Received: 12 October 2021 | Revised: 7 March 2022 | Accepted: 21 March 2022

DOI: 10.1002/ptr.7455

RESEARCH ARTICLE

WILEY

Traditional Vietnamese medicine Kovir capsule in patients with mild COVID-19: A double-blind randomized controlled trial

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Funding information
This work was funded by the Sunstar Joint Stock Company (Sao Thai Duong JSC.), address: Lot CC1-III.13.4, Phap Van - Tu Hiep New Urban Area, Hoang Liet Ward, Hoang Mai District, Hanoi, Vietnam. The funding body had no role in the design of the study, collection, analysis, and interpretation of data, and writing the manuscript.

Abstract

Kovir capsule, a polyherbal medicine developed from *Ren Shen Bai Du San* formulation, has been used in various diseases including respiratory infections. A randomized, placebo-controlled, double-blind study was conducted to evaluate the safety and efficacy of Kovir capsule (TD0069) in the treatment of mild COVID-19 patients. Patients aged from 18 to 65 years who were PCR-confirmed with SARS-CoV-2 and had the mild disease were recruited and randomized to either Kovir capsule (34 patients) or placebo (32 patients) for up to 14 days or until discharge. Efficacy outcomes were time to viral clearance, daily viral load, time to symptom resolution, daily symptom score based on 16 pre-defined symptoms, and progression to severe/critical COVID-19. Safety outcomes were adverse events. Viral load decreased over time similarly in the two groups. Viral clearance time was also similar in both groups (median: 8 days). Kovir group had a more rapid decrease of symptom score and significantly lower time to symptom resolution than placebo (median: 4 vs. 7 days). Two patients in the placebo group developed severe COVID-19. No patient experienced adverse events. Kovir capsule is safe and can improve symptom resolution in mild COVID-19 patients. A large-scale trial is required to confirm these findings.

KEYWORDS
COVID-19, herbal, SARS-CoV-2, traditional medicine

1 | INTRODUCTION

Since first reported in December 2019 in Wuhan, China, coronavirus disease 2019 (COVID-19) has been spreading all over the world and causes the most serious pandemic ever. This is an acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of November 9, 2021, over 250 million people have been diagnosed with COVID-19 worldwide with more than 5 million deaths, according to the World Health Organization (WHO) (World Health Organization, 2021c). More than 7 billion vaccine doses have been administered and the vaccination is starting to have a substantial effect on the number of hospitalizations and severe cases in some countries (Ritchie et al., 2020; World Health Organization, 2021c). However, there is still inequity in vaccine access globally so many countries are still vulnerable, particularly low-to-middle income countries (LMICs). Even with full vaccination all the world, the duration of protection and efficacy against new SARS-CoV-2 variants of current vaccines are uncertain. Therefore, there remains an urgent need for effective treatments for COVID-19. Many drugs and treatments have been studied for COVID-19 during the last

2 years with more than 4,200 trials registered or ongoing, but very few treatments have been recommended by the WHO (Maguire & Guérin, 2020; World Health Organization, 2021b).

In some countries including Vietnam, traditional medicine plays an important role in the prevention and treatment of various diseases. In the theory of traditional medicine, COVID-19 is deemed as a category of "dampness–toxin pestilence" (Lyu et al., 2021; Zhao, Hou, Gao, & Wang, 2020). According to traditional medicine, COVID-19 can be divided into mild, moderate, severe, and critical. The main patterns in mild stage are cold–damp constraint and damp–heat accumulation in the lung, where dispersing lung, removing pathogenic factors, and resolving turbidity with aroma are needed. *Ren Shen Bai Du San*, a traditional herbal formulation, has been recommended by Vietnamese Ministry of Health to prevent and treat COVID-19 (Vietnam's Ministry of Health, 2020). Recently, Kovir, a hard-capsule Vietnamese herbal medicine, has been developed based on the formula of *Ren Shen Bai Du San* remedy in order to support the treatment for patients with COVID-19 in Vietnam. This polyherbal medicine consists of 12 herbal ingredients which are grouped in four categories: Chief (Jun), Deputy (Chen), Assistant (Zuo), and Envoy (Shi). The "Chief" component is effective for fever, chills, headache, sore throat, and muscle pain. The "Deputy" component can enhance "Chief" component's activities and increase the antipyretic and analgesic effects. The "Assistant" and "Envoy" components have a harmonization activity and can speed up the recovery of the body. Kovir has been used in various diseases such as respiratory infections, parotid gland infection, and hepatitis B with good results (Chen & Chen, 2009). With well-known components in treating acute respiratory infectious diseases, Kovir capsule is expected to be a good treatment of COVID-19.

Vietnam has witnessed a large outbreak of COVID-19 in the second half of 2021. The number of severe cases rapidly increased which promptly overwhelmed the healthcare system. There has been an urgent need for effective treatments that can prevent the progression to severe/critical illness. In this context, this trial was conducted to evaluate the safety and efficacy of Kovir capsule as a combination regimen with standard treatment in terms of reduction of viral load, clearance of signs and symptoms, and prevention of progression to severe/critical disease, in the comparison with placebo for patients with mild COVID-19.

2 | METHODS

2.1 | Study design

This was a double-blind randomized, placebo-controlled, single-centre study to assess the safety and efficacy of oral Kovir capsule (TD0069) in adults (aged ≥18 years) admitted to hospital with mild COVID-19. The trial was done at Temporary Hospital for COVID-19 No. 3 (Ho Chi Minh city, Vietnam) from July to September 2021. At the time of conducting this study, in Vietnam, all people with a positive reverse transcription-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 had to be quarantined in a hospital. When the outbreak in Ho Chi Minh city was ongoing in July, there were four levels of the hospital for COVID-19 patients: level 1 was for positive cases without symptoms and comorbidities, level 2 was for positive cases with symptoms but without comorbidities, level 3 was for positive cases with comorbidities because they were considered as high-risk patients, and level 4 was for severe/critical COVID-19 patients. The hospital where this study was conducted was at level 2.

Ethical approval was obtained from the institutional review board of the Traditional Medicine Institute of Ho Chi Minh City. Written informed consent was obtained from all patients. The study was performed in accordance with the ethical principles of the Declaration of Helsinki (World Medical Association, 2013) and the International Conference on Harmonization-Good Clinical Practice guidelines. This study was registered with ClinicalTrials.gov, NCT05042141.

2.2 | Patients

Eligible patients were men and women who were aged from 18 to 65 years and were RT-PCR positive with SARS-CoV-2 with a cycle threshold (CT) value of <30, had mild disease with signs and symptoms of COVID-19, were able to be compliant with their treatment in the study, and agreed to participate by giving written informed consent. Exclusion criteria included any sign or symptom suggested severe or critical COVID-19 at enrolment according to the WHO severity definitions (World Health Organization, 2021a), known allergy or intolerance to any of the product ingredients, inability to administer the study drugs, and inability to comply with study procedures or inability to ensure compliance with study drug administration as assessed by investigators. Patients with known comorbidities such as hypertension, diabetes, cardiovascular diseases, malignancy and other chronic diseases were not included because they were considered as high-risk patients and were admitted to other hospitals.

2.3 | Investigational product

Kovir capsule (TD0069) was developed based on the *Ren Shen Bai Du San* formulation. Each 800 mg hard capsule contained 600 mg fine powder of mixed herbal medicines and 200 mg excipient (corn starch, calcium carbonate, aerosil, talc, magnesium stearate, and sodium benzoate). The powder of herbal mixture was extracted from 12 herbal ingredients (Table 1) with water as the extraction solvent. Placebo was with the same appearance (color, shape, size and smell) to Kovir capsule.

2.4 | Randomisation and masking

Eligible participants were randomly assigned in a 1:1 ratio to receive either Kovir capsule or placebo. Block randomisation with block size of four was prepared using SAS software version 9.4. Envelopes with ordered numbers were used to contain the randomisation codes. Only

TABLE 1 Composition of herbal mixture in one Kovir capsule

No.	Latin name	Scientific name	Common name	Parts of plant used	Content (mg)
1	Radix Bupleuri chinensis	Bupleurum chinense DC.	Bupleurum Root/Chinese Thorowax Root/Chaihu	Root	245
2	Poria	Poria cocos (Schw.) Wolf.	Poria/Indian Bread/Fuling	Sclerotium without skin	245
3	Radix Codonopsis pilosulae	Codonopsis pilosula (Franch.) Nannf.	Codonopsis Root/Tangshen/ Dangshen	Root	245
4	Radix Peucedani	Peucedanum decursivum Maxim (or) Peucedanum praeruptorum Dunn.	Hogfennel Root/Qianhu	Root	245
5	Radix et Rhizoma Glycyrrhizae	Glycyrrhiza uralensis Fisch. or Glycyrrhiza glabra L.	Liquorice Root and Rhizome/ Gancao	Rhizome and root	163
6	Radix Platycodi grandiflori	Platycodon grandiflorum (Jacq.) A. DC.	Platycodon Root/Jiegeng	Root	163
7	Rhizoma Ligustici wallichii	Ligusticum wallichii Franch.	Sichuan Lovage Rhizome/ Chuanxiong	Rhizome	163
8	Fructus Aurantii	Citrus aurantium L.	Immature Bitter Orange Fruit/ Zhiqiao	Fruit	163
9	Rhizoma et Radix Notopterygii	Notopterygium incisum Ting ex H. T. Chang	Notopterygium Root and Rhizome/Qiang Huo	Rhizome and root	163
10	Radix Angelicae pubescentis	Angelica pubescens Maxim.	Pubescent Angelica Root/Duhuo	Root	163
11	Rhizoma Zingiberis	Zingiber officinale Rose.	Fresh Ginger/Shengjiang	Rhizome	82
12	Herba Menthae	Mentha arvensis L.	Mint/Bohe	Whole plant	82

one study member knew the true study drug of each randomisation code until the data were locked on September 1, 2021. Eligible patients were allocated to receive study drugs according to the sequential order of the recruitment.

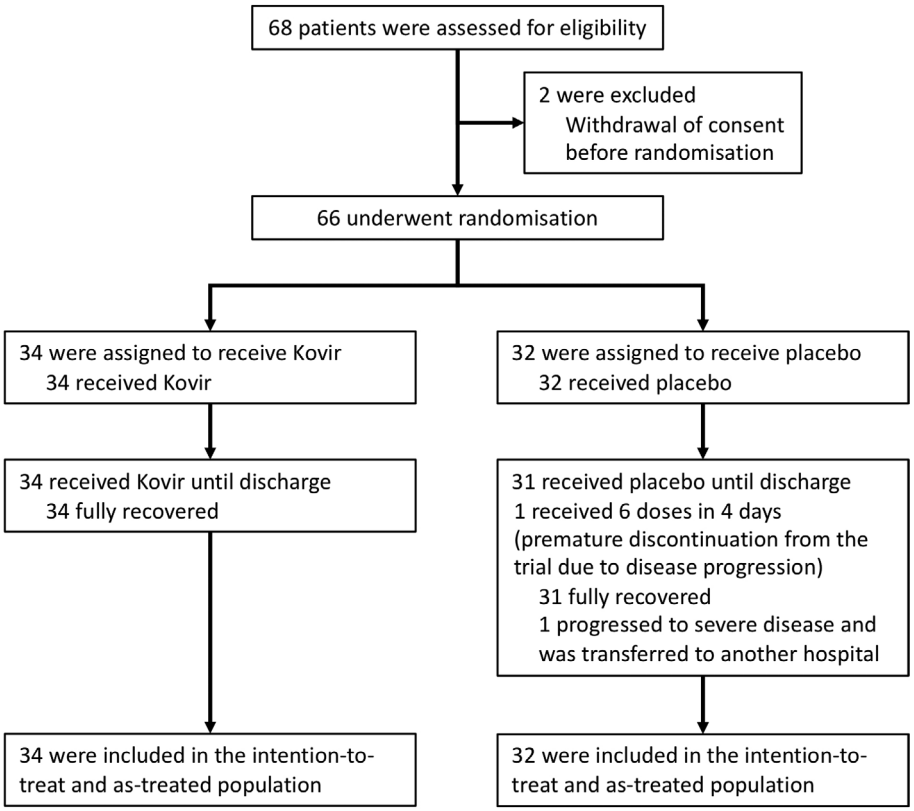
2.5 | Procedures

After randomisation, patients received either oral Kovir capsule (3 tablets 3 times a day [7,200 mg daily in total]) or the same amount of placebo for up to 14 days or until discharge. Patients were assessed once daily by study doctors and nurses to collect data on the severity of symptoms and safety. Study doctors evaluated 16 symptoms that were combined into four categories: respiratory group contained seven symptoms (nasal secretion, nasal congestion, sneeze, sore throat, hoarseness, cough, and chest pain); neurological group contained two symptoms (headache and loss of smell), skeleto-muscular group contained two symptoms (fatigue and muscle pain), general group contained four symptoms (fever, chill, sweating, and feeling sleepy), and other symptoms. Each symptom was assessed to four grades where 0 represented absence of the troublesome symptom, 1 represented mild, 2 represented moderate, and 3 represented severe symptom. The global symptom score was the total score of all 16 symptoms. Safety assessment included daily vital signs (body temperature, heart rate, blood pressure, and saturation of peripheral oxygen [SpO_2]), monitoring for adverse events, and clinical laboratory testing (day 0 [randomisation] and another time-point on days 4–8).

Standard care was symptomatic treatment such as antipyretics, adequate nutrition and rehydration in accordance with the WHO guidelines (World Health Organization, 2021a). Patients were discharged when having no fever for at least 2 days and two negative RT-PCR results or RT-PCR results with a CT value of >30 on two consecutive specimens taken at least 24 hr apart.

Nasopharyngeal swabs were collected daily until discharge for viral RNA detection and quantification. Virological testing was done at the laboratory of the International Institute of Gene and Immunology (Ho Chi Minh City, Vietnam) using quantitative RT-PCR. RNA was extracted from samples using the QIAamp® Viral RNA mini kit (QIAGEN Group, Germantown, Maryland, US), detected and quantified by one-step RT-rPCR using specific primers and probe targeted the E gene of SARS-COV-2 followed strictly the protocol given by the WHO in 2020 (Corman et al., 2020). The limit of detection of this procedure was 5.2 copies/reaction. CD4 and CD8 T-cell counts were assessed by flow cytometry using BD FACSCanto II System (BD Biosciences, Erembodegem, Belgium). Among leukocyte population separated by anti-human CD45-APC, CD4 and CD8 T-cells were distinguished by monoclonal antibodies (anti-human CD3-PE, anti-human CD4-FITC and anti-human CD8-PerCP). All tests were done in accordance with the manufacturer's specifications.

FIGURE 1 Study flow chart



2.6 | Outcomes

The antiviral efficacy outcomes were time to viral RNA clearance, viral clearance after 7 days of the treatment, and daily viral load. Viral clearance time was defined as days since randomisation to the first timepoint where viral RNA was undetectable. The clinical efficacy outcomes were time to symptom resolution, daily severity of symptoms, and progression to severe/critical COVID-19. Time to symptom resolution was defined as days since randomisation to the first timepoint that all symptoms were resolved, that is, the global symptom score was 0. The daily severity of symptoms was assessed by daily global symptom score. Severe/critical COVID-19 was defined according to the WHO guidelines (World Health Organization, 2021a). Other efficacy outcomes were the changes of CD4 and CD8 T-cell counts, white blood cell count, neutrophil/lymphocyte ratio, and liver enzymes from baseline to 4–8 days after treatment. Safety outcomes included all adverse events, serious adverse events, and premature discontinuations of study drugs due to adverse events.

2.7 | Statistical analysis

As this is the first study to explore the efficacy and safety of Kovir capsule on mild COVID-19 patients, we decided to recruit a convenient sample of 30 participants in each treatment group. Considering a dropout rate of 10%, we recruited 66 patients for the study.

The efficacy analyses were done with an intention-to-treat (ITT) dataset. In the ITT dataset, all patients who were randomized to study drugs were included irrespective of their protocol adherence and continued participation in the study. Patients were analyzed according to their randomized study drugs. The safety analysis was done with the dataset of actual treatments (as-treated dataset). All patients who received at least one dose of the study drugs were included in this dataset. Patients were analyzed according to their actual treatment group.

Time to viral clearance and symptom resolution were illustrated using Kaplan–Meier plot and compared between groups by log-rank test. Daily viral load (in log-transformation), daily symptoms severity score and other continuous outcomes were compared by Wilcoxon Mann–Whitney-*U* test. Dichotomous outcomes (viral clearance after 7 days, progression to severe/critical COVID-19, and safety outcome) were compared by Fisher's exact test. Analyses were done using statistical software R version 4.1.0. All tests were two-sided and the statistical significance level was set at 0.05. We did not perform multiple testing adjustments as this study was exploratory.

3 | RESULTS

Between July 28, 2021 and August 2, 2021, 68 patients were screened, of whom 66 were eligible for randomisation: 34 patients were assigned to receive Kovir capsule and 32 were assigned to receive placebo. All patients in the Kovir group completed their

TABLE 2 Baseline patient characteristics

	Kovir ($n = 34$)	Placebo ($n = 32$)
Age, years	34 (28; 42)	35 (29; 46)
Sex male	18 (52.9)	14 (43.8)
BMI, kg/m^2	21.8 (20.0; 23.0)	22.2 (20.3; 23.7)
Overweight/obesity (BMI ≥25 kg/m^2)	3 (8.8)	4 (12.5)
Diabetes	1 (2.9)	1 (3.1)
Body temperature, °C	36.8 (36.6; 36.9)	36.8 (36.6; 37.0)
Fever (body temperature ≥ 37.5°C)	5 (14.7)	3 (9.4)
SpO_2, %	97 (96; 98)	97 (96; 98)
Global symptom score	3.0 (2.0; 4.0)	3.0 (3.0; 4.2)
White blood cell count, $\times 10^9$/L	6.4 (5.2; 7.8)	5.7 (4.8; 6.1)
4–10	31 (91.2)	30 (93.8)
<4	1 (2.9)	1 (3.1)
>10	2 (5.9)	1 (3.1)
Lymphocyte count, $\times 10^9$/L	2.5 (1.9; 3.0)	2.0 (1.7; 2.3)
≥1.0	33 (97.1)	30 (93.8)
<1.0	1 (2.9)	2 (6.2)
Neutrophil/lymphocyte ratio	1.5 (1.2; 2.1)	1.8 (1.5; 2.6)
1–3	28 (82.4)	23 (71.9)
<1	4 (11.8)	4 (12.5)
>3	2 (5.9)	5 (15.6)
Serum creatinine, μmol/L	81.5 (70.5; 92.2)	77.0 (69.5; 86.5)
≤133	34 (100.0)	31 (96.9)
>133	0 (0.0)	1 (3.1)
Aspartate aminotransferase, U/L	28.0 (22.2; 45.0)	35.5 (27.8; 54.0)
≤40	23 (67.6)	19 (59.4)
>40	11 (32.4)	13 (40.6)
Alanine aminotransferase, U/L	32.5 (23.0; 51.8)	38.0 (22.0; 53.0)
≤50	24 (70.6)	22 (68.8)
>50	10 (29.4)	10 (31.2)
Viral load (log_{10} copies/mL)	5.9 (4.6; 6.6)	5.5 (3.9; 6.7)
CD4 count, cells/μL	870 (686; 1,019)	714 (529; 835)
CD8 count, cells/μL	643 (494; 822)	440 (382; 595)
CD4/CD8 ratio	1.4 (1.2; 1.6)	1.3 (1.1; 1.7)
≥1	30 (88.2)	26 (81.2)
<1	4 (11.8)	6 (18.8)
Time from first symptom onset to randomisation, days		
1	2 (5.9)	0 (0.0)
2	31 (91.2)	32 (100.0)
4	1 (2.9)	0 (0.0)

Note: Summary statistics are median (25th; 75th percentiles) or *n* (%).
Abbreviations: BMI, body mass index; SpO_2, saturation of peripheral oxygen.

treatment until discharge, whereas one patient in the placebo group stopped the treatment after 4 days because of the progression to severe disease and was transferred to another hospital. Finally, all 66 patients were included in the ITT and as-treated populations (Figure 1).

The median (25th; 75th percentiles) age of included patients was 34 (25; 44) years. Sex distribution was 18 men (52.9%) in the Kovir group versus 14 men (43.8%) in the placebo group. There were three patients (8.8%) with overweight/obesity and one (2.9%) with newly diagnosed diabetes in the Kovir group versus four patients (12.5%)

TABLE 3 Treatment received after enrolment and safety outcome

	Kovir ($n = 34$)	Placebo ($n = 32$)	p value
Duration of study drug use, days	10 (10; 11)	10 (9; 10)	.060
Total number of tablets use	75 (72; 84)	74 (66; 79)	.144
Antipyretic treatment	5 (14.7)	1 (3.1)	.198
Antibiotic treatment	0 (0.0)	6 (18.8)	.010
Antitussive treatment	0 (0.0)	4 (12.5)	.050
Cough suppressants	2 (5.9)	4 (12.5)	.420
Antihistamine treatment	0 (0.0)	5 (15.6)	.023
Corticosteroids therapy	0 (0.0)	1 (3.1)	.485
Anticoagulant treatment	0 (0.0)	1 (3.1)	.485
Oxygen supports	0 (0.0)	2 (6.2)	.231
Hospital length of stay, days	9 (9; 10)	9 (8; 9)	.164
Any adverse event	0 (0.0)	0 (0.0)	–

Note: Summary statistics are median (25th; 75th percentiles) or *n* (%).

with overweight/obesity and one (3.1%) with newly diagnosed diabetes in the placebo group. None of the patients had received any dose of COVID-19 vaccine. Global symptom score and clinical laboratory results at enrolment were balanced between the groups. The Kovir group had a fairly higher viral load, CD4 and CD8 counts at baseline compared to the placebo group. Most patients were randomized at day 2 after the first symptom onset (Table 2).

The duration and amount of study drug used were balanced between groups. Some imbalances existed regarding other treatments, including more patients receiving antipyretic drugs in the Kovir group and more patients receiving antibiotic, antitussive, and antihistamine drugs, and oxygen supports in the placebo group. The median hospital length of stay was 9 days in both groups. No patient experienced any clinical or laboratory adverse event (Table 3).

Viral RNA load decreased over time similarly in the two groups without a significant difference at any day since randomisation (Figure 2a). Viral clearance time was similar in both groups with a median of 8 days (Figure 2b). On day 7 after randomisation, 13 patients (38.2%) in the Kovir group and 10 (31.2%) in the placebo group had viral clearance (Table 4). Viral clearance time was unknown in 14 patients, including one patient with the progression to severe disease at day 3 who was then transferred to another hospital for intensive care, and 13 patients with full recovery whom the viral load was still detectable at discharge. All other patients had viral clearance before day 12.

Symptom severity score however differed between groups. The median global symptom score was similar between groups at days 0 and 1 (3 points) but the score decreased more rapidly in the Kovir group than in the placebo group thereafter (Figure 3a). Significant difference was found at day 2 (median score of 2 vs. 4), day 3 (1 vs. 2), day 4 (0 vs. 2), day 5 (0 vs. 2), and day 6 (0 vs. 1) when comparing Kovir and placebo groups, respectively. Time to symptom resolution was also significantly lower in the Kovir group than in the placebo group (median of 4 vs. 7 days) (Figure 3b). Two patients (6.3%) in the placebo group developed the severe disease; one was transferred to another hospital for intensive care (Table 4).

Both CD4 and CD8 counts increased from baseline to day 4–8 in the two groups but the change was lower in the Kovir group than in the placebo group (median CD4 and CD8 count changes were 124 and 86 versus 180 and 166 cells/μL, respectively). Regarding other laboratory parameters (white cell count, neutrophil/lymphocyte ratio, and liver enzymes), the changes were not marked and similar between the two groups (Table 4).

4 | DISCUSSION

Our trial found that Kovir capsule, a Vietnamese polyherbal medicine, significantly improved daily symptom severity and the time to symptom resolution for patients with mild COVID-19 compared with placebo. However, viral load and viral clearance time were similar between the treatments. Only two patients in the placebo group developed severe disease so we could not draw any conclusion in preventing disease progression to severe/critical COVID-19. Without adverse events, this study showed a good safety profile of Kovir capsule in patients with mild COVID-19.

Several herbal/traditional medicines have been investigated for the treatment of mild and severe/critical COVID-19. They come from countries with well-known traditional medicine such as China (Xia et al., 2021; Xiao et al., 2020; Xu et al., 2021; Zhang et al., 2021; Zhou et al., 2021), India (Devpura et al., 2021; Natarajan et al., 2021; Srivastava et al., 2021), and Iran (Karimi et al., 2021; Valizadeh et al., 2020). These studies showed that herbal medicines could reduce SARS-CoV-2 viral load, hospital length of stay, time to symptom resolution in mild COVID-19 patients, and mortality rate in patients with severe/critical COVID-19, when compared with placebo. These herbal medicines share a remarkable feature which is symptom relief. Only some of them showed evidence of reducing viral load. Nevertheless, it is not necessary to reduce SARS-CoV-2 viral load in order to improve the clinical outcomes of COVID-19 patients. Until now, there is no evidence that the viral load is associated with disease severity (Abdulrahman, Mallah, & Alqahtani, 2021;

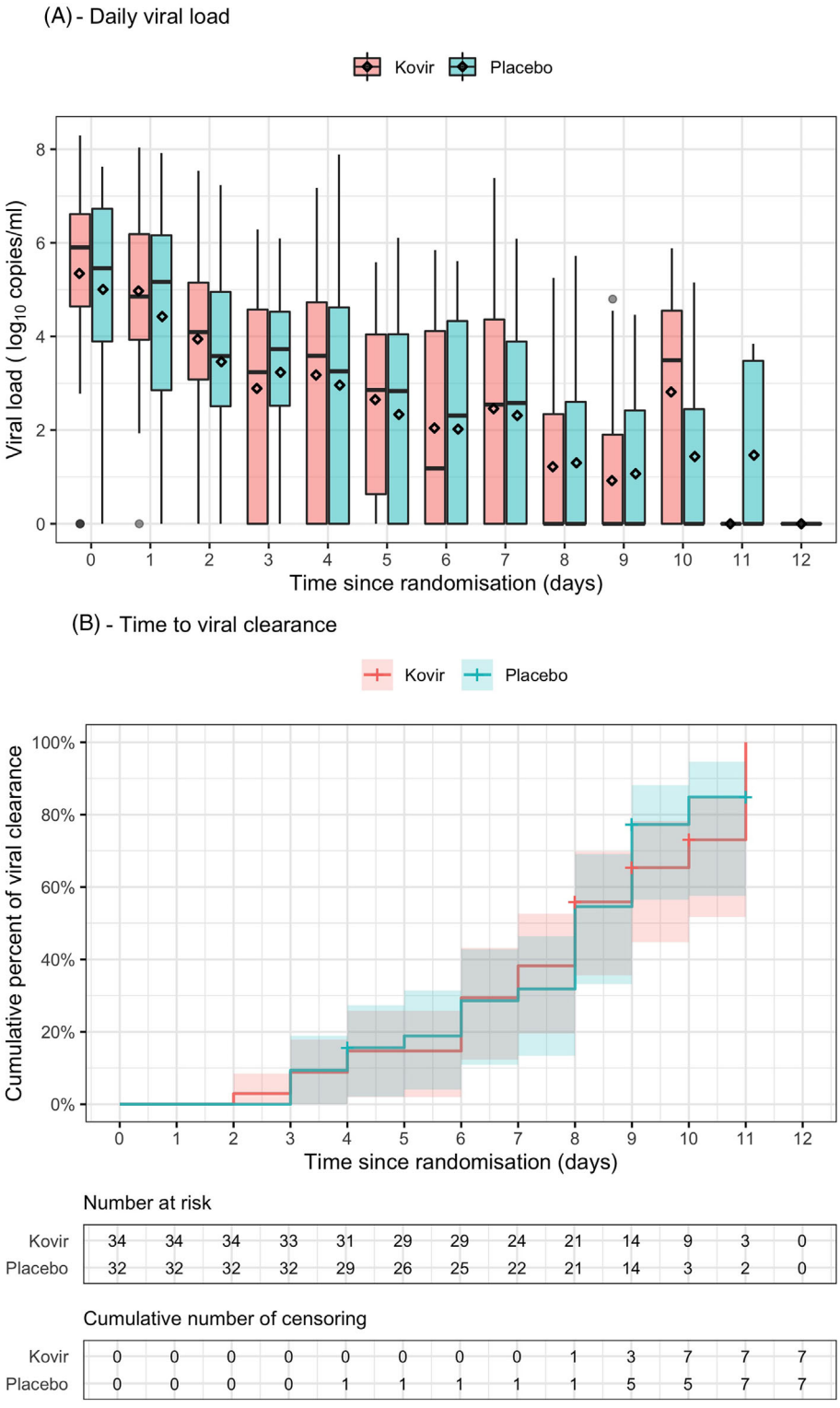


FIGURE 2 Daily viral load and time to viral clearance. In (a), the line inside each box is the median, the upper and lower margins of each box represent the interquartile range (25th; 75th percentiles), and the diamond inside each box is the mean of viral load (in $\log_{10}$ transformation). In (b), viral clearance time was censored in 14 patients, including one patient with progression to severe disease at day 3 who was then transferred to another hospital for intensive care, and 13 patients with full recovery whom the viral load was still detectable at discharge. Lines are the Kaplan–Meier estimates and colored regions are 95% confidence intervals

Shenoy, 2021). The underlying pathological mechanism of severe COVID-19 remains largely unexplored. The pathogenesis of the disease involves a complex interplay between the virus and the host immune response (Zhang et al., 2021). Currently, recommended drugs by the WHO for COVID-19 patients are mostly those that affect the host immune system which might be the crucial part of severe disease, particularly at later phases.

Our study showed similar effects of Kovir capsule on COVID-19 to other herbal medicines. We could not find an antiviral effect of Kovir capsule, but it had a marked improvement of clinical symptoms. Similar to traditional Chinese medicine, the principles of traditional Vietnamese medicine are for diagnosing and describing the location and nature of the body's imbalance. Treatments are then catered toward each individual patient mainly based on the symptoms, among

TABLE 4 Efficacy outcomes

	Kovir ($n = 34$)	Placebo ($n = 32$)	p value
Viral clearance at day 7	13 (38.2)	10 (31.2)	.612
Progression to severe/critical COVID-19	0 (0.0)	2 (6.3)	.231
CD4 count at day 4–8, cells/μL	1,001 (855; 1,162)	895 (762; 1,154)	.229
CD4 count change, cells/μL	124 (38; 306)	180 (104; 386)	.078
CD8 count at day 4–8, cells/μL	702 (586; 794)	692 (620; 810)	.859
CD8 count change, cells/μL	86 (−27; 145)	166 (122; 257)	.002
CD4/CD8 ratio at day 4–8	1.44 (1.19; 1.75)	1.35 (1.08; 1.71)	.407
CD4/CD8 ratio change	0.06 (−0.04; 0.13)	−0.12 (−0.20; 0.11)	.049
White blood cell count at day 4–8, $\times 10^9$/L	7.69 (6.50; 8.65)	7.32 (6.04; 7.83)	.482
White blood cell count change, $\times 10^9$/L	1.03 (0.45; 1.83)	1.63 (0.56; 2.30)	.205
Neutrophil/lymphocyte ratio at day 4–8	1.68 (1.40; 2.11)	1.74 (1.55; 2.22)	.461
Neutrophil/lymphocyte ratio change	0.03 (−0.29; 0.40)	−0.02 (−0.33; 0.40)	.518
Aspartate aminotransferase at day 4–8, U/L	26 (21; 42)	27 (20; 32)	.839
Aspartate amonotransferase change, U/L	−4 (−9; 2)	−6 (−18; −2)	.165
Alanine aminotransferase at day 4–8, U/L	32 (24; 62)	36 (26; 51)	.845
Alanine amonotransferase change, U/L	1 (−7; 6)	2 (−6; 13)	.888

Note: Summary statistics are median (25th; 75th percentiles) or n (%).

those, herbal medicines with their healing properties are used to restore balance in the body. The mechanism of action in COVID-19 patients is similar: Kovir capsule resolves the symptoms more rapidly than placebo. This is important in preventing severe/critical disease since an outbreak can easily overwhelm fragile health systems in LMICs. As of November 9, 2021, only human antibody drugs are recommended by the WHO for patients with non-severe COVID-19 (World Health Organization, 2021b), but they have limited applicability given the cost and availability of the drugs and the requirement for intravenous administration. However, the effects of Kovir capsule in severe/critical COVID-19 patients need to be investigated in future studies.

The role of T-cell immune responses in COVID-19 pathogenesis and long-term protective immunity is still questionable. For many viral infections, it usually takes 7–10 days to develop adaptive T-cell immune responses to control the virus. CD4 and CD8 T-cell counts were found to decrease in the early phase of COVID-19 (Jiang et al., 2020) and most recovered patients established CD4 and CD8 responses to SARS-CoV-2 (Grifoni et al., 2020). A meta-analysis showed that oral Chinese herbal medicine improved CD4, CD4/CD8 ratio, CD3, and reduced TNF-alpha (Shi et al., 2021). However, the level of evidence is low-to-moderate. Whether herbal medicines improve clinical parameters of COVID-19 patients through the immunity profile requires more studies. In our study, we observed both CD4 and CD8 T-cell counts increased from baseline to days 4–8, but Kovir group had lower changes than placebo. Since the sample size was relatively small and we measured only CD4 and CD8 T-cell counts at only two time-points, the effects of Kovir capsule on modulating immune effectors during COVID-19 are unclear and require further investigations. Other inflammatory responses are also unclear because we did not aim to investigate the effects of Kovir capsule on some laboratory parameters such as C-reactive protein, ferritin, D-dimer, and lactate dehydrogenase. However, the changes in total leukocyte count and neutrophil/lymphocyte ratio were not marked and similar between the two groups. Another issue of herbal medicines in COVID-19 patients is the effect on the digestive system and liver functions, which should not be neglected (Shi et al., 2021). In our study, we did not focus on digestive signs and symptoms but we did not observe any noticeable side effects of Kovir capsule in the digestive system. With respect to liver enzymes, no remarkable change was found in both Kovir and placebo groups.

This study has several limitations. First, this trial is exploratory and the sample size is small, thus, the study does not have enough power to prove the efficacy of Kovir capsule in preventing the progression to severe/critical COVID-19. Second, most included patients are young and without comorbidities. This limits the generalizability of the results to the general population of mild COVID-19 patients. A large-scale trial is required to solve these two limitations and better demonstrate the efficacy of the drug. Third, we did not test some inflammatory markers so we could not investigate the effect of Kovir capsule on the inflammatory response of the patients. Also, the follow-up period might be inadequate to determine the effect of Kovir capsule on liver functions.

In conclusion, Kovir capsule, a Vietnamese polyherbal medicine, is safe and potentially effective in the treatment of mild COVID-19 patients. It significantly improves symptoms of the patients and reduces the time to symptom resolution when compared to placebo. The effects on the reduction of SARS-CoV-2 viral load and immune responses are unclear. This study's results encourage the integration of traditional Vietnamese medicine with standard treatment for

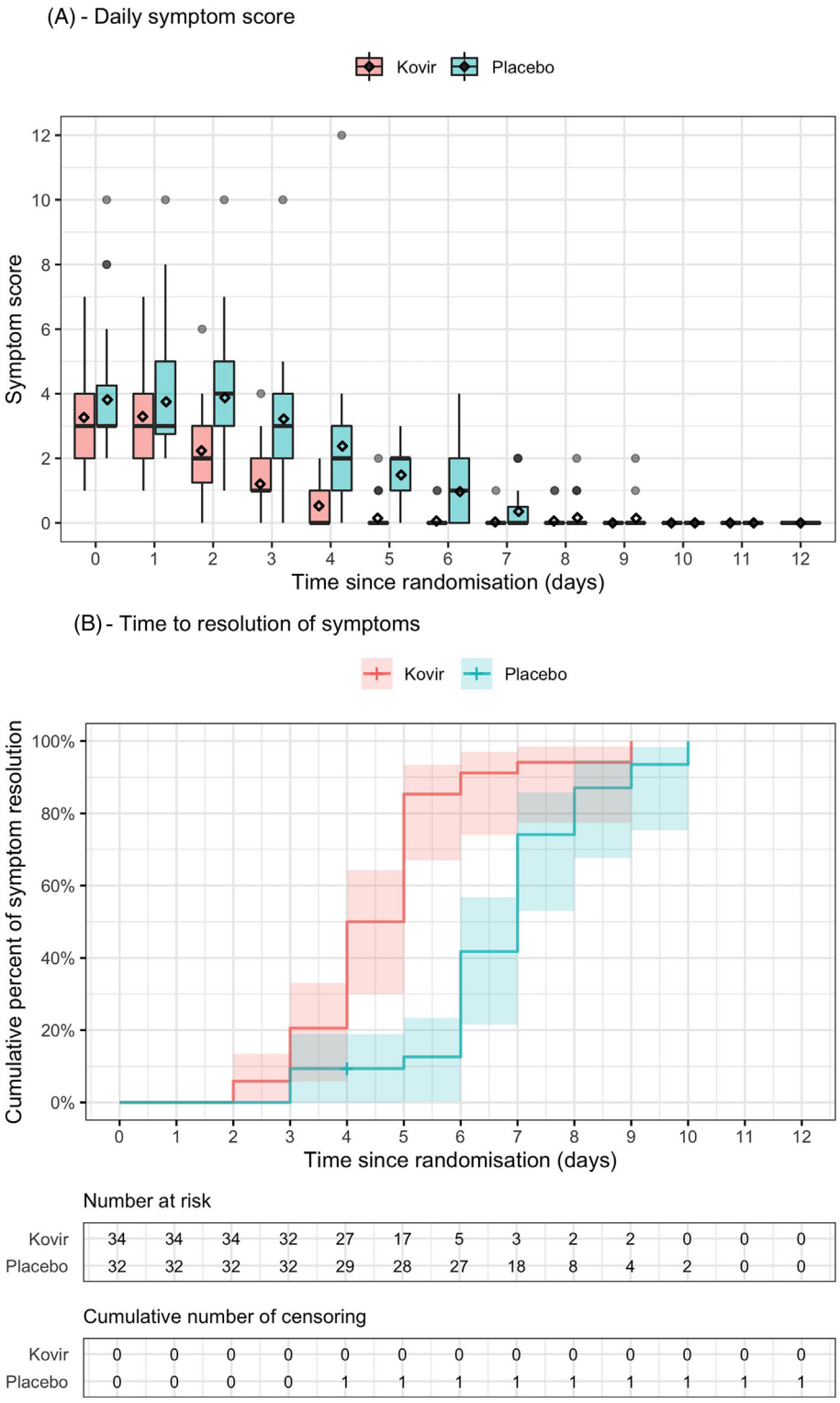


FIGURE 3 Daily symptom score and time to resolution of symptoms. In (a), the line inside each box is the median, the upper and lower margins of each box represent the interquartile range (25th; 75th percentiles), and the diamond inside each box is the mean of symptom score. In (b), time to resolution of symptoms was censored in one patient, this patient was with progression to severe disease at day 3 and was then transferred to another hospital for intensive care. Lines are the Kaplan–Meier estimates and colored regions are 95% confidence intervals

COVID-19 patients. A large-scale trial is required to strengthen the findings of this study.

ACKNOWLEDGEMENTS

We acknowledge all the patients who participated in this study and the medical staff who looked helped in their management at the Temporary Hospital for COVID-19 No. 3 (Ho Chi Minh City, Vietnam).

CONFLICT OF INTEREST

All authors confirm that they have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, [Nguyen Lam Vuong], upon reasonable request.

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REFERENCES

Abdulrahman, A., Mallah, S. I., & Alqahtani, M. (2021). COVID-19 viral load not associated with disease severity: Findings from a retrospective cohort study. *BMC Infectious Diseases*, *21*(1), 688. https://doi.org/10.1186/s12879-021-06376-1

Chen, J. K., & Chen, T. T. (2009). *Chinese herbal formulas and applications: Pharmacological effects & clinical research*. City of industry, CA: Art of Medicine Press.

Corman, V. M., Landt, O., Kaiser, M., Molenkamp, R., Meijer, A., Chu, D. K., … Drosten, C. (2020). Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveillance*, *25*(3), 2000045. https://doi.org/10.2807/1560-7917.Es.2020.25.3.2000045

Devpura, G., Tomar, B. S., Nathiya, D., Sharma, A., Bhandari, D., Haldar, S., … Varshney, A. (2021). Randomized placebo-controlled pilot clinical trial on the efficacy of ayurvedic treatment regime on COVID-19 positive patients. *Phytomedicine*, *84*, 153494. https://doi.org/10.1016/j.phymed.2021.153494

Grifoni, A., Weiskopf, D., Ramirez, S. I., Mateus, J., Dan, J. M., Moderbacher, C. R., … Sette, A. (2020). Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell*, *181*(7), 1489–1501.e1415. https://doi.org/10.1016/j.cell.2020.05.015

Jiang, M., Guo, Y., Luo, Q., Huang, Z., Zhao, R., Liu, S., … Wan, L. (2020). T-cell subset counts in peripheral blood can be used as discriminatory biomarkers for diagnosis and severity prediction of coronavirus disease 2019. *The Journal of Infectious Diseases*, *222*(2), 198–202. https://doi.org/10.1093/infdis/jiaa252

Karimi, M., Zarei, A., Soleymani, S., Jamalimoghadamsiahkali, S., Asadi, A., Shati, M., … Zargaran, A. (2021). Efficacy of Persian medicine herbal formulations (capsules and decoction) compared to standard care in patients with COVID-19, a multicenter open-labeled, randomized, controlled clinical trial. *Phytotherapy Research*, *35*(11), 6295–6309. https://doi.org/10.1002/ptr.7277

Lyu, M., Fan, G., Xiao, G., Wang, T., Xu, D., Gao, J., … Zhang, B. (2021). Traditional Chinese medicine in COVID-19. *Acta Pharmaceutica Sinica B*, *11*(11), 3337–3363. https://doi.org/10.1016/j.apsb.2021.09.008

Maguire, B. J., & Guérin, P. J. (2020). A living systematic review protocol for COVID-19 clinical trial registrations. *Wellcome Open Research*, *5*, 60. https://doi.org/10.12688/wellcomeopenres.15821.1

Natarajan, S., Anbarasi, C., Sathiyarajeswaran, P., Manickam, P., Geetha, S., Kathiravan, R., … Balaji, P. (2021). Kabasura Kudineer (KSK), a poly-herbal Siddha medicine, reduced SARS-CoV-2 viral load in asymptomatic COVID-19 individuals as compared to vitamin C and zinc supplementation: Findings from a prospective, exploratory, open-labeled, comparative, randomized controlled trial, Tamil Nadu, India. *Trials*, *22*(1), 623. https://doi.org/10.1186/s13063-021-05583-0

Ritchie, H., Mathieu, E., Rodés-Guirao, L., Appel, C., Giattino, C., Ortiz-Ospina, E., … Roser, M. (2020). Coronavirus Pandemic (COVID-19). Retrieved November 9, 2021 from https://ourworldindata.org/covid-vaccinations. Published online at OurWorldInData.org

Shenoy, S. (2021). SARS-CoV-2 (COVID-19), viral load and clinical outcomes; lessons learned one year into the pandemic: A systematic review. *World Journal of Critical Care Medicine*, *10*(4), 132–150. https://doi.org/10.5492/wjccm.v10.i4.132

Shi, S., Wang, F., Li, J., Li, Y., Li, W., Wu, X., … Wang, Z. (2021). The effect of Chinese herbal medicine on digestive system and liver functions should not be neglected in COVID-19: An updated systematic review and meta-analysis. *IUBMB Life*, *73*(5), 739–760. https://doi.org/10.1002/iub.2467

Shi, S., Wang, F., Yao, H., Kou, S., Li, W., Chen, B., … Wang, Z. (2021). Oral Chinese herbal medicine on immune responses during coronavirus disease 2019: A systematic review and meta-analysis. *Frontiers in Medicine*, *8*, 685734. https://doi.org/10.3389/fmed.2021.685734

Srivastava, A., Rengaraju, M., Srivastava, S., Narayanan, V., Gupta, V., Upadhayay, R., … AarthiVelmurugan. (2021). Efficacy of two siddha polyherbal decoctions, Nilavembu Kudineer and Kaba Sura Kudineer, along with standard allopathy treatment in the management of mild to moderate symptomatic COVID-19 patients-a double-blind, placebo-controlled, clinical trial. *Trials*, *22*(1), 570. https://doi.org/10.1186/s13063-021-05478-0

Valizadeh, H., Abdolmohammadi-Vahid, S., Danshina, S., Ziya Gencer, M., Ammari, A., Sadeghi, A., … Ahmadi, M. (2020). Nano-curcumin therapy, a promising method in modulating inflammatory cytokines in COVID-19 patients. *International Immunopharmacology*, *89* (Pt B), 107088. https://doi.org/10.1016/j.intimp.2020.107088

Vietnam's Ministry of Health. (2020). *About enhancing the prevention and management of acute respiratory distress syndrome due to SARS-CoV-2 using traditional medicine (1306/BYT-YDCT)*. Hanoi: Ministry of Health Retrieved November 9, 2021 from http://ydct.moh.gov.vn/documents/13157/65019/C%C3%B4ng%20v%C4%83n%20s%E1%BB%91%20201306_BYT_YDCT%20huong%20dan%20cac%20don%20vi%20kbcb%20yhct%20phong%20chong%20viem%20dhhc%20do%20sars%20cov%202.pdf

World Health Organization. (2021a). Clinical management of COVID-19: living guidance. Retrieved November 9, 2021 from https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021a-1

World Health Organization. (2021b). Therapeutics and COVID-19: living guideline. Retrieved November 9, 2021 from https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021b.3

World Health Organization. (2021c). WHO Coronavirus (COVID-19) Dashboard. Retrieved November 9, 2021 from https://covid19.who.int/

World Medical Association. (2013). World medical association declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA*, *310*(20), 2191–2194. https://doi.org/10.1001/jama.2013.281053

Xia, L., Shi, Y., Su, J., Friedemann, T., Tao, Z., Lu, Y., … Schröder, S. (2021). Shufeng Jiedu, a promising herbal therapy for moderate COVID-19: Antiviral and anti-inflammatory properties, pathways of bioactive compounds, and a clinical real-world pragmatic study. *Phytomedicine*, *85*, 153390. https://doi.org/10.1016/j.phymed.2020.153390

Xiao, M., Tian, J., Zhou, Y., Xu, X., Min, X., Lv, Y., … Tong, X. (2020). Efficacy of Huoxiang Zhengqi dropping pills and Lianhua Qingwen granules in treatment of COVID-19: A randomized controlled trial. *Pharmacological Research*, *161*, 105126. https://doi.org/10.1016/j.phrs.2020.105126

Xu, X., Zhang, J., Zheng, W., Yang, Z., Zhao, X., Wang, C., … Liu, Q. (2021). Efficacy and safety of Reduning injection in the treatment of COVID-19: A randomized, multicenter clinical study. *Annals of Palliative Medicine*, *10*(5), 5146–5155. https://doi.org/10.21037/apm-20-2121

Zhang, Q., Xiang, R., Huo, S., Zhou, Y., Jiang, S., Wang, Q., & Yu, F. (2021). Molecular mechanism of interaction between SARS-CoV-2 and host cells and interventional therapy. *Signal Transduction and Targeted Therapy*, *6*(1), 233. https://doi.org/10.1038/s41392-021-00653-w

Zhang, X. Y., Lv, L., Zhou, Y. L., Xie, L. D., Xu, Q., Zou, X. F., … Ye, X. Q. (2021). Efficacy and safety of Xiyanping injection in the treatment of COVID-19: A multicenter, prospective, open-label and randomized

controlled trial. *Phytotherapy Research*, *35*(8), 4401–4410. https://doi.org/10.1002/ptr.7141

Zhao, Y., Hou, X., Gao, Z., & Wang, T. (2020). Research on medication for severe type of COVID-19 based on Huashi Baidu prescription. *Chinese Archives of Traditional Chinese Medicine*, *38*(6), 14–17.

Zhou, S., Feng, J., Xie, Q., Huang, T., Xu, X., Zhou, D., … Fang, B. (2021). Traditional Chinese medicine shenhuang granule in patients with severe/critical COVID-19: A randomized controlled multicenter trial. *Phytomedicine*, *89*, 153612. https://doi.org/10.1016/j.phymed.2021.153612

How to cite this article: Loc, H. N., Lan, T. T. N., Huong, D. T. L., Tuyen, N. T., Quang, T. M., Dao, L. M., Van, P. H., & Vuong, N. L. (2022). Traditional Vietnamese medicine Kovir capsule in patients with mild COVID-19: A double-blind randomized controlled trial. *Phytotherapy Research*, *36*(7), 2878–2888. https://doi.org/10.1002/ptr.7455