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Effect of garlic essential oil in 97 patients hospitalized with covid-19: A multi-center experience

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Abstract: To observe the synergistic effect of garlic essential oil in patients with novel coronavirus disease (COVID-19), in addition to the routine treatment, we used garlic essential oil in COVID-19 patients with mild to moderate symptoms and compared their results to those of patients who did not receive the essential oil. We conducted a quasi-experimental study with COVID-19 patients from 3 hospitals. In the experimental group, 97 patients received garlic essential oil combined with conventional treatment. In the control group, 100 patients received only the conventional treatment for COVID-19. The effectiveness and safety of the garlic essential oil were assessed. Compared to the control group, the group receiving garlic essential oil showed a shorter duration of symptoms, shorter time to negative nucleic acid testing (NAT) results and shorter time to improvement on the computed tomography (CT). In the same period, the experimental group showed an increase in the rate of the disappearance of symptoms and the improvement rates of NAT and CT. Due to its effectiveness and safety in patients with COVID-19, garlic essential oil is recommended as a preventive measure or a supportive therapy during the COVID-19 pandemic.

Keywords: ACE2, COVID-19, garlic, garlic essential oil, SARS-CoV-2.

INTRODUCTION

Novel coronavirus disease 2019 (COVID-19), which is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), began rapidly spreading across the world in December 2019. This new respiratory illness has become one of the major public health emergencies seriously endangering human health and public safety. By 2 March 2022, there were more than 43.7 million confirmed cases of COVID-19, including 5960972 deaths reported to the WHO. COVID-19 was found to have higher rates of transmissibility and pandemic risk than SARS-CoV and Middle East respiratory syndrome coronavirus (MERS‐CoV) (Zhou *et al.,* 2021) and although several approved drugs and investigational agents have shown antiviral activity against SARS-CoV-2 in vitro (Wang *et al.,* 2020), at present there is no evidence that these antiviral drugs could significantly impact the course of COVID-19 pandemic (Martinez, 2021). Patients with severe illness from COVID-19 can develop acute respiratory distress syndrome (ARDS) and require admission to the intensive care unit (ICU), oxygen therapy and endotracheal intubation (Zhao *et al.,* 2020).

The SARS-CoV-2 spike glycoprotein (S protein) interacts with human angiotensin‐converting enzyme 2 (ACE2) as the receptor (Hussain *et al.,* 2020) and then enters the body cells, starts to replicate and causes infection. The ACE2 protein is an integral membrane glycoprotein that is known for its highest expression in most tissues such as the heart and kidney (Qiu *et al.,* 2020). During viral infection, the trimeric S protein is cleaved into S1 and S2 subunits. S1 contains the receptor-binding domain (RBD), which directly binds to the ACE2. S2 is responsible for membrane fusion and can achieve a more stable post fusion state (Yan *et al.,* 2020, Lan *et al.,* 2020). Therefore, as a receptor protein, binding to ACE2 is a critical initial step in the entire infection mechanism and selective disruption of the specific binding process between the ACE2 and S proteins could effectively prevent and treat COVID-19.

Garlic is an important herb that not only is used as a common ingredient in family meals but also has been used as a medication for common colds, influenza and other kinds of infections for centuries (Asif *et al.,* 2020, Romeilah *et al.,* 2010). Garlic essential oil, which is extracted from the garlic bulb, is an exceptional source of organosulfur compounds, possessing strong antioxidant, antibacterial, antivirus, anticancer and antithrombotic properties (Thuy *et al.,* 2020). In addition, the oil has also been proven to exhibit good ACE2 activity inhibition (Yu *et al.,* 2020). Organosulfur compounds of the oil have an

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inhibitory effect on the amino acids of the ACE2 protein and the main protease PDB6LU7 of SARS-CoV-2 (Thuy *et al.,* 2020).

As mentioned above, the unique antivirus effect of garlic essential oil suggests that it may help prevent the invasion of coronavirus in the human body. In this study, we conducted a multicenter clinical trial, attempting to use garlic essential oil as a supportive therapy combined with routine treatment and compare the results with those of patients who did not receive the essential oil. Therefore, we were able to observe the synergistic effect of garlic essential oil in patients with mild to moderate COVID-19 symptoms and guide clinical use of garlic essential oil.

MATERIALS AND METHODS

Study design and participants

This was a quasi-experimental study conducted from January 15, 2020 to June 30, 2020 to assess the synergistic effect of garlic essential oil in patients admitted to the hospital with COVID-19. All patients recruited in our research were positive in throat swab nucleic acid testing (NAT) and were diagnosed with COVID-19 by doctors within 24 hours after admission. We divided patients into an experimental group and control group, with each group in a different ward. The trial was conducted at three hospitals, including the First Affiliated Hospital of Soochow University, the First People's Hospital of Jiangxia District, Wuhan city and the Fifth People's Hospital of Suzhou.

The patients recruited for this study met the following inclusion criteria: (1) patients who were aged 20-60 years old and diagnosed with mild or moderate COVID-19; (2) patients who had stable vital signs and were not allergic to garlic and (3) patients who were informed about and voluntarily participated in the study. Patients with the following conditions were excluded from our study: (1) patients with a gastric ulcer or intolerance to garlic essential oil capsule because of gastrointestinal irritation; (2) patients who failed to use the garlic essential oil capsule as required; (3) patients whose therapeutic schedules changed because of a sudden deterioration of their illness during the study.

From January 15 to June 30, 2020, 100 patients were recruited for each group. Three patients in the experimental group were excluded because they received the garlic essential oil capsule for < 5 days because their digestive tract could not tolerate it and therefore, 197 patients participated in the study.

Procedures

Based on *Diagnosis and Treatment of Pneumonia Infected by Novel Coronavirus issued by the National Health Commission of China*, patients in the control group received the conventional treatment for COVID-19, including nutritional support, symptomatic treatment, antiviral therapy and antimicrobial therapy. The main drugs used were Cravit, Interferon alfa-2b, Arbidol, Glucocorticoid, Lianhua Qingwen granules, etc. On the basis of the conventional treatment, patients in the experimental group also took five garlic essential oil capsules before breakfast and dinner (each capsule contained 10 mg garlic essential oil; the dose was 100 mg per day and was provided by Lvyuan perfume Co, Ltd, Kunshan City, China, batch number: LY 191022). When combined with the conventional treatment for COVID-19. The treatment cycle for most mild to moderate patients was within 10 days; therefore, the intervention time for both groups was > 10 days.

Data collection

We collected data including the patients' demographics, clinical indications, laboratory results, comorbidities and treatments from the medical records. The outcome data of the clinical symptoms were assessed once daily by trained nurses (who were unaware of the treatment allocation) using a self-made medication observation record. In addition, the safety assessment included adverse reactions as well as daily vital sign measurements were also needed.

Ethical approval

The trial was conducted according to the principles of the Declaration of Helsinki and was approved by the institutional ethics board of the First Affiliated Hospital of Soochow University [(2020) LSP No.012].

STATISTICAL ANALYSES

We conducted the statistical analysis using SPSS software, version 23.0 (SPSS Inc, Chicago, IL, USA) for Windows. Means and standard deviations (SDs) were used for continuous variables and frequencies and percentages were used for categorical variables. To assess the differences between the two groups, we used the independent sample t-test or nonparametric Wilcoxon rank-sum test for the quantitative data and the chi-square test for the qualitative data. A p value of less than 0.05 was considered statistically significant.

RESULTS

Basic characteristics of the study group

In total, 197 patients (97 in the experimental group and 100 in the control group) with COVID-19 were included in this study. Among those patients, there was no significant difference in age (49.15±14.85 vs. 50.98±13.36) or sex (men 44.33% vs. 47.00%, women 55.67% vs. 53.00%) between the two groups (p>0.05). Most of the patients' main initial clinical symptoms were

fever (94.85% vs. 91.00%), cough (85.57% vs. 87.00%) and weakness (62.89% vs. 68.00%) (p>0.05). The laboratory results were low white blood cell count (4.85±1.89 vs. 4.74±1.83), low lymphocyte count (22.38±9.15 vs. 20.75±9.65) and high C-reactive protein (51.45±35.05 vs. 52.41±34.27) (p>0.05). The number of days from symptom onset to start of treatment between the two groups was 4.65±1.45 vs. 5.01±1.59 (p>0.05). The comorbidities were hypertension (31.96% vs. 25.00%), coronary heart disease (12.37% vs. 16.00%), diabetes (7.22% vs. 13.00%) and cerebral infarction (15.46% vs. 11.00%) (p>0.05). All patients in both groups received the conventional treatment, included Cravit (88.66% vs. 89.00%), Interferon alfa-2b (87.63% vs. 84.00%), Arbidol (85.57% vs. 84.00%), Glucocorticoid (37.11% vs. 34.00%) and Lianhua Qingwen granules (91.75% and 91.00%) (p>0.05) (table 1).

Primary outcome improvement rates of the study group

After 10 days of the intervention, we compared the disappearance of the main symptoms between the two groups. In the experimental group, 87 of 92 patients' fevers disappeared, whereas in the control group, 72 of 91 patients improved (disappearance rate: 94.57% vs. 79.12%) (p=0.002). Cough symptoms disappeared for 55/83 patients vs. 42/87 patients in the two groups (disappearance rate: 66.27% vs. 48.28%) (p=0.018). Weakness symptoms disappeared for 36/61 patients vs. 20/68 patients in the two groups (disappearance rate: 59.02% vs. 29.41%) (p=0.001). NAT resulting in a negative reaction was observed for 74/97 patients vs. 61/100 patients after 10 days of treatment in the two groups (negative rate: 76.29% vs. 61.00%) (p=0.021). Of the 97 patients in the experimental group, 81 patients showed improvement in the lung computed tomography (CT) and in the control group, 71 of 100 patients showed improvement (improvement rate: 83.51% vs. 71.00%) (p=0.037) (table 2).

Primary outcome improvement time of the study group

In this research, we also measured the duration of the main symptoms and signs in both groups of patients under the different interventions. The median duration of fever in the experimental group was 4 days (IQR 3-5), whereas it was 5 days in the control group (IQR 4-6) (p<0.001). The median duration of cough was 5 days vs. 7 days in the two groups (IQR 0-10 vs. IQR 0-12) (p=0.018). The median duration of weakness was 7 days vs. 9 days in the

Table 1: The characteristics of COVID-19 patients treated with garlic essential oil

Characteristics	Experimental Group (N=97)	Control Group (N=100)	t/χ^2	*P* Value
Age, years	49.15±14.85	50.98±13.36	-0.908	0.365
Sex Men Women	 43 (44.33%) 54 (55.67%)	 47 (47.00%) 53 (53.00%)	 0.141	 0.707
Body temperature, ℃	36.44±0.17	36.46±0.22	-0.719	0.473
Heart Rate, per min	83.39±6.47	82.98±7.45	0.414	0.680
Respiratory rate, per min	19.39±1.09	19.26±1.10	0.847	0.398
Low White blood cell, %	4.85±1.89	4.74±1.83	0.415	0.679
Low lymphocyte, %	22.38±9.15	20.75±9.65	1.216	0.226
High C-reactive protein, %	51.45±35.05	52.41±34.27	-0.194	0.846
Initial symptoms Fever Cough Weakness	92 (94.85%) 83 (85.57%) 61 (62.89%)	91 (91.00%) 87 (87.00%) 68 (68.00%)	1.103 0.085 0.570	0.294 0.770 0.450
Time from symptom onset to starting treatment, days	4.65±1.45	5.01±1.59	-1.659	0.099
Any comorbidities Hypertension Coronary heart disease Diabetes Cerebral infarction	 31 (31.96%) 12 (12.37%) 7 (7.22%) 15 (15.46%)	 25 (25.00%) 16 (16.00%) 13 (13.00%) 11 (11.00%)	 1.172 0.532 1.806 0.856	 0.279 0.466 0.179 0.355
Conventional treatment Antibiotic (cravit) Antiviral (interferon alfa-2b) Antiviral (arbidol) Glucocorticoid Lianhua Qingwen Granules	 86 (88.66%) 85 (87.63%) 83 (85.57%) 36 (37.11%) 89 (91.75%)	 89 (89.00%) 84 (84.00%) 84 (84.00%) 34 (34.00%) 91 (91.00%)	 0.006 0.532 0.094 0.208 0.035	 0.940 0.466 0.760 0.648 0.851

Table 2: Comparison of the primary outcome improvement rates of patients between two groups

Group	Fever disappearance	Cough disappearance	Weakness disappearance	NAT negative	CT improvement
Experimental group (N=97)	87/92(94.57%)	55/83(66.27%)	36/61(59.02%)	74/97(76.29%)	81/97(83.51%)
Control group (N=100)	72/91(79.12%)	42/87(48.28%)	20/68(29.41%)	61/100(61.00%)	71/100(71.00%)
χ^2	9.577	5.610	11.472	5.336	4.369
P Value	0.002	0.018	0.001	0.021	0.037

Table 3: Comparison of the duration of primary outcome of patients between two groups

Group	Duration of fever	Duration of cough	Duration of weakness	Duration of NAT positive	Duration of CT improvement
Experimental group (N=97)	4 (3, 5)	5 (0, 10)	7 (5, 10)	7 (6, 10)	7 (7, 8)
Control group (N=100)	5 (4, 6)	7 (0, 12)	9 (7, 11)	8 (8, 12)	9 (8, 10)
Z	-5.882	-2.373	-3.322	-5.031	-6.338
P Value	<0.001	0.018	0.001	<0.001	<0.001

two groups (IQR 5-10 vs. IQR 7-11) (p=0.001). The median time to a negative NAT result was 7 days vs. 8 days in the two groups (IQR 6-10 vs. IQR 8-12) (p<0.001). The median time to the CT showing improvement was 7 days vs. 9 days in the two groups (IQR 7-8 vs. IQR 8-10) (p<0.001) (table 3).

Safety analysis

No patients in the control group had adverse reactions. Only 3 patients in the experimental group experienced gastrointestinal irritation; the incidence rate of adverse reactions to the garlic essential oil capsules was 3%. The adverse reactions improved in all of these 3 patients when they stopped taking the garlic essential oil capsules.

DISCUSSION

In this study, we found a synergistic effect of garlic essential oil capsules in COVID-19 patients when combined with routine treatment. Based on our clinical observations and treatment experience, the main symptoms of mild to moderate COVID-19 were fever, cough and weakness. Therefore, we chose the improvement of those 3 symptoms as the outcomes of the intervention.

Our findings supported the positive effect of the garlic essential oil capsules in shortening the duration of symptoms such as fever, cough and weakness; shortening the time to negative NAT results and shortening the time to improvement on the CT. Additionally, in the same period, the disappearance rate of symptoms, the negative conversion rate of NAT and the improvement rate on the CT were higher in the experimental group than in the control group.

Garlic, a traditional food among Chinese people, is produced in large volumes and has been used as a traditional Chinese herb to treat infectious diseases for centuries. Through in-depth research, Chinese scholars have gradually discovered the role of garlic in immune regulation and cardiovascular disease, etc (Wang *et al.,* 2017, Tianwei *et al.,* 2020). Similarly, garlic is also used as a traditional medicine to treat the common cold, fever, coughs, asthma, sexually transmitted diseases, respiratory tract infections and wounds in Asia, Africa and Europe (Rouf *et al.,* 2020).

It is worth mentioning that several clinical trials have shown the antiviral effects of garlic against viral respiratory infections and suggested that the reduction of viral infections and reinfections can be decreased through daily garlic supplementation (Rouf *et al.,* 2020). Many functions of garlic stem from the antiviral, immune-enhancing and other therapeutic activities of its sulfur compound (Hall *et al.,* 2017, El-Saber Batiha *et al.,* 2020).

For the SARS-CoV-2, a present study has shown that allicin derived from garlic can prevent receptor binding, replication or transcription by S-thioallylation of host or viral proteins (Mösbauer *et al.,* 2021). These activities can effectively inhibit SARS-CoV-2 infection at different stages of the viral life cycle.

One study also pointed out that ACE2 is involved in the viral invasion of host cells, while viral main protease is involved in viral replication and 17 compounds analyzed from garlic essential oil can interact with the host protein (ACE2) as well as with viral proteases, indicating that garlic essential oil has great potential to treat COVID-19 patients (Asif *et al.,* 2020, Thuy *et al.,* 2020).

Our findings on the synergistic effect of garlic essential oil on COVID-19 verify the hypothesis above. However, there are no mechanisms or clinical studies to date that have determined the antiviral mechanisms of garlic essential oil that are at work in COVID-19. Therefore, based on the current findings and literature review, we also carried out two other studies. First, we conducted research on the bidirectional regulating and controlling mechanism of garlic essential oil on ACE2 and this research is still in the peer review stage; Second, we conducted qualitative research on the medication experience of people who taking garlic essential oil as supportive therapy in the epidemic of COVID-19 and now it has been accepted by a domestic journal.

Our study had several limitations. First, only 3 centers were included and since this was a clinical study in an emergency, we inevitably used a nonstrictly randomized controlled design to simply evaluate the synergistic effect of garlic essential oil. Therefore, a long-term cohort study and pharmacokinetic investigation are needed to further explore the effect of garlic essential oil in COVID-19 patients. Second, we only evaluated patients with mild to moderate COVID-19 and therefore did not determine the effect of garlic essential oil in patients with severe COVID-19.

CONCLUSION

Currently, many countries are still suffering from COVID-19. Research related to the developmental trials of a vaccine is still in progress and may require a long time. Isolation and social distancing are the primary interventions(Donma and Donma, 2020). However, our findings show that for people with no gastrointestinal irritation symptoms, garlic essential oil may be beneficial as a preventive measure or a supportive therapy during the COVID-19 pandemic.

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