



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Original Research Paper

Efficacy of the barley-based remedy, a Persian medicine formula, in coronavirus disease 2019 (COVID-19) hospitalized patients: An open-labeled randomized controlled trial

Fatemeh Sadat Hasheminasab^a, Maryam Azimi^{b,c}, Mahmood Khodadoost^d, Bahram Chouban^e, Nezhat Shakeri^f, Saeedeh Ghasemi^e, Azam Farokhi^e, Roshanak Mokaberinajad^{d,*}

^a Pharmacology Research Center, Zahedan University of Medical Sciences, Zahedan, Iran

^b Gastroenterology and Hepatology Research Center, Kerman University of Medical Sciences, Kerman, Iran

^c Department of Traditional Medicine, School of Persian Medicine, Kerman University of Medical Sciences, Kerman, Iran

^d Department of Traditional Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

^e Shahid Mofateh Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

^f Department of Biostatistics, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:

Persian medicine
Pneumonia
Hordeum vulgare L.
Ziziphus jujuba Mill
Cordia myxa L.

ABSTRACT

Background: With the pandemic of coronavirus disease 2019 (COVID-19), and the growing attention of people around the world to the use of traditional and complementary medicines to control of the disease, evaluating the effectiveness of these treatments has received special attention.

Aim: This study aimed to assess the clinical efficacy of a barley-based (*Hordeum vulgare*) remedy combined with conventional medicine in comparison to the conventional therapy in confirmed COVID-19 patients.

Materials and methods: Seventy COVID-19 patients were randomly divided into barley-based remedy plus conventional medicine (barley-based remedy group) and conventional therapy (control group). Both groups were treated for 5 days. The outcomes were oxygen saturation, main symptoms (fever, respiratory rate, cough, and fatigue), and laboratory data (lymphocytic count, and CRP); they were measured for 6 days.

Results: In comparison to the control group, the oxygen saturation level in the barley-based remedy group significantly increased, from the second day of the intervention ($P < 0.05$). The herbal remedy significantly improved fatigue from the third day ($P < 0.05$). Meanwhile, the severity and frequency of cough between the groups were not significantly different. The herbal remedy had no significant effect on the CRP and the lymphocytic count of every time points of measurement. The average of respiratory rate and temperature of patients were in the normal range in both groups during the intervention.

Conclusion: Barley-based remedy could significantly enhance the blood oxygen saturation and reduce fatigue. However, it needs to be confirmed by large sample size trials.

1. Introduction

In late December 2019, the first case of coronavirus disease 2019 (COVID-19) was reported in Wuhan, China. As of May 2021, nearly 3.4 million and 160 million laboratory-confirmed cases have been recorded in Iran and throughout the world, respectively. COVID-19 has become a major problem in human societies, [1] with the real number of cases likely to be more than reports partly because of asymptomatic carriers, patients with mild symptoms or those who have atypical clinical manifestations [2]. COVID-19 is due to severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2), and older patients and those with comorbidity disorders such as diabetes or obesity potentially experience more severe disease [3]. Cytokine storm, pulmonary infiltration, alveolar damage and progressive respiratory failure caused by COVID-19 may lead to worse conditions, and even death [4].

It is not practical to develop novel medication classes within short spans of time during public emergencies. As such, research in modern and complementary medicine (i.e. Chinese herbal medicine, Persian medicine, acupuncture) are ongoing to find potential solutions to reduce the costs from the health care systems and reserve resources [5–7]. The

* Correspondence to: Velenjak, 7th Floor, Bldg No.2 SBUMS, Arabi Ave., Postal code: 9816743463, Tehran Province, Iran.

E-mail address: rmokaberi@gmail.com (R. Mokaberinajad).

<https://doi.org/10.1016/j.aimed.2022.04.001>

Received 4 July 2021; Received in revised form 10 April 2022; Accepted 17 April 2022

Available online 20 April 2022

2212-9588/© 2022 Published by Elsevier Ltd.

experience during previous epidemics including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) have demonstrated the effectiveness of some complementary medicines such as traditional Chinese medicine for better management of the infection [8]. Integration of Chinese herbal medicine with conventional medicine has also been suggested to increase the cure rate and reduce the illness severity, hospital stay and mortality rate of COVID-19 cases, which have been indicated in previous studies [9]. The universal psychosocial impact caused by COVID-19 has led to raising panic and fear among the general population, with many individuals preferring to try well-known non-conventional therapies such as complementary medicine [10–12]. A recent Turkish cross-sectional study almost 40% of the participants reported the usage of the traditional and complementary medicine. A significant proportion of those participating believed that these modalities have fewer side-effects, are effective, and should be used for managing COVID-19 [12]. An Iranian research study indicated that 84% of general population applied at least one type of complementary and alternative medicine during the COVID-19 pandemic [13]. The overview of recent literatures of the efficacy of various forms of complementary and alternative interventions including Traditional Chinese medicine, acupuncture, Qigong, and relaxation showed that several of these modalities have a potentially positive effect on ameliorating different COVID-19 dimensions, including improvement of various physical symptoms (physical activity, inflammatory factors, and respiratory function), and psychological symptoms (quality of life, depression, anxiety, negative emotions, sleep quality) in patients with COVID-19 [14].

Persian medicine has been applied to ameliorate respiratory illness such as pneumonia for thousands of years. Several papers have introduced the Persian medicinal herbs used traditionally for this purpose, their relevant pharmacological properties, and also their possible mechanisms to alleviate COVID-19 signs and symptoms [15–17]. It should be emphasized that conducting clinical trials to evaluate the efficacy of these remedies against current epidemic is a necessity. These trials will pave the way to design further researches to identify and extract the bioactive phytochemical components, and potentially lead to the discovery of new drugs against SARS-CoV-2.

The mixture of *Hordeum vulgare* L., *Ziziphus jujube* Mill., and *Cordia myxa* L. have been recommended in Persian medicine manuscripts as a type of barley-based remedy (*Ma-al-Shaer* in Persian) for treating pneumonia. *H. vulgare* is the main component of this formula [18,19]. Not only, it has been widely used as a popular food, but also as a safe remedy since ancient time. Its anti-inflammatory property is remarkable [20]. *Z. Jujuba* traditionally is considered as a good remedy for controlling infection, fever and cough. Recent studies confirmed the anti-viral, immunomodulatory, anti-inflammatory, and neuroprotective effects of this medicinal plant [21–24]. The other herb in the mixture is *C. Myxa*, which alleviates sore throat, cough and respiratory infections traditionally, and according to the scientific research has various therapeutic potentials such as anti-viral, anti-inflammatory, analgesic, and antitussive actions [25–27].

In this project, we aimed to evaluate the efficacy of the barley-based remedy in adult COVID-19 hospitalized patients.

2. Materials and methods

2.1. Patients' recruitment

Seventy COVID-19 hospitalized patients were recruited from an Iranian hospital between May 13th to July 10th, 2020. Inclusion criteria included confirmed COVID-19 and age of 18 years old or greater. The COVID-19 was confirmed based on the positive nasopharyngeal real-time reverse transcription (PCR) or findings of chest CT scan. Exclusion criteria consisted of pregnancy, lactation, tracheal intubation, indication for ICU admission, taking corticosteroid, recent usage of herbal medicine, diabetes, hypertension, asthma, allergy, chronic renal

failure, chronic heart failure, chemotherapy, and immune deficiency.

2.2. Study design and setting

At first, written informed consent was obtained from the eligible participants, who were then randomized into intervention (barley-based remedy) or control groups. All participants received conventional therapy based on the Protocol for Diagnosis and Treatment of Novel Coronavirus Pneumonia (5th edition). The barley-based remedy was added to the conventional medication regimen of the patients in the intervention group. The dosage of herbal water extract was 200 ml, two times a day, for five days.

2.3. Randomization

All eligible participants were randomly allocated to the intervention (barley-based remedy) and control groups. A randomization list was generated by a biostatistician, in Blocked Randomization Method (non-stratified, four patients in each block) using Random Allocation Software.

2.4. Outcome measures

The primary outcome was oxygen saturation percentage (O₂). The secondary outcomes were: body temperature, cough severity (range from 0 for no cough to 4 for severe cough with chest discomfort), and cough frequency (0 for no cough to 10 for cough all day (Fisman Cough Score [28])), fatigue (visual analog scale (VAS)) [4], Respiratory rate, C-Reactive Protein (CRP), lymphocyte count, mortality rate, and adverse effects. The primary and the secondary outcomes were measured daily during whole six days of intervention.

2.5. Sample size and statistical analysis

Due to lack of previous study, the sample size of 35 participants in each group was deemed sufficient [29].

Demographic information was compared between the two groups via the Chi-square and student t-Test. The student t-test was also used for comparing the changes between the two groups in different time point. The statistical analysis was performed using SPSS 24 and the resultant $p < 0.05$ was considered significant.

2.6. Study drug

The *H. vulgare* (*Jo* in Persian, and *Barley* in English) seeds, *Z. Jujuba* (*Anlab* in Persian, and *Jujube* in English) dried fruits, and *C. Myxa* (*Sepestan* in Persian, and *Cordia* in English) dried fruits were obtained commercially from a local market in Tehran city, the center of Tehran province, Iran. Herbal samples were transferred to the Department of Traditional Pharmacy, School of Persian Medicine at Shahid-Beheshti University of Medical Sciences. They were authenticated with a pharmacognosist.

Afterwards total ash, loss on drying and extractive value percent were determined according to herbal pharmacopeia method to evaluate the quality of purchased herbs.

In order to quantify the active compounds of herbs, total phenolic content and flavonoid content of *Z. jujuba* and *C. myxa* were determined.

Total phenolic content of mentioned plants was determined spectrophotometrically using the Folin-Ciocalteu reagent assay according to a previously described method with slightly modification [30]. Briefly, 100 μ L aqueous extract of the herbs or a standard solution of gallic acid was added to a test tube, then mixed with 500 μ L of diluted Folin-Ciocalteu reagent (1:10 v/v) and the resulted mixture was slightly shaken for a minute. Afterwards, 400 μ L of an aqueous solution of Na₂CO₃ (7.5% w/v) was added and the obtained mixture was incubated for 30 min in the darkness at room temperature. After incubation, the

absorbance, relative to that of a blank prepared using distilled water, was measured at 765 nm using multi-mode microplate reader (BioTek®, USA).

The concentration of total phenolic compounds was determined as mg of gallic acid/ g of the dry weight of extract by using regression equation that obtained from the calibration curve of the gallic acid.

Colorimetric method was used to measure the amounts of total flavonoids in the plant [31]. For this purpose, different concentration of rutin and quercetin standard (500–62 µg/ml) was prepared in methanol 60%. One ml of aqueous extract of *Z. jujuba* or *C. myxa* or methanolic solution of rutin and quercetin standard was mixed with 1 ml distilled water. Then 100 µL sodium nitrate 5% was added to each sample and shacked for 6 min afterwards 200 µL aluminum chloride 10% was added to each test tube. After 5 min incubation at room temperature, 1 ml aqueous solution of NaOH (1 N) was added and the absorbance, relative to that of a blank prepared using methanol 60%, was determined at 510 nm using multi-mode microplate reader (BioTek®, USA). All tests were carried out in triplicate and the results were expressed as mean±SD.

Finally, the medicinal plants were delivered to the Mofatteh hospital, Varamin city.

On a daily basis, 60 g of crushed herbs mixture (in equal proportion) was gently boiled with 1200 ml of water, until 400 ml liquid was remained. Then, it was filtered. The participants took the 400 ml water extract in two divided doses (200 ml morning, and 200 ml evening). The hospital nutritionist made this decoction.

2.7. Ethical considerations

The Local Medical Ethics Committee of Shahid Beheshti University of Medical Sciences approved the protocol of the present study (Code: IR.SBMU.RETECH.REC.1399.074, Ethical approval date: 2020-05-02, webpage of ethical approval code is: yun.ir/jigyge). In addition, the protocol was registered at the Iranian Registry of Clinical Trials website (Code: IRCT20180923041093N6). This study was conducted in accordance with the guidelines of Declaration of Helsinki. The study procedure was fully explained to the patients, who met the criteria for participation in the project; each one had to give their consent to participate to the trial, and voluntarily signed an informed written consent.

3. Results

3.1. Physicochemical analysis

The phytochemical analysis of herbs of barley-based formulation is presented in Table 1. The total ash is under 11% and loss on drying is below 6% for all evaluated herbs. In the study of total phenolic content, *C. myxa* significantly showed more phenolic content (119.85 ± 4.84). Also, the amount of flavonoid compounds including rutin and quercetin in *C. myxa* fruits was significantly higher than *Z. jujuba*.

3.2. Flowchart of the study

Seventy eligible participants were equally entered into two groups. In the barley-based remedy group, two cases were excluded as lost to

follow up, and one was excluded because of discontinued intervention; the remaining 32 subjects completed the trial. In the control group, two patients were omitted from the project as lost to follow up and 33 subjects completed the study. Fig. 1 shows the flow chart of the study.

3.3. Demographic and baseline characteristics

In term of gender, 14 (43.8%) of patients in barley-based remedy group, and 17 (51.5%) of cases in control group were male. The mean age of participants in barley-based remedy and the control groups were 51.49 ± 11.61 and 53.28 ± 13.22 year, respectively. There was no significant difference in terms of age and gender between the groups ($p > 0.05$).

The baseline clinical manifestations of the participants are shown in Table 2. No significant difference was detected regarding the initial clinical characteristics including temperature, respiratory rate, cough, O₂ saturation, fatigue, CRP and lymphocyte count ($p > 0.05$).

3.4. Clinical response and safety

The participants were re-assessed at the first six days after starting the intervention. The average of the respiratory rate and body temperature was in the normal ranges during intervention days. The barley-based remedy significantly improved blood oxygen saturation. The barley-based remedy also significantly improved fatigue from the third day. Based on Fisman Score, the cough severity averages of both groups were below 1 during the intervention and their cough frequency were below 2, both indicating a mild cough symptom. Comparing the severity and frequency of cough between the groups showed no significant difference. There was no significant effect on CRP and lymphocytic count in any time points of measurement. Details of results and the comparison between groups during the intervention are showed in Table 2.

Except for one participant, who did not tolerate the taste of barley-based remedy and was excluded from the study, most patients tolerated the herbal remedy very well and there were no complaints about taking it. No serious adverse effects were reported by the patients.

4. Discussion and conclusion

This study investigated the efficacy of a traditional Persian medicine barley-based remedy on patients with COVID-19. According to the results of this study, the herbal remedy significantly improved the level of oxygen saturation one day after starting the intervention, and remained meaningful until the end of the study. The fatigue was significantly reduced on the third day and remained significant until the sixth day. The difference in the severity and frequency of cough, body temperature, respiratory rate, CPR, and lymphocyte percentage were not significant between the two groups.

The significant outcome of this trial is the improving effect of barley-based remedy on oxygen saturation of COVID-19 patients compared to the control group; although during the intervention period, the average of oxygen saturation could not reach higher than 94.3% in the barley-based remedy. It should be noted that the mean oxygen level of the control group was not higher than 89.25% during the intervention period. The improvement in oxygen levels may be due to the potent anti-

Table 1
Phytochemical analysis of *H.vulgaris*, *Z. jujuba* and *C. myxa*.

| Parameters → | Extract yield (%) | Total ash (%) | Loss on drying (%) | mg gallic acid/ g dried extract (Mean±SD) | mg rutin/ g dried extract (Mean±SD) | mg quercetin/ g dried extract (Mean±SD) |
|------------------------|-------------------|---------------|--------------------|---|-------------------------------------|---|
| <i>Hordeum vulgare</i> | 29.8 | 4.6 ± 0.1 | 2.9 ± 0.1 | – | – | – |
| <i>Ziziphus jujuba</i> | 43.8 | 8.8 ± 0.4 | 5.6 ± 0.4 | 92.18 ± 3.18 | 43.13 ± 2.17 | 69.13 ± 3.82 |
| <i>Cordia myxa</i> | 31.4 | 10.9 ± 0.5 | 4.5 ± 0.3 | 119.85 ± 4.84*** | 92.29 ± 4.16**** | 167.46 ± 8.32** * |

: P value < 0.001, *: P value < 0.0001

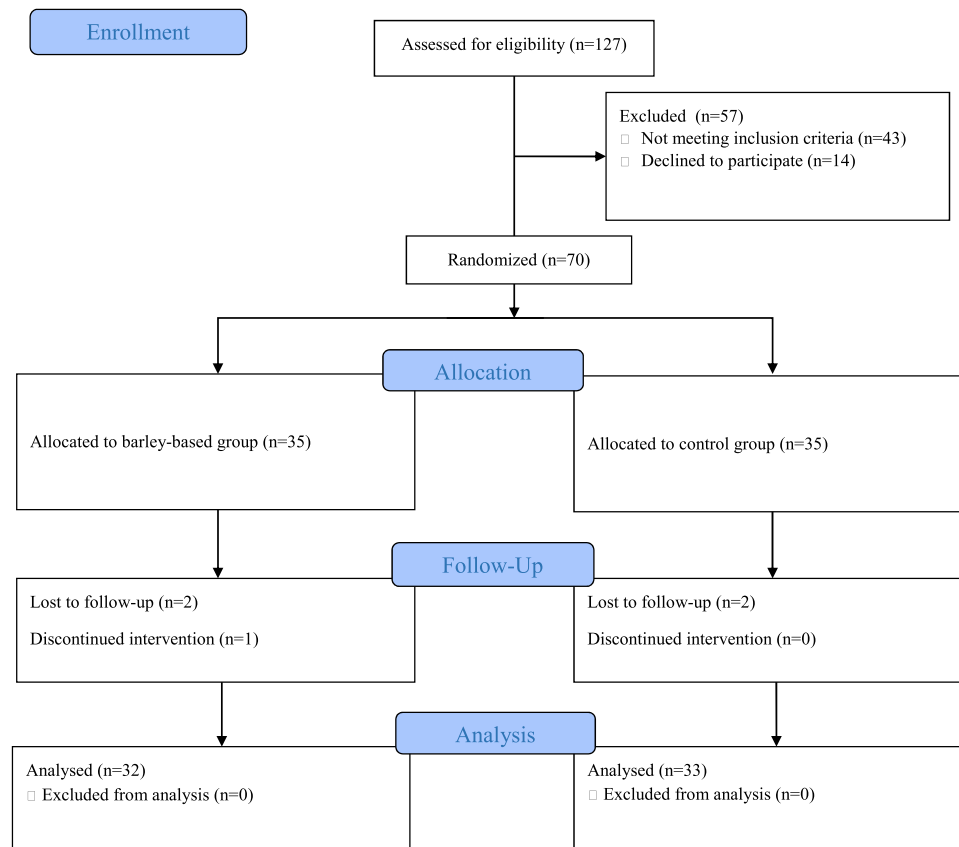


Fig. 1. CONSORT flow diagram of the study.

Table 2

Average of different clinical characteristics of COVID-19 patients at the different time point of both groups (barley-based remedy (B) and control (C) groups).

| Variables ↓ | Time point → | Day (1) (baseline) | Day (2) | Day (3) | Day (4) | Day (5) | Day (6) |
|---------------------------|--------------|-----------------------|-------------------|------------------|------------------|-------------------|-------------------|
| Temperature | B (M±SD) | 37.41 ± 0.91 | 37.21 ± 0.77 | 36.96 ± 0.54 | 37.07 ± 0.91 | 36.92 ± 0.40 | 36.86 ± 0.25 |
| | C (M±SD) | 37.02 ± 0.62 | 36.99 ± 0.85 | 36.90 ± 0.72 | 37.05 ± 0.53 | 37.04 ± 0.55 | 36.99 ± 0.55 |
| | P.value | 0.05 | 0.31 | 0.70 | 0.88 | 0.29 | 0.22 |
| Respiratory rate | B (M±SD) | 19.34 ± 4.58 | 18.00 ± 4.10 | 17.09 ± 3.99 | 18.09 ± 4.01 | 16.75 ± 3.16 | 16.06 ± 3.82 |
| | C (M±SD) | 17.42 ± 3.41 | 17.36 ± 3.29 | 17.61 ± 3.55 | 17.63 ± 4.02 | 16.97 ± 3.86 | 17.56 ± 4.58 |
| | P.value | 0.06 | 0.49 | 0.58 | 0.64 | 0.81 | 0.16 |
| Cough (severity) | B (M±SD) | 0.59 ± 0.87 | 0.62 ± 0.97 | 0.56 ± 1.01 | 0.48 ± 0.95 | 0.37 ± 0.79 | 0.19 ± 0.53 |
| | C (M±SD) | 0.97 ± 1.51 | 0.94 ± 1.48 | 0.82 ± 1.36 | 0.78 ± 1.31 | 0.68 ± 1.25 | 0.75 ± 1.21 |
| | P.value | 0.22 | 0.31 | 0.39 | 0.28 | 0.24 | 0.02 |
| Cough (frequency) | B (M±SD) | 1.34 ± 1.88 | 1.34 ± 1.88 | 1.00 ± 1.72 | 0.94 ± 1.66 | 0.87 ± 1.84 | 0.53 ± 1.63 |
| | C (M±SD) | 1.63 ± 2.34 | 1.76 ± 2.41 | 1.76 ± 2.31 | 1.47 ± 2.33 | 1.28 ± 2.22 | 1.37 ± 2.15 |
| | P.value | 0.58 | 0.44 | 0.14 | 0.30 | 0.43 | 0.08 |
| Fatigue | B (M±SD) | 1.37 ± 1.72 | 1.37 ± 1.71 | 0.81 ± 1.33 | 0.60 ± 1.34 | 0.56 ± 1.27 | 0.39 ± 0.59 |
| | C (M±SD) | 2.18 ± 2.64 | 2.24 ± 2.59 | 1.91 ± 2.53 | 1.97 ± 2.62 | 1.79 ± 2.48 | 1.66 ± 2.39 |
| | P.value | 0.15 | 0.12 | 0.03 | 0.01 | 0.02 | 0.01 |
| O ₂ saturation | B (M±SD) | 90.91 ± 7.34 | 92.72 ± 0.4.45 | 92.72 ± 0.3.35 | 93.59 ± 3.01 | 93.37 ± 4.11 | 94.28 ± 4.71 |
| | C (M±SD) | 88.12 ± 5.85 | 88.42 ± 6.04 | 89.42 ± 6.05 | 89.03 ± 7.42 | 89.25 ± 6.76 | 89.06 ± 7.97 |
| | P.value | 0.10 | 0.002 | 0.002 | 0.003 | 0.005 | 0.002 |
| CRP | B (M±SD) | 2.64 ± 1.17 | 2.87 ± 1.18 | 2.65 ± 1.45 | 2.87 ± 1.55 | 2.58 ± 1.50 | 2.31 ± 1.49 |
| | C (M±SD) | 2.56 ± 1.24 | 2.50 ± 1.16 | 2.34 ± 1.26 | 2.21 ± 1.12 | 2.24 ± 1.04 | 1.93 ± 1.10 |
| | P.value | 0.79 | 0.41 | 0.50 | 0.20 | 0.42 | 0.43 |
| Lymphocytic Count | B (M±SD) | 1712.54 ± 1068.84 | 1385.75 ± 761.39 | 1849.90 ± 982.22 | 1488.90 ± 661.10 | 1822.72 ± 1009.28 | 2206.65 ± 1130.83 |
| | C (M±SD) | 1726.03 ± 1927.18 | 1805.71 ± 1234.48 | 1415.40 ± 750.77 | 1299.54 ± 845.73 | 1503.90 ± 761.57 | 1561.43 ± 642.15 |
| | P.value | 0.97 | 0.28 | 0.13 | 0.52 | 0.271 | 0.07 |

inflammatory effects of the components of the barley-based formula. Barley contains a group of polysaccharides named β-glucans, which are responsible for a variety of biological activities such as regulation of the immune responses [32]. Recent research demonstrated that barley β-glucans decrease systemic inflammation, and that it reduces leukocyte superoxide and TNFα production, as well as lessening stimulation of

interferon genes expression [20]. Another study showed that polysaccharide conjugates of the *Z. Jujuba* could decrease IL-10 levels of the chronic fatigue syndrome rats [21]. Moreover, saponins isolated from the fruits of *Z. Jujuba* significantly reduces inflammation via several pathways such as COX-2 inhibition [22]. Another study indicated that Betulinic acid, an active substance of *Z. Jujuba* may have satisfactory

antiviral activity against influenza A/PR/8 virus. In addition, betulinic acid is able to alleviate the symptoms of edema and lung necrosis due to influenza A/PR/8 virus in mice [23].

The phytochemical screening conducted on *C. myxa* fruit extract showed the presence of flavonoids, glycosides, saponins, alkaloids, terpenoids, phenolic acids, tannins, and mucilage [33]. Regarding to different pharmacological investigations, *C. myxa* revealed anti-inflammatory, analgesic, immunomodulatory, antimicrobial, respiratory, and cardiovascular protective properties [27]. Recent study indicated that *C. myxa* extract have broncho-relaxant activity. The extract inhibited contraction induced by acetylcholine in both denuded, and epithelium-intact trachea rings of the sheep [34]. The anti-inflammatory property of ethanol extract and various fractions of *C. myxa* was assessed through the carrageenan-induced paw edema method. The results indicated that the dichloromethane fraction and total ethanol extract of this medicinal plant may have more anti-inflammatory effects in comparison to the indomethacin [35].

Based on traditional Persian medicine manuscripts the ingredients of the barley based remedy have tonifying effects on lung or heart [36]. Recent research also suggests the cardio-protective activity of *Z. Jujuba*. According to these studies, polyphenols of *Z. Jujuba*, and also jujuboside A, which is a saponins isolated from this herb could prevent isoproterenol-induced cardiomyocytes injury [37,38].

The temperature averages of patients in both groups were blow 37.2 °C every day during the six days of follow up, except for patients in barley-based remedy group at the onset of admission with temperature of 37.4 °C. All participants were afebrile, due to all participants receiving naproxen.

During the intervention days, the average respiratory rate in both groups was in normal range, and no significant difference was detected between groups, despite differences in oxygen levels. The normal rate of respiration at the same time as the oxygen saturation level decreases, may be justified by the silent hypoxia mechanism reported in COVID-19. 'Silent' or 'happy' hypoxia has been generally defined as hypoxia in the absence of dyspnea and tachypnea [39]. Recent studies have theorized some possible mechanisms of this event in COVID-19 patients, such as possible direct interaction between the virus and hemoglobin, and neural cell damage due to viral infection and consequently imbalance of neurotransmitters or endogenous neuropeptides [40,41].

Overall, this study suggests that barley-based remedy, as an adjunct treatment may be able to significantly enhance the blood oxygen saturation in patients with COVID-19. Even though the final level of oxygen was less than normal levels, this improvement as a result of a safe remedy consumption is considerable, and on improvement on those who had not taken the remedy. Barley-based remedy and each of its components not only have been consumed as food, but also as a supplement for better management of pneumonia, dyspnea and some other disorders throughout centuries in different regions. However, conducting further trials with larger sample size are necessary for accurate judgment on the effectiveness of barley-based remedy as an adjunct therapy on various manifestation of COVID-19, especially hypoxia, as well as its utility in broader applications.

Authors' contributions

All authors contributed to the research conception and design. Material preparation, collection of data and analysis were performed by Hasheminasab FS, Azimi M, Khodadoost M, Choubani B, Shakeri N, H, Ghasemi S, Farokhi A, and Mokaberinajad R. The first draft of the manuscript was written by Hasheminasab FS, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical statement

Local Medical Ethics Committee of Shahid Beheshti University of

Medical Sciences approved the protocol of this trial (code: IR.SBMU.RETECH.REC.1399.074); It was also registered at the Iranian Registry of Clinical Trials website under the code of IRCT20180923041093N6.

Conflict of interest

There was no conflict of interest in this study.

References

- https://www.worldometers.info/coronavirus/#countries.
- K. Hu, W.-j. Guan, Y. Bi, W. Zhang, L. Li, B. Zhang, Q. Liu, Y. Song, X. Li, Z. Duan, Efficacy and Safety of Lianhuaqingwen Capsules, a repurposed Chinese Herb, in Patients with Coronavirus disease 2019: A multicenter, prospective, randomized controlled trial, *Phytomedicine* (2020), 153242.
- C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, *Lancet* 395 (10223) (2020) 497–506.
- Z. Yang, Z. Zeng, K. Wang, S.-S. Wong, W. Liang, M. Zanin, P. Liu, X. Cao, Z. Gao, Z. Mai, Modified SEIR and AI prediction of the epidemics trend of COVID-19 in China under public health interventions, *J. Thorac. Dis.* 12 (3) (2020) 165.
- M. Azimi, F.S. Hasheminasab, Evaluating the efficacy and safety of the myrtle (*Myrtus communis*) in treatment and prognosis of patients suspected to novel coronavirus disease (COVID-19): study protocol for a randomized controlled trial, *Trials* 21 (1) (2020) 1–5.
- R. Qiu, X. Wei, M. Zhao, C. Zhong, C. Zhao, J. Hu, M. Li, Y. Huang, S. Han, T. He, Outcome reporting from protocols of clinical trials of Coronavirus Disease 2019 (COVID-19): a review, *medRxiv* (2020).
- M.P. Lythgoe, P. Middleton, Ongoing clinical trials for the management of the COVID-19 pandemic, *Trends Pharmacol. Sci.* (2020).
- H.-T. Cui, Y.-T. Li, L.-Y. Guo, X.-G. Liu, L.-S. Wang, J.-W. Jia, J.-B. Liao, J. Miao, Z.-Y. Zhang, L. Wang, Traditional Chinese medicine for treatment of coronavirus disease 2019: a review, *Tradit. Med. Res.* 5 (2) (2020) 65–73.
- M. Liu, Y. Gao, Y. Yuan, K. Yang, S. Shi, J. Zhang, J. Tian, Efficacy and safety of integrated traditional Chinese and western medicine for Corona Virus Disease 2019 (COVID-19): a systematic review and meta-analysis, *Pharmacol. Res.* (2020), 104896.
- S. Dubey, P. Biswas, R. Ghosh, S. Chatterjee, M.J. Dubey, S. Chatterjee, D. Lahiri, C. J. Lavie, Psychosocial impact of COVID-19, *Diabetes Metab. Syndr.: Clin. Res. Rev.* 14 (5) (2020) 779–788.
- F. Ornell, J.B. Schuch, A.O. Sordi, F.H.P. Kessler, "Pandemic fear" and COVID-19: mental health burden and strategies, *SciELO* (2020) 232–235.
- Y. Karataş, Z. Khan, Ç. Bilen, A. Boz, E.S.G. Özagil, A.B. Abussuutoğlu, H. Rahman, Traditional and Complementary Medicine use and beliefs during COVID-19 outbreak: a cross-sectional survey among the general population in Turkey, *Adv. Integr. Med.* 8 (4) (2021) 261–266.
- M. Dehghan, A. Ghanbari, F.G. Heidari, P.M. Shahrbabaki, M.A. Zakeri, Use of complementary and alternative medicine in general population during COVID-19 outbreak: a survey in Iran, *J. Integr. Med.* 20 (1) (2022) 45–51.
- M. Badakhsh, M. Dastras, Z. Sarchahi, M. Doostkami, A. Mir, S. Bouya, Complementary and alternative medicine therapies and COVID-19: a systematic review, *Rev. Environ. Health* (2021).
- M. Iranzadasl, Y. Karimi, F. Moadeli, M. Pasalar, Persian medicine recommendations for the prevention of pandemics related to the respiratory system: a narrative literature review, *Integr. Med. Res.* (2020), 100483.
- H.M. Vardanjani, S.T. Heydari, B. Dowran, M. Pasalar, A cross-sectional study of Persian medicine and the COVID-19 pandemic in Iran: rumors and recommendations, *Integr. Med. Res.* 9 (3) (2020), 100482.
- R. Bahramoltani, R. Rahimi, An evaluation of traditional Persian medicine for the management of SARS-CoV-2, *Front. Pharmacol.* 11 (2020), 571434, <https://doi.org/10.3389/fphar>.
- M. Nazem Jahan, Exir-e-Azam, Tehran: Iran University of medical sciences- Institute of history of medicine, Islamic and complementary medicine (2008).
- H. Ibn-Sina, *Al-Qanon fi teb*, Institute of medical investigations, New Delhi, India (1981).
- M.V. Arcidiacono, N. Carrillo-López, S. Panizo, A.L. Castro-Grattoni, P. Valcheva, C. Ulloa, J. Rodríguez-Carrio, A. Cardús, C. Quirós-Caso, L. Martínez-Arias, Barley-β-glucans reduce systemic inflammation, renal injury and aortic calcification through ADAM17 and neutral-sphingomyelinase2 inhibition, *Sci. Rep.* 9 (1) (2019) 1–14.
- A. Chi, C. Kang, Y. Zhang, L. Tang, H. Guo, H. Li, K. Zhang, Immunomodulating and antioxidant effects of polysaccharide conjugates from the fruits of *Ziziphus Jujube* on Chronic Fatigue Syndrome rats, *Carbohydr. Polym.* 122 (2015) 189–196.
- A.M. Chowdari, D. Giles, Anti-inflammatory, antiulcer and anticancer activities of saponin isolated from the fruits of *Ziziphus jujuba*, *Nat. Prod. J.* 10 (4) (2020) 395–399.
- E.-H. Hong, J.H. Song, K.B. Kang, S.H. Sung, H.-J. Ko, H. Yang, Anti-influenza activity of betulinic acid from *Ziziphus jujuba* on influenza A/PR/8 virus, *Biomol. Ther.* 23 (4) (2015) 345.
- A. Kaedi, M. Taati, Z. Hajjalizadeh, F. Jahandari, M. Rashidipour, Aqueous extract of *Ziziphus jujuba* fruit attenuates glucose induced neurotoxicity in an in vitro model of diabetic neuropathy, *Iran. J. Basic Med. Sci.* 18 (3) (2015) 301.

- [25] K. Rashed, M.-T. Luo, L.-T. Zhang, Y.-T. Zheng, Evaluation of anti-HIV-1 activity of *Cordia myxa* L. and phytochemical profile, *Banar's J. Biotechnol.* 5 (9) (2014) 51.
- [26] S. Salimimoghadam, A. Ashrafi, F. Kianidehkordi, H. Najafzadehvarzi, Hypoglycemic, antitussive and analgesic effects of nanoparticles of *Cordia myxa* fruits extract, *Int. J. Pharm. Investig.* 9 (4) (2019) 205–209.
- [27] A.E. Al-Snafi, The Pharmacological and therapeutic importance of *Cordia myxa*-A review, *IOSR J. Pharm.* 6 (6) (2016) 47–57.
- [28] E.Z. Fisman, I. Shapira, M. Motro, A. Pines, A. Tenenbaum, The combined cough frequency/severity scoring: a new approach to cough evaluation in clinical settings, *J. Med.* 32 (3–4) (2001) 181–187.
- [29] A.L. Whitehead, S.A. Julious, C.L. Cooper, M.J. Campbell, Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable, *Stat. Methods Med. Res.* 25 (3) (2016) 1057–1073.
- [30] M. Raeiszadeh, A. Pardakhty, F. Shariffar, M. Mehrabani, Phytoniosome: a novel drug delivery for myrtle extract, *Iran. J. Pharm. Res.* 17 (3) (2018) 804.
- [31] M. Rameshk, F. Shariffar, M. Mehrabani, A. Pardakhty, A. Farsinejad, In vitro proliferation and wound healing effects of *Narcissus tazetta* L. bulb on primary human dermal fibroblasts, *J. Pharm. Res. Int* 20 (6) (2018) 1–11.
- [32] Y. Jin, P. Li, F. Wang, β -glucans as potential immunoadjuvants: a review on the adjuvanticity, structure-activity relationship and receptor recognition properties, *Vaccine* 36 (35) (2018) 5235–5244.
- [33] A. Aberoumand, Preliminary evaluation of some phytochemical and nutrients constituents of Iranian *Cordia myxa* fruits, *Int. J. Agric. Food Sci.* 1 (2) (2011) 3033.
- [34] M.A. AlBayaty, Mechanism of the tracheal smooth muscle relaxant activity of the *Cordia myxa* plant extract in sheep, *Iraqi J. Vet. Med.* 32 (2) (2008) 214–226. Muhannad AA AlBayaty and Farid J. AlTahan.
- [35] E.R. Abdel-Aleem, E.Z. Attia, F.F. Farag, M.N. Samy, S.Y. Desoukey, Total phenolic and flavonoid contents and antioxidant, anti-inflammatory, analgesic, antipyretic and antidiabetic activities of *Cordia myxa* L. leaves, *Clin. Phytosci.* 5 (1) (2019) 1–9.
- [36] R. Bahramsoltani, R. Rahimi, An evaluation of traditional persian medicine for the management of SARS-CoV-2, *Front. Pharmacol.* 11 (2020).
- [37] D. Han, C. Wan, F. Liu, X. Xu, L. Jiang, J. Xu, Jujuboside protects H9C2 cells from isoproterenol-induced injury via activating PI3K/Akt/mTOR signaling pathway, *Evid. -Based Complement. Altern. Med.* 2016 (2016).
- [38] D. Cheng, C. Zhu, J. Cao, W. Jiang, The protective effects of polyphenols from jujube peel (*Ziziphus Jujube* Mill) on isoproterenol-induced myocardial ischemia and aluminum-induced oxidative damage in rats, *Food Chem. Toxicol.* 50 (5) (2012) 1302–1308.
- [39] N.J.U. Fuglebjerg, T.O. Jensen, N. Hoyer, C.K. Ryrso, B.L. Madsen, Z.B. Harboe, Silent hypoxia in patients with SARS CoV-2 infection before hospital discharge, *Int. J. Infect. Dis.* 99 (2020) 100–101.
- [40] M. Nouri-Vaskeh, A. Sharifi, N. Khalili, R. Zand, A. Sharifi, Dyspneic and non-dyspneic (silent) hypoxemia in COVID-19: possible neurological mechanism, *Clin. Neurol. Neurosurg.* (2020), 106217.
- [41] S. Dhont, E. Derom, E. Van Braeckel, P. Depuydt, B.N. Lambrecht, The pathophysiology of 'happy' hypoxemia in COVID-19, *Respir. Res.* 21 (1) (2020) 1–9.