Evaluating the Efficacy and Safety of the Myrtle (Myrtus Communis) in Treatment and Prognosis of Patients Suspected to Novel Coronavirus (COVID-19) Pneumonia: Study Protocol for a Randomized Controlled Trial

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Study protocol

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Abstract

Background: Since December 2019, the outbreak of corona virus pneumonia was observed in China and quickly propagate in all of the world. Nowadays many trials are underway on this disease in which the efficacy of various therapeutic remedies including chemical or natural agents as well as different non pharmacological methods such as acupuncture are evaluated. This study aim at investigating the effect of myrtle fruit for treatment of COVID-19 disease.

Methods: We are performing a randomized controlled trial on outpatients clinically suspected to COVID-19 disease in the age range of 18-65 years old with mild to moderate symptoms and without respiratory distress. Patients in both groups (myrtle and control) receive conventional therapy, but those in myrtle group get myrtle preparation in addition to conventional therapy. Intervention will continue for 5 days and the study outcomes including clinical statues as well as mortality rate and adverse effects will be measured up to 14 days.

Discussion: The protocol describes the design of an ongoing randomized controlled trial to establish the evidence for the usage of water extract of myrtle fruit in clinically suspected COVID-19 disease and identify any safety concerns.

Trial registration: The trial has been registered at the Iranian Registry of Clinical Trials website under the code *IRCT20180923041093N3* on March 28th, 2020 (https://www.irct.ir/trial/46721). The results will be disseminated through manuscript publications, and presentations to scientific meetings.

Background

The outbreak of the pneumonia caused by novel corona virus (COVID-19) was first observed in Wuhan, Hubei province, China in December 2019 and quickly spread all over the country, and then almost all throughout the world, it formed a global concern as a pandemic (1, 2). The infection caused by the novel corona virus has a wide range from asymptomatic infectious to mild upper respiratory tract disease which may lead to severe pneumonia and even death (3, 4). At the onset of clinical symptoms, most patients have such complaints as fever, cough, shortness of breath, muscular pain, and fatigue. Some patients also experience loss of taste and smell, headaches, or diarrhea. Patients with mild symptoms may have only fever and fatigue, whereas in severe cases, patients experience shortness of breath, hypoxia, and acute respiratory distress syndrome, which may include severe metabolic acidosis, coagulation disorders, and septic shock. The mortality rate varies in different age groups and under different conditions and underlying diseases, but it is generally not high compared to similar diseases; nevertheless, due to the high probability of transmission of this disease, mortality and economic costs are significant (5-7).

This pandemic makes physicians and healers deal with different therapeutic approaches, including classic medicine, herbal medicine, acupuncture, Chinese medicine, Persian medicine, etc. with the intention to find a solution to cure or lessen the signs and symptoms of this contagious disease (7, 8). Exploring the clinical trials registered on different World Health Organization Primary Registries proved a notable attention to complementary and alternative medicine (CAM) for controlling the novel corona virus pneumonia (7). Previously, considerable studies had been designated in the field of CAM for prevention, treatment, and rehabilitation of SARS and influenza (9).

The aqueous extract of myrtle fruit in combination with sugar as a myrtle syrup is an ancient remedy for pneumonia recommended in Persian medicine manuscripts. Heart tonic, lung tonic, antitussive, and anti-diarrhea activities are some of the properties mentioned for myrtle (10, 11). Recent studies demonstrated the antioxidant, anti-inflammatory, anti-viral, and anti-microbial properties of this herb. Therefore, considering the pharmacological activities of myrtle in addition to traditional approval, this remedy seems to be a promising candidate for performing clinical trials and assessing its efficacy on controlling this disease.

Methods/design

Study objectives and hypothesis

The main purpose of the proposed trial is to determine whether myrtle preparation can accelerate the healing process of patients clinically suspected to COVID-19 pneumonia and decrease the hospital admission and other related complications.

Primary hypothesis: taking myrtle fruit preparation in the first days of clinically suspicion to COVID-19 will subside the sign and symptoms of the disease, as well as decrease the respiratory distress and enhance the wellbeing.

Public involvement

The present trial is designed against the uncertainties about the value of applying alternative therapy and herbal medicine for alleviating the symptoms and promoting the prognosis of the mentioned disease. This issue is a popular subject raised by both people and health professionals involving the current pandemic.

Ethical aspects

The protocol of this study is approved by the Local Medical Ethics Committee of Kerman University of Medical Sciences under the approval code *IR.KMU.REC.1399.015*; it is also registered at the Iranian Registry of Clinical Trials website under the code *IRCT20180923041093N3*. This study will be conducted in accordance with the guidelines of Declaration of Helsinki (2008 revision). The procedure will be explained to the patients complying with the inclusion criteria, and each participant will voluntarily sign an informed written consent.

Patients recruitment

Patients clinically suspected to the COVID-19 pneumonia are considered and enrolled as suspected cases if they meet either an epidemiological history and two clinical manifestations or three clinical manifestations without epidemiological history, are in the age range of 18-65 years old, without respiratory distress, and candidate for outpatient care and home isolation. They would be eligible if they do not have exclusion criteria including pregnancy, lactation, allergy to myrtle, diabetes, hypertension, hepatic disorder, and renal disorder. Exclusion criteria further covered recent consumption of herbal drugs.

Study design

This prospective randomized controlled clinical trial will be conducted to determine the effect of myrtle on subjects clinically suspected to COVID-19 pneumonia. In this trial, the allocation ratio was considered 1:1.

Study setting

This study will be conducted in referral clinic of Afzalipour Hospital affiliated to Kerman University of Medical Sciences, Kerman, southeastern Iran. A trained general physician will visit the patients. Next, in case of clinical diagnosis of COVID-19 pneumonia, they will be introduced to researchers. Finally, patients who meet eligibility criteria will be invited to the study. Patients' recruitment started from April 2, 2020.

Randomization

All eligible patients will be randomly allocated to intervention and control groups. A biostatistician generated a randomization list via blocked randomization method (non-stratified, four patients in each block) using Microsoft Excel® software. A secretary enroll participants to intervention groups via sequentially numbered opaque envelopes.

Intervention

After obtaining the written informed consent from the participants, they were randomly divided into intervention (myrtle) and control groups. All patients will receive conventional therapy according to the fifth edition of novel Corona virus pneumonia guideline of the Iranian Ministry of Health and Medical Education. Patients in intervention group should take myrtle preparation in addition to classic medication. So, they received packets containing myrtle fruit and sugar. On a daily basis, they should gently boil the contents of a pack containing 10 grams of myrtle fruit and 10 grams of sugar in 3 glasses of water until 2 glasses of the liquid remain; next, they should percolate it and drink 1 glass in the morning and 1 glass in the evening for 5 days.

The compliance of the participants will be evaluated via telephone survey to record the usage of study medication and any side effect. The test schedule and procedures are provided in Table 1.

Outcome measures

Primary and secondary outcomes will be determined in different time points including 0,1,2,3,4,7, and14 days after the intervention.

The primary outcomes and their method of measurement are as follows:

- Temperature, via thermometer
- Cough (severity and frequency), via Fisman Cough Severity Score

- Weakness, via visual analog scale (VAS)
- Muscular pain, via VAS
- Respiratory rate, via counting the number of breaths per minute

The secondary outcomes include the following:

- Hospital admission
- Taste and smell disorder
- Mortality rate
- Adverse effect

Statistical analysis

Due to the lack of a similar study, the sample size was initially considered to be 70 (35 in each arm). Differences between treatment groups in different variables will be measured using analysis of covariance (ANCOVA).

Definition of end of the study

The end of study will be the last patient's last visit. However, ethics committee makes the final decision to terminate the trial.

Potential weakness in study design

The protocol of this study was conceived when the PCR test was not adequately available for confirming the diagnosis of COVID-19 infection; on the other hand, the placebo-controlled setting can enhance the value of the study. Hence, it can be concluded that another placebo-controlled study on the confirmed COVID-19 patients is required and ethically justifiable.

Lack of monitoring such laboratory data as inflammatory factors, lymphocyte count, renal and liver function, as well as the lack of following the chest radiography are the other limitations of this study.

Table 1. The test schedule and procedures of suspected COVID-19 patients participating the study

Study phase	screening	Randomization/intervention phase	Follow up					
Study days	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Day 14
Informed consent	O							
Assessing the eligibility	O							
Demographics	O							
History and Physical examination	O							
Assessing the variables	O	O	O	O	O	O	O	O
Pulse oximetery	O							
Randomization		O						
Recording the adverse effect			O	O	O	O		

Discussion

The efficacy, safety, and availability of the treatment are the key factors indicating the success of any drug in being welcomed. Previous successful experiences on the efficacy of herbs of traditional Chinese medicine in managing SARS, MERS, and influenza have resulted in designing various researches on different aspects and capacities of alternative medicine for alleviating COVID-19 disease (8). The present research will provide evidences as to whether myrtle is safe and appropriate for treating COVID-19 pneumonia. *Myrtus Communis*, as a potent anti-viral agent, may be useful especially in early stage of the disease (12); on the other hand, its anti-inflammatory property can reduce the cytokine storm (13). The efficacy of this herb on diarrhea has been proved in several researches (14). In addition, based on the ancient Persian medicine resources, myrtle extract can be recommended for pneumonia especially when accompanied by cough and diarrhea (11).

The evaluation of the safety of the plant is very crucial especially in such significant projects as COVID-19 disease. Previous clinical trials on myrtle did not mention any serious adverse effects (15). On the other hand, myrtle has been used only for 5 days. Therefore, there are no major concerns regarding the possible side effects of a long-term consumption. In addition, the growing trend of this disease, its high costs of treatment and hospitalization, and resource constraints proves the need to explore safe, effective and inexpensive COVID-19 medications for shortening the disease course and enhancing the prognosis. Hence, an evidence-based clinical trial to evaluate the effectiveness of myrtle in treating pneumonia induced by COVID-19 certainly has merit.

Resultantly, we have described a clinical trial for treatment of COVID-19 pneumonia using myrtle in Kerman, Iran. Moreover, based on the results of this study, we will hold a large-scale clinical trial, with the aim to comprehensively assess the efficacy and safety of myrtle against COVID-19 infection.

Trial status

The protocol version number is two with revision ID: *137273* and registration date: June 3th, 2020. The patient recruitment for this research has been begun on April 18th, 2020. It is expected to continue till July 30th, 2020.

Declarations

Ethics approval and consent to participate: The protocol of this study is approved by the Local Medical Ethics Committee of Kerman University of Medical Sciences under the approval code IR.KMU.REC.1399.015. Written, informed consent to participate will be obtained from all participants.

Consent for publication: Not applicable.

Availability of data and materials: The results of this study have the potential for public health applicability. The target audience will be reached through oral presentations, publications, and seminars. The researchers will have to be sure that the participant's privacy is maintained. Data and source documents will be archived for the purposes of any need for monitoring or inspection by the Ethics Committee. At the end of the study, participants will be able to access a copy of the results of the trial from the researchers.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: FS. H. is the Chief Investigator; she conceived the study, led the proposal and protocol development. M. A. contributed to study design and to development of the proposal. Both authors read and approved the final manuscript.

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