Effect of Allicin (L-cysteine) on COVID-19
Eur J Transl Myol 31 (2): 9518, 2021 doi: 10.4081/ejtm.2021.9518

Evaluate the Therapeutic Effect of Allicin (L-cysteine) on Clinical Presentation and Prognosis in Patients with COVID-19

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Abstract

The antiviral effectiveness of allicin (L-cysteine) has been shown by numerous studies in both levels of clinical and animals. The aim of this study was to evaluate the therapeutic effect of allicin (L-cysteine) on clinical presentation and prognosis. In the current study, 66 patients with COVID-19 based on clinical, radiological presentations and RT-PCR results, were enrolled in two groups of placebo and allicin. In the both allicin (L-cysteine) and placebo groups (n=33 in each group), the capsules were prescribed two times a day for two weeks. Clinical signs and symptoms, blood parameters and chest CT scan were evaluated before and two weeks after treatment. The results showed that allicin (L-cysteine) could significantly impact on improvement of signs and symptoms of COVID-19 after two weeks of treatment in comparison to placebo. Allicin (L-cysteine) not only improve the clinical signs, but also ameliorate the lab and radiological data, which suggest a therapeutic effect for this agent in COVID-19. Our data suggest the therapeutic effect of allicin (L-cysteine) on COVID-19 through improvement of clinical symptoms and acceleration of the healing process.

Key Words: COVID-19; Allicin; chest CT; laboratory findings; clinical trial.
Materials and Methods

Research design
In this randomized double-blinded clinical trial, 83 patients were enrolled with COVID-19 according to the diagnosis by the emergency medicine specialist and the approval of the infectious disease specialist and based on RT-PCR results, referred to Emergency Department of Imam Reza Hospital, Mashhad. Patients were selected based on following inclusion and exclusion criteria:

1. **Inclusion criteria:** Patients diagnosed with COVID-19 based on the patients’ clinical, radiological findings and RT-PCR results; age between 18-70 years; absence of pregnancy or lactation;
2. **Exclusion criteria:** History of allergies to allicin, garlic or onions; patient with a history of hypotension or gastrointestinal bleeding; low blood pressure at the beginning of the study; immunodeficient patients; chemotherapy; organ and bone marrow transplantation, and patients with autoimmune diseases; patient who require ventilation

In this study, 83 patients were randomly and equally allocated to allicin (L-cysteine) (90 mg/kg) or placebo groups. However, 66 patients completed the treatment period. In the allicin (L-cysteine) and placebo groups (n=33 in each group), the capsules were prescribed three times a day for two weeks (every 8 hours). The molecule of allicin (L-cysteine) with stable oxidation capacity by a new allotropic process is one of the active ingredients in organosulfur as the main composition of this supplement. In order to blinding the results, allicin (L-cysteine) and placebo capsules with similar appearance were prepared and given to the patients by a nurse or a physician. It should be noted that both groups were treated with routine treatment of COVID-19 based on the latest regional guidelines. Patients in allicin (L-cysteine) group were treated with routine treatment plus allicin (L-cysteine) 90 mg/kg, and placebo groups were treated with routine treatment plus placebo capsules. Evaluation of clinical symptoms and vital signs (cough, dyspnea, myalgia, anosmia, chill, consciousness, diarrhea, headache, nasal congestion, nausea and vomiting, sore throat, weakness, taste disorder, respiratory rate, pulse rate, temperature, O2 saturation), blood parameters (total and differential white blood cells, red blood cells, hemoglobin, platelet, C-reactive protein) and chest CT scan were performed pretreatment and two weeks after treatment. This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by Mashhad University of Medical Sciences (Code # Ir.mums.rec.1399.289Iran). Written informed consent was obtained from all patients.

Statistical analysis
The data was described by frequency [percentage (%)] or mean±S.D. Comparisons within each group were performed using McNemar and Wilcoxon Tests and the comparison between the two groups was tested by Mann–Whitney U test and κ2 test. All statistical analysis was implemented in SPSS 25.0, p values <0.05 were considered statistically significant.

Results
In this study, 33 patients in placebo group (66.7% men and 33.3% women) and 33 patients in allicin (L-cysteine) group (72.7% men and 27.3% women) were included. The average age of patients in placebo and allicin (L-cysteine) groups was (52.9±5.0) and (51.4±5.1) years, respectively. There were no differences in these values between groups. Demographic characteristics of the subjects are displayed in Table 1.

The most common symptom in both placebo and allicin (L-cysteine) groups was dyspnea (77.8% and 75.8%, respectively); and the most uncommon symptom was diarrhea in both groups (3% in both groups). At the beginning of study, there was no significant changes in clinical symptoms between two groups. However, frequency of anosmia and nasal congestion in allicin (L-cysteine) group were significantly higher than placebo group (P=0.031 and P=0.009, respectively). At the end of the study, allicin (L-cysteine) led to a significant decrease of cough, dyspnea and myalgia in treated patients compared to placebo group (p<0.05 to p<0.01),

| Table 1. Demographic characteristics of patients. |
|-----------------------------------------------|
| **Variables** | **Groups** | **P-value** |
| | **Placebo** | **Allicin** | |
| Sex (%) | | | |
| Male | 66.7% | 72.2% | 0.618* |
| Female | 33.3% | 27.3% | |
| Age (Mean ± SD) | 39.2±8.40 | 38.97±8.37 | 0.903** |

* Chi-Square test
** T-independent sample test
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Table 2. Measured parameters pre-treatment (day 0) and post-treatment (day 14).

| Variables          | Placebo | Allicin (L-cysteine) | Placebo | Allicin (L-cysteine) | Placebo | Allicin (L-cysteine) |
|--------------------|---------|---------------------|---------|---------------------|---------|---------------------|
|                    | p-value | p-value#            | p-value | p-value##           |         |                     |
| Symptoms           |         |                     |         |                     |         |                     |
| Cough              | 15.2%   | **0.000**           | 0%      | 0%                  | 99.9%   | 15.2%               |
| Dyspnea            | 28.7%   | **0.004**           | 12.6%   | **0.014**           | 40.6%   | 28.6%               |
| Myalgia            | 6.8%    | 0.051               | 31%     | 0.009               | 12.5%   | 0.051               |
| Anosmia            | 16.8%   | 0.001               | 9.4%    | 0.863               | 9.4%    | 0.863               |
| Chill              | 20%     | 0.031               | 10.3%   | 0.031               | 9.4%    | 0.031               |
| Consciousness      | 59.3%   | 0.031               | 49.3%   | 0.031               | 59.3%   | 0.031               |
| Diarrhea           | 4%      | 0%                  | 0%      | 0%                  | 0%      | 0%                  |
| Headache           | 45.4%   | 0.009               | 27.6%   | 0.009               | 21.9%   | 0.009               |
| Nausea and Vomiting| 6.6%    | 0.031               | 0%      | 0%                  | 0%      | 0%                  |
| Sore Throat        | 14.4%   | 0.031               | 1%      | 0.031               | 99.9%   | 0.031               |
| Weakness           | 20.6%   | 0.031               | 99.9%   | 0.031               | 99.9%   | 0.031               |
| Taste Disorder     | 9.9%    | 0.009               | 1%      | 0.009               | 3%      | 0.009               |
| Respiratory rate   | 31.4%   | 0.009               | 10%     | 0.009               | 21.9%   | 0.009               |
| Pulse rate         | 79.5%   | 0.009               | 87.6%   | 0.009               | 85.6%   | 0.009               |
| Temperature        | 37.3%   | 0.009               | 90.3%   | 0.009               | 90.3%   | 0.009               |
| O2saturation       | 36.6%   | 0.009               | 93.3%   | 0.009               | 93.3%   | 0.009               |
| Laboratory test    |         |                     |         |                     |         |                     |
| White blood cell   | 5.5±0.7 | 6.5±0.9            | 6.8±1.2 | 5.4±0.8            | 0.098   | NS                  |
| Lymphocyte         | 22.5±3.7| 23.5±4.3           | 23.5±5.9| 28.3±4.5           | 0.706   | NS                  |
| Eosinophil         | 7.5±1.0 | 6.1±0.4            | 2.9±0.3 | 3.6±0.4            | 0.228   | NS                  |
| PMN                | 69.2±4.6| 71.8±4.8           | 69.9±6.6| 60.7±5.8           | 0.461   | NS                  |
| Platelet           | 202.5±28.5| 209.9±33.7      | 252.1±9.7| 298.4±8.7        | 0.071   | NS                  |
| Red blood cell     | 4.8±0.2 | 4.8±0.3            | 4.7±0.2 | 4.8±0.2            | 0.990   | NS                  |
| Hemoglobin         | 13.6±0.7| 13.4±0.6           | 13.6±0.6| 14.8±0.7           | 0.338   | NS                  |
| Chest CT scan (n=52)|       |                    |         |                     |         |                     |
| Sever diffuse      | 27.2%   | 27.2%              | 18.9%   | 22.2%              | 12.2%   | 0.378               |
| Moderate           | 26.5%   | 31.9%              | 36.9%   | 41.0%              | 0.457   | p<0.05              |
| Mild diffuse       | 39.6%   | 24.3%              | 41.2%   | 39.9%              | 0.733   | NS                  |
| Normal             | 6%      | 16.1%              | 26.9%   | **0.000**          | 26.9%   | **0.000**           |

PMN: polymorphonuclear leukocytes; NS: non-significant. *, Comparison between Allicin (L-cysteine) and placebo groups in pre-treatment, by Chi-square and Mann-Whitney U tests. **, Comparison between Allicin (L-cysteine) and placebo groups in post-treatment, by Chi-square and Mann-Whitney U tests. **, Comparison between data of pre- and post-treatment in in placebo group, by McNemar and Wilcoxon Signed rank tests. #, Comparison between data of pre- and post-treatment in Allicin (L-cysteine) group, by McNemar and Wilcoxon Signed rank tests.

(Thetab2). Significant statistical different did not show in blood parameters between groups in both pre- and post-treatment (Table 2). In this study, the results of chest CT scan categorized to four levels including normal, mild, moderate, and severe based on the lung involvement in chest CT scan. Before treatment, the number of patients with normal and mild chest CT scan were significantly different between two groups (p < 0.05 to p < 0.001). However, there was a significant increase rate of normal chest CT scan in allicin (L-cysteine) group compared to placebo group after two weeks of treatment (p < 0.001, Table 2). In addition, Figure 1 illustrated the chest CT scan study in some patients before and after treatment. The results showed the significant improvements of lung based on lesions distribution and involvement of various regions of lungs as well as CT score. Comparison of the measured parameters before and after the intervention showed that in placebo group, all parameters (except cough, myalgia, chill, nausea and vomiting, sore throat, weakness, and taste disorder, as well as chest CT) were showed that in placebo group, all parameters (except cough, myalgia, chill, nausea and vomiting, sore throat, weakness, and taste disorder, as well as chest CT) were not significantly changed after two weeks treatment compared to baseline values. However, lots of symptoms except diarrhea and blood parameters as well as chest CT scan were improved after treatment compared to before treatment in the allicin (L-cysteine) group (p < 0.05 for all cases) (see Table 1).

Discussion

In this study, we showed that allicin (L-cysteine) could significantly improve clinical symptoms of COVID-19 after two weeks of treatment in comparison to placebo. Allicin (L-cysteine) not only improve the clinical signs,
but also ameliorate the lab and radiological data, which suggest a therapeutic effect for this agent in COVID-19. Plants and their extracts have been used to treat human diseases since ancient times. Previous experiments have shown that phytochemicals are good therapeutic agents for the treatment of various diseases, including viral pathogens, either by blocking the virus from penetrating host cells or by attacking viral proteins in host cells. Inhibition of proteolytic action of viral proteases has been studied in the production of various antiviral drugs such as atazanavir, lopinavir, nelfinavir, ritonavir and saquinavir. Protease inhibitory potentials have been found to exist in the extracts of cloves *A. sativum* and rhizomes of *C. longa*, and *Z. officinale*. Allicin, curcumin and gingerol have been listed by the Phytochemical and Ethnobotanical Databases as the key phytochemicals in cloves *A. sativum* and rhizomes of *C. longa*, and *Z. officinale*. These compounds have been retrieved from the PubChem database in ligand file format (SDF). Plants have been known as a good source of protease inhibitors. However, in addition to their antiviral potential, a detailed examination of the pharmacokinetics and bioavailability of the described compounds was required to ensure protection. Recent reports have suggested that these phytocompounds could be valuable for the development of drugs useful for the prevention of coronavirus entry and replication. Although, the effectiveness of allicin (L-cysteine) has been evaluated in vitro, no clinical study has been conducted to evaluate this issue. In this regard, this study is the first to evaluate the effectiveness of this drug on COVID-19.

In the current study, we observed that allicin (L-cysteine) was effective in improvement of both clinical and laboratory parameters in patients with COVID-19. The results indicated that allicin (L-cysteine) could improve the chest involvement based on the radiological findings. Although, some signs and symptoms might be reified during the two weeks, but allicin (L-cysteine) could accelerate this process. In addition, since the toxicity and hyperallergic reaction to allicin (L-cysteine) have not been reported yet, this drug might be a novel treatment in clinical settings.

![Image of chest CT scans](image-url)
In conclusion, we showed that allicin (L-cysteine) could significantly improve and accelerate the healing process within two weeks of treatment. Allicin (L-cysteine) not only improve signs and symptoms of COVID-19, but also could induce high impact on both laboratory and radiological findings.

List of acronyms
OA – osteoarthritis
TKA – total knee arthroplasty
SPPB – Short Physical Performance Battery
6MWT – Six-Minute Walk test

Authors contributions
HY, SE, HN, APY, VGH, MMR, and AMH conceived and designed the experiments, performed the data analyses and wrote the paper. All authors have read and approved the manuscript.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Acknowledgments
This research is the result of a student thesis of Mashhad University of Medical Sciences. Authors thank Saeideh Ebrahimpour for her help in this study

Funding
None.

Conflict of Interest
The author declares no competing interests.

Ethical Publication Statement
We confirm that we have read the Journal's position on the issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Submitted: November 19, 2021
Revision received: April 18, 2021
Accepted for publication: April 18, 2021