time was significantly shorter in the SFJDC treatment group, but there were no obvious differences in the virus negative rate between the two groups at the end of the 7-day follow-up. These results suggest that patients with the Omicron infection may benefit from SFJDC treatment. Double-blind, randomized controlled trials are warranted to comprehensively evaluate the efficacy and safety of SFJDC in a large cohort study in the future.

Keywords Shufeng Jiedu capsule, Omicron, COVID-19, fatigue, fever, cough

The coronavirus disease 2019 (COVID-19) has been a global epidemic for over two years, and multiple mutations of the SARS-CoV-2 virus have occurred (1). The Omicron variant was first identified in Africa in November 2021 and is believed to be a very highly transmissible variant (2). Analysis of the genomic sequences of Omicron has revealed a number of non-synonymous mutations, several of which have been proven to be associated with transmissibility, disease severity, and immune escape (3). Omicron had been reported to have lower replication competence in lung parenchyma compared to earlier variants and to lead to less severe illness in patients (4,5). Upper respiratory infection symptoms such as a sore throat and coughing are reported to be the predominant clinical manifestations of Omicron (6,7).

Antivirals that are effective at treating an Omicron infection are limited and scarce. Traditional Chinese medicines (TCM) such as Shufeng Jiedu capsule (SFJDC) and Lianhua Qingwen capsule have been recommended to treat COVID-19 patients with a fever and fatigue by the Guidance for Coronavirus Disease

2019: Prevention, Control, Diagnosis and Management in China since the COVID-19 outbreak in 2020. SFJDC is indicated to treat an acute upper respiratory infection and it has displayed efficacy in alleviating a fever, fatigue, and coughing in patients with COVID-19 in previous studies (8,9). SFJDC consists of eight medicinal herbs: Rhizoma Polygoni Cuspidati (Huzhang), Fructus Forsythiae (Lianqiao), Radix Isatidis (Banlangen), Radix Bupleuri (Chaihu), Herba Patriniae (Baijiangcao), Herba Verbenae (Mabiancao), Rhizoma Phragmitis (Lugen), and Radix Glycyrrhizae (Gancao). SFJDC was reported to reduce the virus load, reduce the inflammatory factors IL-6, IL-10, TNF- α , and IFN- γ , and increase the number of CD4+ and CD8+ cells in a mouse model of infection with the HCoV-229E species of coronavirus (8). A meta-analysis of active ingredients in SFJDC found that SFJDC has the potential to suppress SARS-CoV-2 and regulate immunomodulatory and anti-inflammatory targets via multiple pathways (10,11).

In January 2022, Omicron was first identified in Shanghai and subsequently spread in the community.

As an emergency response to the COVID-19 outbreak in April, mobile cabin hospitals were built in Shanghai to provide a safe treatment site for patients with mild COVID-19 symptoms and to provide an effective isolation area to prevent the spread of SARS-CoV-2. From April 2, 2022 to May 1, 2022, an open-label, randomized controlled trial (RCT) was initiated to evaluate the efficacy and safety of SFJDC in patients infected with the Omicron variant in a mobile cabin hospital. Patients in the control group received best supportive care while patients in the test group received additional SFJDC treatment (0.52 g per capsule, 4 capsules at a time, *t.i.d.*) for 7 days. In this study, efficacy was evaluated based on 1) recovery from symptoms including a sore throat, coughing, fatigue, and a fever and 2) RT-PCR measurements of COVID-19 viral RNA. Safety was evaluated via adverse event monitoring. The outcomes of this clinical trial are reported here.

Of the 415 patients screened, 240 patients who met the enrollment criteria (Supplementary Table S1 and Supplementary Figure S1, <http://www.biosciencetrends.com/action/getSupplementalData.php?ID=102>) were included in this study. All of the patients had mild COVID-19 with symptoms mainly including a sore throat, coughing, fatigue, and a fever. Patients were randomized into the SFJDC treatment group or the control group at a ratio of 1:1 (120 patients in each

group). A major protocol violation occurred with 3 patients in each group, so they were therefore excluded from the final analyses. Primary baseline demographic and clinical features of the patients are shown in Supplementary Table S2 (<http://www.biosciencetrends.com/action/getSupplementalData.php?ID=102>). There are no significant differences between two groups in terms of age, gender, clinical symptoms, duration from symptom onset to hospitalization, and vaccination status.

Results indicated that all of the symptoms including a sore throat, coughing, fatigue, and a fever were eliminated in 98 patients in the SFJDC treatment group (recovery rate: 83.8%) and 82 patients in the control group (recovery rate: 70.1%) after 7 days of treatment ($p < 0.05$) (Figure 1A). In addition, recovery time from all symptoms was significantly shorter in the SFJDC treatment group compared to the control group (4.9 days vs. 5.9 days, $p < 0.001$) (Figure 1B). Recovery time from a single symptom such as coughing (5.4 days vs. 6.5 days, $p < 0.001$), fatigue (4.2 days vs. 5.4 days, $p < 0.001$), and a sore throat (4.2 days vs. 6.1 days, $p < 0.001$) was also shorter in the SFJDC treatment group than in the control group (Figure 1C). Of the eligible patients, 61.1% (143) developed transient signs of a fever at the onset of the disease before admission to the hospital. During the 7-day treatment period, only a small percentage of patients (18 (15.4%) in the treatment group, and 20 (17.1%) in the control group)

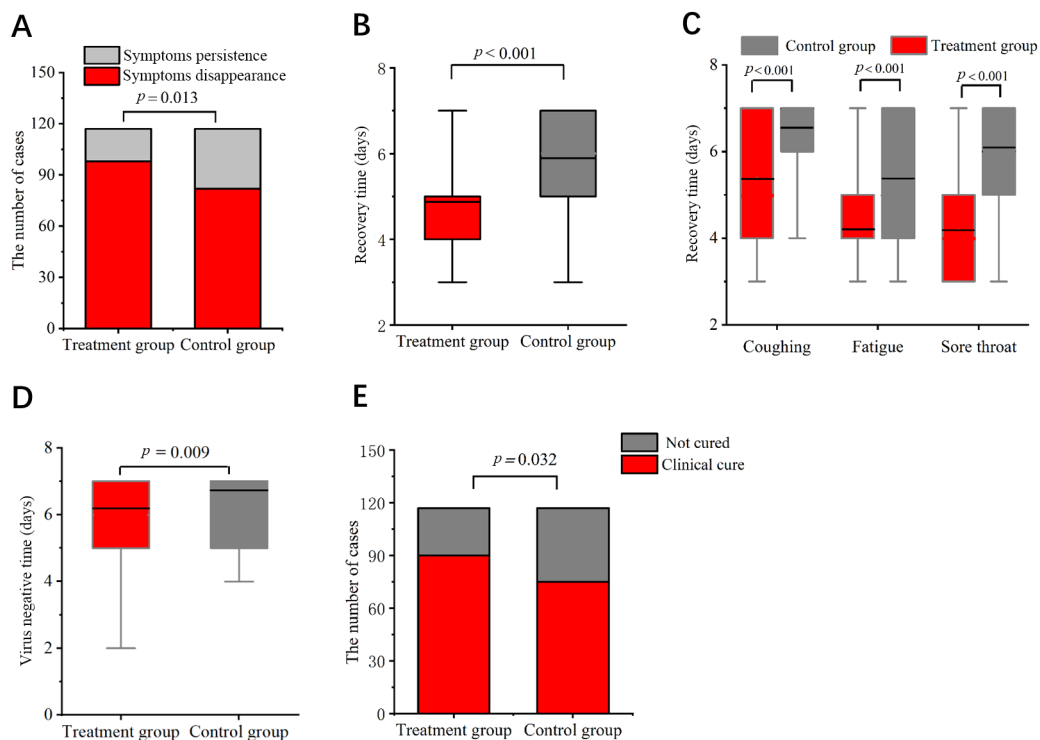


Figure 1. The efficacy of SFJDC in the treatment of patients infected with Omicron. Patients in the control group received best supportive care while patients in the treatment group received additional SFJDC treatment (0.52 g per capsule, 4 capsules at a time, *t.i.d.*) for 7 consecutive days. The number of patients without disease symptoms (A), recovery time from all disease symptoms (B), recovery time from a single disease symptom (C), virus negative time (D), and the number of clinically cured cases (E) were analyzed in each group and compared between the two groups.

exhibited a persistent fever. After 7 days of treatment, all of the patients in the treatment group had a normal temperature while 3 patients in the control group still exhibited a persistent fever. Fever duration did not differ significantly between the two groups (2.0 days vs. 2.7 days, $p > 0.05$).

Real-time PCR was used to measure virological outcomes in this study. The SFJDC group tested negative for the virus more quickly than the control group (6.2 days vs. 6.7 days, $p = 0.012$) (Figure 1D). However, there were no obvious differences in the virus negative rate between the two groups at the end of the 7-day follow-up ($p > 0.05$). In addition, the clinical cure rate was analyzed. It was defined as follows: 1) a normal temperature for longer than 3 days; 2) disappearance of symptoms (coughing, fatigue, or a sore throat); 3) no abnormalities in chest CT images; and 4) virus negative in two consecutive PCR tests (at an interval of at least 24 h). Results indicated that more patients in the SFJDC treatment group were clinically cured and that the clinical cure rate was significantly higher in the treatment group than in the control group (76.9% vs. 64.1%, $p = 0.032$) (Figure 1E). Few patients (0 patients in the treatment group vs. 3 patients in the control group) had disease progression, and no significant differences in progression were noted (0.0% vs. 2.6%, $p > 0.05$).

During the 7 days of treatment, adverse events such as gastrointestinal discomfort, loss of appetite, and headache were recorded in both groups. No serious adverse events were noted in this study (Supplementary Table S3, <http://www.biosciencetrends.com/action/getSupplementalData.php?ID=102>). There were no significant differences in the occurrence of adverse events between the two groups ($p > 0.05$).

This study had several limitations. A blinded or placebo-controlled design was not implemented due to the urgency of the disease outbreak and the timeliness of treatment. In addition, limited resources at the mobile cabin hospital precluded performing some laboratory tests (such as tests of liver and kidney function) in a timely and comprehensive manner. A multi-center study with a detailed safety evaluation would help to shed more light upon the clinical value of and potential adverse reactions to SFJDC in the treatment of COVID-19.

In summary, this study indicated that SFJDC is capable of alleviating a sore throat, coughing, fatigue and a fever in patients infected with Omicron. The virus negative time was significantly shorter in the SFJDC treatment group, suggesting that SFJDC may inhibit the virus replication. Double-blind, randomized controlled trials are warranted to comprehensively evaluate the efficacy and safety of SFJDC in a large cohort study in the future.

Ethical considerations: The First Affiliated Hospital

of Anhui University of Chinese Medicine dispatched a medical team to a mobile hospital in Shanghai for medical support, and this clinical trial was initiated by the First Hospital. The Ethics Committee of the First Affiliated Hospital of Anhui University of Chinese Medicine approved the protocol used in this study (2022AH-18). All patients consented to participate in this study, and informed consent was obtained in writing from each adult patient.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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