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A Herbal Remedy Exhibiting Potent Therapeutic Effects Against Covid-19: A Post-Hoc Analysis of Outpatient Clinical Observations

Jiangnan Feng[1*], Zhenghua Ma[1], Chengsheng Yi[1] , Meiying Gao[2], Dengbin Zhu[1], Minghai Ma[1], Xia Liu[1], Shuzhen Wang[3], Xue Feng[1], Xianfu Li[4] and Yu Yan[1]

[1]Department of Medicine, Tongrun Tang Traditional Chinese Medicine Clinic, Nanchong, China
[2]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China
[3]Center for Disease Control and Prevention, Qichun, China
[4]Zhognde Institute of Psychology, Wuhan, China

***Correspondence:** Jiangnan Feng, Department of Medicine, Tongrun Tang Traditional Chinese Medicine Clinic, Nanchong, China, E-mail: jnfengyale@qq.com; DOI: https://doi.org/10.56147/jidpc.1.1.1

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Abstract

Background: There is no specific evidence-based therapy with proven efficacy for COVID-19. Marecipe AV, an ancient Chinese herbal compound, has been utilized in our clinic for over a decade to treat viral infectious diseases, demonstrating remarkable therapeutic benefits. We present the outcomes of Marecipe AV herbal therapeutics in treating COVID-19 at our clinic during the outbreak in China.

Methods: The efficacy of Marecipe AV in treating COVID-19 was assessed through a comparative analysis of the duration of fever, the time to sustained resolution of clinical symptoms and the incidence of hospitalization due to progression to severe COVID-19 between a treated patient cohort and an untreated control group.

Results: Data were collected from 524 individuals diagnosed with COVID-19, of whom 159 received Marecipe AV, while 365 did not. All 122 patients treated with Marecipe AV experienced resolution of fever within 24 hours of initiating treatment, with the COVID-19 clinical course concluding within the subsequent 24 hours. The incidence of fever among the 37 individuals exposed to Omicron who were undergoing anti-tumor treatment with Marecipe was 0%, in contrast to 98% among their close contacts. Among 78 individuals at high-risk of progressing to severe COVID-19, the hospitalization rate was 0% for those treated with Marecipe AV, while it was 68% for untreated patients.

Conclusion: Marecipe AV herbal therapy has demonstrated a clear and potent therapeutic effect against COVID-19. The use of Marecipe therapeutics has the potential to terminate the clinical course of mild to moderate COVID-19 in all patients treated within a 48-hour window, while also effectively preventing the development of severe cases in all high-risk patients.

Key words: COVID-19; Herb; Herbal therapeutic; Therapy; Viral infectious diseases

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Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic continues to spread rapidly worldwide and severe acute respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has evolved into variants with increasing transmissibility and capability of evading human immunity (*e.g.,* the B.1.1.529 (omicron) variant) [1,2]. In late 2022 to early 2023, following the lifting of COVID-19 containment measures, an Omicron variant infection swept across China [3-5]. In just a short span of two months, more than 80% of China's urban population was infected simultaneously. Currently,

there is no evidence-based specific therapy with proven efficacy for COVID-19. The World Health Organization (WHO) recommends Nirmatrelvir–ritonavir (Paxlovid) for the treatment of mild-to-moderate COVID-19. Although Paxlovid brings hope for the treatment and prevention of COVID-19, it does not fully meet clinical needs [6,7]. During the recent outbreak of Omicron infections, the vast majority of COVID-19 patients in China were unable to obtain Paxlovid or even other medications in a timely manner [8-12].

Ma Recipe is an ancient herbal formula composed of powders derived from plants and rare freshwater fishes [13-15]. Marecipe AV is a modified version of Ma Recipe, featuring adjusted proportions of the herbs. Although the active ingredients and the mechanisms of action against viral infectious diseases have not been elucidated, it has been utilized in our clinic for over ten years to treat various viral conditions, including influenza, HPV infection, HBV infection, herpes zoster and postherpetic neuralgia [16]. In our clinical practice, we have observed that fever associated with influenza typically resolves within 12 hours following the administration of Marecipe AV, with sustained clinical recovery achieved within the subsequent 24 hours. Furthermore, clinical trials of Marecipe AV for the treatment of various life-threatening viral infections in animals have shown its remarkable efficacy in saving lives threatened by diseases such as African swine fever, avian influenza, canine distemper and canine parvovirus [17,18]. Based on clinical experience suggesting that Marecipe AV herbal therapeutics may effectively treat influenza within 24 hours, we utilized this therapy to treat COVID-19 patients in our clinic, considering the lack of available treatment options during the COVID-19 pandemic. This study provides a retrospective analysis of the outcomes of Marecipe AV in the management of COVID-19.

Methods

Study design

This study is a post-hoc analysis of clinical observations, rather than a prospective clinical trial with a robust design. Data on all COVID-19 outpatients at our clinic and their close contacts during the COVID-19 outbreak were collected through telephone interviews. The efficacy of Marecipe AV in addressing these conditions was assessed based on the duration of fever caused by COVID-19, the time to sustained clinical symptom resolution and the rates of hospitalization for progression to severe COVID-19 in both the treated and untreated groups. The administration of Marecipe AV follows the daily practice of Traditional Chinese medicine (TCM) . TCM practitioners prescribe herbal formulas for patients who then take these prescriptions to the pharmacy to obtain the herbs. Patients prepare and consume the Marecipe AV extract orally at home. This process is consistent with the ethical principles of TCM and complies with relevant laws and regulations governing TCM practice.

Population

As this study was not a pre-planned clinical trial, there were no specific inclusion or exclusion criteria for selecting patients to receive Marecipe AV herbal therapy. Data were collected from all adult patients who presented to our clinic with fever during the COVID-19 pandemic. We conducted telephone interviews to gather information about family members who were considered close contacts and lived with the patients treated with Marecipe AV, as well as to collect data from patients with advanced cancer who were receiving treatment with Marecipe in our clinic, along with their close contacts. Additionally, we collected data on the treatment of severe COVID-19 patients who were hospitalized in various hospitals and received Marecipe AV. Given that most Chinese herbal medicines lack indications and that there are no standardized prescriptions for specific diseases, the requirement for additional informed consent is not necessary when prescribing these herbal remedies, even if they have not been previously utilized for treating conditions such as COVID-19. This framework ensures that TCM practices remain within the bounds of legal and ethical standards.

Procedures

Each febrile patient visiting our clinic during the COVID-19 pandemic undergoes COVID-19 dipstick and SARS-CoV-2 nucleic acid tests to confirm SARS-CoV-2 infection. The TCM doctors at the clinic prescribe a treatment regimen for the patient, who then collects the herbs from the TCM pharmacy and prepares the Marecipe AV extract at home according to the preparation method provided by the physician, which is subsequently taken orally. The standard treatment for patients with mild to moderate COVID-19 involves the oral administration of 10 grams of Marecipe AV preparation three times a day, with a reduction to twice daily on the fourth and fifth days. For patients with severe and critical COVID-19, Marecipe AV is administered orally at a dose of 10 grams every four hours for a duration of 3 to 5 days, followed by a dosage adjustment to 10 grams twice daily.

Daily telephone interviews were conducted with patients who received Marecipe AV treatment, as well as with their close contacts, starting the day after the patients were discharged from the clinic. The collected data were entrusted to a third-party statistical professional for analysis.

Outcomes

The primary endpoint included the duration of fever and the time to sustained clinical symptom resolution for two consecutive days. The secondary endpoints focused on hospitalization rates associated with the progression to severe and critical COVID-19. The study endpoints were determined based on the treatment design for the COVID-19 study conducted by Xiaohong Fan et al. The duration of fever is defined as the time from the administration of the

initial dose to the absence of fever for two consecutive days. The time for sustained clinical symptom resolution for two consecutive days is defined as the duration from the initial dose to the first of two consecutive days without moderate to severe symptoms. The main criterion for resolution was near-complete, but not total, alleviation of symptoms, allowing patients to return to normal activities such as work and no longer requiring bed rest.

Statistical Analysis

An Analysis of Variance (ANOVA) was conducted for each data set. The Kolmogorov-Smirnov test and the Mann-Whitney U rank sum test were employed to compare the observed indicators among the treatment groups. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 27 for Windows.

Results

Data were collected from a total of 524 observed individuals, including 122 patients who received Marecipe AV therapy and 365 who did not. Among the 524 patients, 37 individuals with advanced cancer who were undergoing anti-tumor treatment with Ma recipe had been exposed to COVID-19 and there were 102 cases involving their close contacts. Additionally, 78 individuals aged 75 years or older, deemed to be at high-risk of developing severe COVID-19, were identified and divided into independent subgroups for analytical purposes. Furthermore, 17 critically ill COVID-19 patients admitted to various hospitals received Marecipe AV therapy, while data from 31 untreated COVID-19 inpatients during the same period were used as controls. Each subject was confirmed to be infected with SARS-CoV-2 through either a COVID-19 dipstick test or a SARS-CoV-2 nucleic acid test. All participants in the study were from urban areas in China and presumably had received SARS-CoV-2 vaccinations.

All 122 patients who received treatment stopped experiencing COVID-19-related fever within 24 hours of initiating the dosing regimen. The mean duration of fever was 14.51 hours for the group of 122 treated individuals, compared to 96 hours for the group of 365 untreated individuals. The median duration of fever was also significantly shorter in the Marecipe AV-treated group than in the untreated group (12.00 hrs (P25=12, P75=18) *vs.* 84.00 hours (P25=84, P75=120); Z value=-16.71, P value <0.001). The difference between the two groups was statistically significant, as determined by the two independent Mann-Whitney U rank sum test. None of the 37 patients receiving Marecipe intervention for advanced cancer experienced COVID-19-related fever during the COVID-19 wave, while 100 out of 102 close contacts developed COVID-19-related fever. The incidence of fever caused by COVID-19 was 0% in the Marecipe AV intervention group, compared to 98% among those without the Marecipe AV intervention.

The moderate to severe influenza-like symptoms of COVID-19 decreased or disappeared within 48 hours of initiating treatment with Marecipe AV in all 122 patients. The average duration of COVID-19 symptoms for individuals treated with Marecipe AV was less than 48 hours, compared to 216 hours for untreated individuals. The median time to sustained clinical symptom resolution for two consecutive days was also significantly shorter in the Marecipe AV-treated group than in the untreated group (48.00 hours (P25=24, P75=48) *vs.* 216.00 hours (P25=216.00, P75=240.00); Z value=-16.94, P value<0.001). The difference between the two groups was statistically significant, as determined by two independent Mann-Whitney U rank sum tests. All patients who received the Marecipe AV intervention concluded their COVID-19 course by the 48-hour mark **(Figure 1)**.

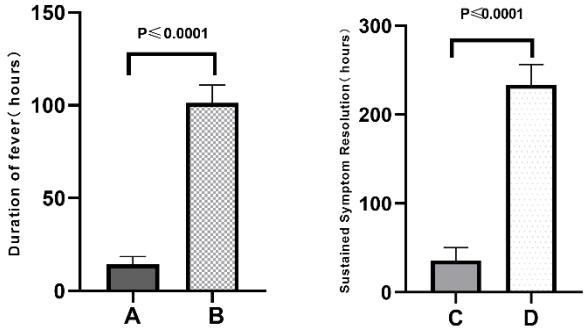

Figure 1: Analysis of fever duration and time to sustained clinical symptom resolution. A: Duration of fever following the first dose of Marecipe AV; B: Duration of fever without Marecipe AV treatment; C: Time to sustained clinical symptom resolution for 2 consecutive days after the first dose of Marecipe AV; D: Time to sustained clinical symptom resolution for 2 consecutive days without Marecipe AV treatment.

There were 78 patients at high-risk for severe COVID-19, of whom 56 received Marecipe AV and 22 did not. In the group of 22 patients who did not receive Marecipe AV, 15 were hospitalized due to progression to severe COVID-19 and 8 died, resulting in a hospitalization rate of 68.18% and a mortality rate of 36.36%. In comparison, the hospitalization and mortality rates for the 56 high-risk COVID-19 patients treated with Marecipe AV were both 0%.

There were no deaths among the 17 in-patients with severe COVID-19 who were treated with Marecipe AV herbal therapeutics. Most of the in-patients treated with Marecipe AV herbal therapeutics experienced a significantly shorter clinical recovery time. All but one critically ill in-patient recovered and was discharged within 8 days after receiving the first dose of Marecipe AV. Three critically ill in-patients with COVID-19 exhibited rapid recovery following Marecipe AV treatment. One patient presented with severe kidney dysfunction, had no urine production and required hemodialysis to sustain life. The other two in-patients with severe COVID-19 required mechanical ventilation and were in critical condition. All three patients were transferred from the intensive care

unit to a general ward within 3 days of receiving their first dose and they were discharged after rehabilitation within the subsequent 5 days. One patient, who required mechanical ventilation and was in critical condition, showed rapid improvement after Marecipe AV treatment and was discharged on the 22nd day following the initiation of dosing. During the same period, none of the 31 COVID-19 patients who did not receive Marecipe AV treatment in the same intensive care unit survived.

Adverse events

There were no adverse events associated with the Marecipe AV treatment throughout the entire course of the study.

Discussion

Given the lack of satisfactory treatments for COVID-19 and our previous clinical experience with Marecipe AV herbal therapeutics, which has demonstrated effectiveness in treating influenza within 24 hours, we administered this treatment to patients with COVID-19 as if they had influenza at our clinic during the COVID-19 pandemic, particularly during the period of drug shortages.

The findings suggest that Marecipe AV has a highly effective therapeutic effect on fever induced by SARS-CoV-2. Fever in all 122 COVID-19 patients returned to the normal range within 24 hours after the administration of Marecipe AV herbal therapeutics. The incidence of fever attributed to COVID-19 among patients receiving the Ma recipe intervention for cancer therapy was 0%, in contrast to 98% among their close contacts who did not receive the Marecipe AV intervention.

The moderate to severe COVID-19 symptoms were alleviated or completely resolved within 48 hours for all treated patients, significantly reducing the duration of the COVID-19 clinical course from an average of 214 hours to 48 hours. The most notable improvement was the complete restoration of appetite in patients, who no longer required bed rest. The use of Marecipe AV herbal therapeutics can substantially shorten the time to sustained clinical symptom resolution of COVID-19. These data suggest that the clinical course of mild to moderate COVID-19 concluded for all patients within 48 hours following the Marecipe AV intervention.

In the subgroup of individuals at high-risk COVID-19, the hospitalization and mortality rates for patients treated with Marecipe AV were 0%, compared to 68.18% and 36.36% for untreated patients, respectively. Based on this data, it is hypothesized that Marecipe AV herbal therapeutics may prevent the progression of mild-to-moderate COVID-19 to severe COVID-19 in all treated cases.

The use of Marecipe AV herbal therapeutics resulted in a significant reduction in the time to sustained clinical symptom resolution, the duration of fever associated with COVID-19 and completely prevented hospitalizations that progressed to severe COVID-19. The differences in these indicators between the Marecipe AV treatment group and the untreated group were substantial, suggesting that Marecipe AV therapy has a significant therapeutic effect on COVID-19. However, given that there has never been an effective treatment for fatal acute viral infectious diseases and considering that Marecipe AV is an herbal therapy that has not been extensively studied, the results of this study should be interpreted with caution. Regardless, a definitive evaluation of the clinical efficacy of Marecipe AV in the treatment of COVID-19 cannot be established from these data, as this study constitutes a retrospective clinical summary rather than a controlled clinical trial. Some research has provided evidence supporting the efficacy of Marecipe AV herbal therapeutics in treating COVID-19. In real-world animal trials, Marecipe AV has been utilized to treat severe and fatal acute viral infectious diseases, including African swine fever, avian influenza, canine distemper and canine parvovirus. It has successfully saved the lives of animals infected with these lethal viruses, reducing mortality rates from nearly 100% to zero and rapidly curing these deadly viral infectious diseases within three to five days [18].

It is not appropriate to evaluate the effectiveness of Marecipe AV herbal therapeutics in treating severe COVID-19 due to the limited number of casese treated by Marecipe AV available. However, among the 17 critically ill COVID-19 patients treated with Marecipe AV, there were no fatalities, whereas all 31 control patients did not survive. This observation suggests that Marecipe AV may provide potential benefits for severe cases.

The study was retrospective rather than a clinical trial of a new drug. Pre-selection of treatment subjects was not feasible; consequently, the quality of the data may have been compromised. We conducted timely telephone interviews with patients undergoing treatment to provide guidance for the subsequent management of COVID-19 patients, as the efficacy of Marrecipe AV for treating COVID-19 was unknown at that time.

The mechanism of action of Marecipe AV herbal therapeutics remains unclear. Several unpublished *in vitro* studies have demonstrated that the Marecipe AV extract exhibits limited inhibitory effects on SARS-CoV-2, while also showing the ability to inhibit and eliminate various other viruses, including HBV, influenza virus, rabies virus and herpes simplex virus. The primary chemical components of MarecipeAV, including betaine, rosmarinic acid, isoorientin and linolenic acid, were identified using mass spectrometry [18]. According to the literature, these components are not associated with viral suppression. In several trials involving Marecipe AV for the treatment of fatal viral infectious diseases in animals, it was observed that the pathogenic virus remained detectable in the animals' bodies even three days after they had fully recovered18. A significant number of COVID-19 patients experienced complete resolution of fever and influenza-

like symptoms within 24 hours after the administration of Marecipe AV. This suggests that the effects of Marecipe AV may extend beyond mere viral clearance, as the process of clearing a virus typically requires time and symptom relief should not occur so rapidly. In conclusion, the primary mechanism of action of Marecipe AV may be more closely associated with inflammatory or immune responses rather than solely with viral inhibition or clearance.

Limitations

The study is a retrospective analysis rather than a rigorously designed prospective clinical trial. The number of treatment cases is insufficient and the quality of the data is suboptimal. Due to these limitations, the efficacy assessments based on the outcomes lack credibility. Consequently, the results of this study should be regarded as a reference for initial exploration rather than a definitive assessment of efficacy. All patients with COVID-19 treated at our clinic received Marecipe AV, which precluded the possibility of selecting participants for enrollment based on their clinical conditions. Furthermore, the limited number of untreated cases in the high-risk COVID-19 control group significantly impacted the outcomes related to hospitalization and mortality, introducing substantial statistical bias.

Conclusion

Marecipe AV herbal therapy has shown a clear and potent therapeutic effect against COVID-19. The oral administration of MarecipeAV effectively alleviates fever in patients with mild to moderate COVID-19 within 24 hours, reduces the COVID-19 clinical course to less than 48 hours. Marecipe AV herbal therapeutics can effectively prevent the progression from mild to moderate COVID-19 to severe illness. Marecipe AV therapeutics may hold potential for the treatment of severe COVID-19 cases.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Role of the Funding Source

All aspects of this study were no funder.

Ethical Clearance

Although the study treatment and pharmaceutical preparations adhere to the established norms and ethical standards of TCM, we have submitted an ethics application to expand the indications for the use of MarecipeAV to include COVID-19. This application has been approved by the ethics committee. Ethics Committee Approval Number: 202101.

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