Clinical Cancer Investigation Journal-ISSN: 2278-0513

The effects of almond porridge, grape extract, and pea syrup on fatigue severity and clinical symptoms of patients with COVID-19: A randomized controlled clinical trial

Abstract

Background: This study is the first randomized controlled trial assessing the beneficial effects of almond porridge, grape extract, and pea syrup in improving fatigue severity and clinical symptoms in patients with coronavirus disease 2019 (COVID-19) with high levels of fatigue.

Methods: This is a randomized, double-blind, placebo-controlled clinical trial conducted at AJA hospital (Tehran, Iran) from March to December 2022.Patients with COVID-19 were randomly divided into two parallel intervention (almond porridge, grape extract, and pea syrup (AGP mixture)) + routine care and placebo + routine care groups. A mixture of almond porridge and grape extract (containing 25 grams of almonds and 8 ccs of grape extract) was given to the patient at 10 o'clock during the hospital stay. Also, in the snack at 16 o'clock, chickpeas (containing 30 grams of chickpeas) were given during the hospital stay. Patients were assessed at baseline, at discharge, 3 months, and 6 months with the Fatigue Assessment Scale (FAS).

Results: A total of 75 patients in the AGP group and 71 patients in the placebo group completed the 6-month course of the trial. The patients in AGP and placebo groups were comparable based on age, sex, and hospital stay. Patients in two trial groups were comparable based on baseline and discharge FAS scores. However, the AGP group showed a significantly lower FAS score at month 3 ($p<0.001$) and month 6 ($p<0.001$) visits. FAS score showed a significantly greater decline in the AGP compared to the placebo group from baseline to month 3 ($p<0.001$) and 6 ($p<0.001$). In agreement, repeated measures analysis showed a significant time × treatment interaction effect for AGP on the FAS score ($F=13.029$; $\eta_p^2=0.083$; $P<0.001$).There was no significant between-group difference based on temperature, O2 saturation, presence of cough, productive cough, or diarrhea, and severity of headache and musculoskeletal pain at baseline or discharge.Finally, data showed that patients in the AGP group had significantly lower levels of C-reactive protein (CRP) at discharge ($p=0.021$).No severe or unforeseen adverse event was reported.

Conclusion: The current study found AGP mixture is effective in reducing fatigue severity in the long-term but not in the short-term, with no side effects. Further studies with larger sample sizes are required to determine the effects of AGP mixture in chronic fatigue post-COVID-19.

Keywords: *COVID-19; Fatigue; almond porridge; grape extract; pea syrup*

Ali Ghandaali[1], Mozhgan Mehri Ardestani[1], Saeid Hadi[2], Fatemeh Nejatbakhsh[3,4], Vahid Hadi[2], Mohammad Hassan Kazemi-Galougahi[5], Seyed Mahdi Mirghazanfari[6]

[1]Department of Persian Medicine. Faculty of Medicine, AJA University of Medical Sciences, Tehran, Iran.
[2]Department of Health, School of Medicine, AJA University of Medical Sciences, Tehran, Iran.
[3]Department of Traditional Medicine, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran.
[4]Food Microbiology Research Center, Tehran University of Medical Sciences, Tehran, Iran.
[5] Department of Social Medicine, Faculty of Medicine, Aja University of Medical Sciences, Tehran, Iran
[6]Department of physiology and Iranian Medicine, School of Medicine, AJA university of Medical Sciences, Tehran, Iran.
Corresponding author: Seyed Mahdi Mirghazanfari, Department of physiology and Iranian Medicine, School of Medicine, AJA university of Medical Sciences, Tehran, Iran.
Email: smmirghazanfari@gmail.com
Tel: +989122765221

Introduction

The coronavirus disease 2019 (COVID-19) pandemic is a significant public health emergency that affects a sizable segment of people and causes a variety of symptoms. Severe fatigue is one of the symptoms that are most common during acute COVID-19, which can last for up to 4 weeks after the infection starts (1-3). Symptoms of COVID-19 are known as Post-Acute Sequelae of SARS-CoV-2 Infection (PASC), Post-COVID-19 Syndrome, Long COVID, or Long-Haul COVID when they last longer than 12 weeks without being explained by an alternative diagnosis (4). Severe fatigue was rapidly suspected to be one of the pandemic's most frequent long-term side effects (5-7). In fact, 17–63% of patients experience fatigue 6–12 months after COVID-19 in patients who needed hospitalization after acute COVID-19 and in patients who were not hospitalized after COVID-19 (8-11). Around 20% of patients with different coronavirus infections, such as Extreme Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and other infectious disorders including Q-fever, have chronic post-infectious severe fatigue,

according to research (12-14). With hundreds of millions of confirmed COVID-19 cases worldwide (15), extreme fatigue following COVID-19 may impact millions of people, resulting in long-term health issues, disability, substantial disease-related expenses, and decreased quality of life. This necessitates investigation into preventive or therapeutic interventions for post-COVID-19 fatigue (16).

The most plausible explanation for fatigue during the acute stage of an infectious illness is an adaptive response to the infection (17). Most people totally recover once the illness has subsided. However, a small percentage of patients still experience fatigue. Severe fatigue that lasts longer than six months after infection and negatively affects a patient's functionality, quality of life, and involvement in society is known as post-infectious chronic fatigue (18). It is unknown what causes fatigue to persist, although a number of processes, such as cytokine dysregulation or neuro-inflammation, have been proposed (19, 20). It has been proposed that COVID-19-related fatigue might be associated with imbalancedinflammatory conditions and increased oxidative stress (21). Thus, interventions leading to decreased inflammation and oxidative stress are potential areas of interest to treat or prevent COVID-19-related fatigue. From the beginning of the COVID-19 pandemic, complementary and alternative medicine interventions have been used as alternative options to treat symptoms of COVID-19 (22). Food and vegetable ingredients, such as almond, grape, and pea, have vast antioxidant and anti-inflammatory properties. In this regard, Pownall et al. have demonstrated that enzymatic protein hydrolysate fractions of pea seed (Pisum sativum L.) have strong antioxidant properties (23). Moreover, research has exhibited strong free radical-scavenging and antioxidant activities for different species of grape, which could be used as healthy sources of natural antioxidants to prevent several disorders induced by oxidative stress, like cardiovascular disease and cancer (24). Furthermore, it has been demonstrated that polyphenols in almond skins or seed modulates plasma biomarkers of oxidative stress in healthy humans (25). Therefore, these alternative interventions might be beneficial for treating fatigue after COVID-19.

Although previous studies have focused on the treatment of chronic fatigue post-COVID-19 months after disease onset, preventive interventions in the acute phase of COVID-19 might be a more desirable option, leading to both decreased levels of fatigue immediately after disease onset and decreased chances of developing chronic fatigue in long-term. The primary objective of this trial is to investigate whether a mixture of almond porridge, grape extract, and pea syrup (AGP mixture) leads to a lower mean fatigue severity score during hospitalization and at 3 and 6 months follow-up as compared to routine care. Secondary goals are to determine whether treatment with AGP mixture results in improved COVID-19 symptoms, balanced laboratory parameters, and decreased hospital stay.

Methods

Trial Design and Settings

This is a single-center, randomized, double-blind, placebo-controlled clinical trial carried out on inpatients with COVID-19 at AJA Hospital (AJA University of Medical Sciences, Tehran, Iran) from Marchto December2022. Written informed consent was obtained from all patients, and thepatients were informed of their rights to withdraw from the studyat any time without giving any reason or any interruption in their health services. Eligible patients were randomly allocated into two parallel AGP and placebo groups. Patients were assessed at baseline, discharge, month 3, and month 6. This trial was conducted in agreement with the ethical principles in the Declaration of Helsinki and its later amendments(26). The protocol of the study was approved by the institutional review board (IRB) of AJA University of Medical Sciences (IR.AJAUMS.REC.1400.322). This trial is registered in the Iranian Registry of Clinical Trials with registration code: **IRCT20220228054150N1**.

Participants

This trial was carried out on individuals aged 18–65 years who had a confirmed diagnosis of COVID-19, were hospitalized for treatment, and had a score >30 on the Fatigue Assessment Scale (FAS). Included patients had positive results on the nasopharyngeal polymerase chain reaction (PCR) test for SARS-COV-2 and were presented with fever (T>38) and at least one of the following symptoms: 1) cough, 2) respiratory rate>24, 3) headache or myalgia, 4) anosmia or hyposmia. The exclusion criteria of the study were: 1) intubation or intensive care unit (ICU) hospitalization, 2) respiratory distress, 3) hospital stay<2 days, 4) severe nausea or vomiting, 5) pregnancy or lactation, 6) smoking, 7) using any other herbal medicine within past 3 months, 8) insulin-dependent diabetes, liver disease or congestive heart failure.

Interventions

Both AGP and placebo groups received routine care. A mixture of almond porridge and grape extract (containing 25 grams of almonds and 8 ccs of grape extract) was given to the patient in a disposable container in the snack at 10 o'clock during the hospital stay. Also, in the snack at 16 o'clock, chickpeas (containing 30 grams of chickpeas) were given in a disposable container during the hospital stay. The placebo was similar to the intervention in terms of shape, taste, color, and smell and was given to the placebo group at 10 and 16 o'clock. No other medication was allowed for trial participants.

Outcomes and Tools

Using FAS, fatigue severity scoreswere assessed at baseline, at discharge, and at follow-up sessions at month 3 and 6. The FAS is a 10-item fatigue questionnaire to evaluate fatigue. Five questions represent physical fatigue, and 5 questions reflect mental fatigue. The raters were experienced clinicians with an inter-reliability of >90%.Also, at baseline and discharge, blood samples were taken from patients, and laboratory parameters, including complete blood count and inflammatory markers were measured. Moreover, the clinical symptoms of patients were recorded.

FAS score was the primary outcome measure of the trial, while clinical symptomsandlaboratory markers comprised the secondary outcome measures.

Adverse Events

Adverse events were reported by a trained rater or patients during the study. All patients were encouraged to inform their physicians about any unexpected adverse events at any time through a 24-hour accessible phone line. Open-ended questioning was conducted about any probable side effects at each session by the investigator.

Sample Size

We considered an effect size of 0.23 for the FAS scoreto calculatethe sample size based on a pilot study. The total sample size of the trial was 160patients (80 in each arm), considering a power of 80%, a 2-sided significance level of5%, and an attrition rate of 20%.

Randomizationand Blinding

The patients were randomized into groups of AGP and placebo in a 1:1ratio. A specific random code was allocated to each participant. The primary investigator of the studyused permuted block randomization with blocks of size 4 to conduct the randomization and allocation. The allocations were confidential and were exposed at the end of the study. Placebo mixtures were indistinguishable from AGP. Randomizations, administration, assessment, data entry, and statistical analysis were conducted by separate investigatorswho were blinded to allocations.

Statistical Methods

The Statistical Package of Social Science Software (SPSS version 20, IBMCompany, USA) was applied to analyze the data. Continuous variables are shown as mean (standard deviation), and categorical variables are shown as frequency (percentage). Independent T-test was used to compare the FAS scores from baseline to the study endpoint between AGP and placebo groups. The Likert variables(i.e., headache) were compared between groups using Mann–Whitney U test. The categorical variables were compared using the Chi-square test or Fisher's exact test. The general linear model (GLM) repeated measures analysis was carried out to assess time × treatment effects for FAS scores between the two groups, assuming the study groups (AGP versus placebo) as the between-subject variable (treatment) and the scores at baseline and follow-up sessions as the within-subject factor (time). Greenhouse-Geisser correction for degrees of freedom was stated if Mauchly's test of sphericity was significant. Partial eta squared (η_p^2) was considered as the effect size(27).A P-value of <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of Participants

A total of 225 inpatients with COVID-19 were screened against the inclusion/exclusion criteria. Ninety-five patients were excluded, and the remaining 160 patients were randomized to two groups of AGP or placebo mixtures in a 1:1 ratio (Fig. 1). Nine patients in the AGP group and five patients in the placebo group were transferred to ICU in the course of hospitalization and were excluded. After discharge, no patient died or withdrew from the study. Eventually, 75 patients in the AGP group and 71 patients in the placebo group completed the 6-month course of the trial. The baseline demographic and clinicalcharacteristics of the participants are shown in Table 1. The patients in AGP and placebo groups were comparable based on age, sex, and hospital stay.

Outcomes

Primary outcome measure

FAS score

FAS scores of AGP and placebo groups at baseline, discharge and two follow-up visits are demonstrated in Table 2. Patients in two trial groups were comparable based on baseline and discharge FAS total scores. However, the AGP group showed significantly lower FASscores at month 3 ($p<0.001$) and month 6 ($p<0.001$) visits. FAS score showed a significantly greater decline in the AGP compared to the placebo group from baseline to month 3($p<0.001$) and 6($p<0.001$) (Fig. 2). In agreement, GLM repeated measures analysis showed significant time × treatment interaction effect for AGP on the FAS score ($F=13.029$; $\eta_p^2=0.083$; $P<0.001$).

Secondary outcome measures

Signs and symptoms

As shown in Table 3, there was no significant between-group difference based on temperature, O2 saturation, presence of cough, productive cough, or diarrhea, and severity of headache and musculoskeletal pain at baseline or discharge.

Laboratory parameters

Laboratory parameters were measured at baseline and discharge. Patients in two trial groups were comparable based on baseline and discharge levels of all laboratory parameters, including ESR, WBC, hemoglobin, platelet, AST, ALT, creatinine, LDH, albumin. However, data showed that patients in the AGP group had significantly lower levels of CRP at discharge ($p=0.021$).

Clinical Complications and Side Effects

No severe or unforeseen adverse event was reported. No participant was excluded for this reason.

Discussion

This study is the first randomized controlled trial assessing the beneficial effects of almond porridge, grape extract, and pea syrup in improving fatigue severity and clinical symptoms in patients with COVID-19 with high levels of fatigue. FAS scores were selected as the primary outcome measure, and COVID-19 symptoms, hospital stay, and laboratory markers were determined as the secondary outcome measures. We demonstrated that adjuvant pharmacotherapy with AGP mixture leads to a considerable reduction in FAS score in the long-term. Although the AGP mixture led to higher reduction of FAS score in short-term (immediately after discharge), it did not reach statistical significance. In addition, we demonstrated that treatment with AGP mixture leads to decreased inflammatory conditions as represented by decreased CRP. However, treatment with AGP did not show any significant effect on other laboratory markers or on clinical symptoms of COVID-19, such as headache, myalgia, and productive or non-productive cough. Of note, it should be considered that both the intervention and the placebo groups had significant improvements in FAS scores over the course of the study, confirming the spontaneous reduction of fatigue with routine care.

Although no study has investigated the effects of almond porridge, grape extract, and pea syrup in patients with COVID-19, there are several studies showing the beneficial effects of herbal and conventional medicine in patients with COVID-19 (28). In regard to fatigue, five controlled trials with a total of 242 participants reported rates of remission from fatigue after treatment with herbal medicine, including Jinhua Qinggan granule (29), Lianhua Qingke granule (30), Keguan-1 (31), Xuanfei Baidu Decoction (32), and Jinyinhua Oral Liquid (33). Meta-analysis of their data demonstrated that combined herbal medicine and standard regimen leads to a significantly greater effect in reducing fatigue compared with alone standard treatment (28). We, here, showed that Iranian herbal medicine can lead to reduced fatigue after COVID-19 in the long run.

Post-infection fatigue is frequently observed in a number of viral and non-viral illness situations (34). As was already established, post-disease fatigue affects a large number of COVID-19 patients. According to Rudroff et al. (35), coronavirus disease-related fatigue is characterized by a decline in physical or mental function as a result of effects on central, psychological, or environmental factors, and these factors depend on the task a person performs, his or her environmental conditions, and the person's physical and mental capacity. The interplay of central, psychological, or environmental components with conditional dependent factors also affects fatigue (36).

According to observational studies, the symptoms of coronavirus disease linger for around 21 days after the sickness starts, and in some patients, they last for more than 4 months. According to studies, anosmia and shortness of breath are the symptoms that are most frequently reported for more than three weeks. Although the cause and pathophysiology of fatigue following COVID19 are not fully understood, it is hypothesized that both central and peripheral pathways contribute to its development. The cytokinin storm, which causes anorexia and inflammations before causing muscular atrophy, weakness, and exhaustion, may be to blame for this fatigue. Additionally, when the immune system is active, infection raises baseline energy consumption (37). At many cases of fatigue syndrome, especially in the beginning, a high release of cytokines seems to be associated with the T-lymphocyte response. The coronavirus disease-induced immune response resembles the traditional paradigm (38). IL-6, TNF, and IL-1 are only a few examples of the proinflammatory chemokines and cytokines that are increased due to SARS-CoV-2 (39). It has been proposed that the novel coronavirus functions as a physiological stressor when combined with fatigue syndrome stressors. The stress center of the brain, a cluster of neuronal cells in the paraventricular nucleus (PVN) of the hypothalamus, may be a significant target of the virus. The PVN is a group of nuclei and neural circuits that respond to a variety of physiological stressors and play a significant role in the neural control of endocrine and autonomic stress responses. The PVN functions as a stressor, absorbing, and processing factor. Infections, pain, mental discomfort, and changes in the cardiovascular system brought on by physical exercise are only a few of the causes of incoming stress signals reaching the PVN of the hypothalamus through a variety of humoral and neurological routes (39). Additionally, there is mounting evidence that severely harmful autoantibodies may result in corona infections. In individuals with COVID-19, these autoantibodies may also play a significant role in the symptoms of chronic fatigue. Evidence suggests that oxidative stress and inflammation might aid the developmentof fatigue after COVID-19. Thus, replacing antioxidants and vitamins might be an effective way to lessen fatigue and disease's clinical symptoms.

We hypothesized that the observed clinical effect of the AGP mixture might be through modulating inflammatory or oxidative processes. There is a bulk of evidence demonstrating the antioxidant and anti-inflammatory effects of AGP mixture (almond porridge, grape extract, and pea syrup). Almonds have been reported to be rich sources of minerals and vitamins, particularly calcium, zinc, and phosphor (40). Almonds also are sources of phenolic compounds with strong antioxidant

activities (40). Moreover, Nile et al. (41) demonstrated that the phenolic and flavonoid contents in extracts of grape skins and pulps showed statistically significant correlations with the free radical scavenging activity. Also, pea is full of antioxidants, including tannin, phenolics, and other phytochemicals, which are non-nutritive elements present in pea (42). Thus, the mixture of these ingredients might lead to clinical effects that we observed in this study.

Our study has strengths and limitations. Our study has an acceptable number of participants and relatively long follow-ups. Moreover, our study is focused on the acute phase after COVID-19 infection. Previous studies have focused on the treatment of chronic fatigue post-COVID-19 months after disease onset, while preventive interventions in the acute phase of COVID-19 might be a more desirable option, leading to both decreased levels of fatigue immediately after disease onset and decreased chances of developing chronic fatigue in long-term. However, we did not assess the effect of AGP mixture on chronic fatigue after COVID-19, and further studies are required in this regard. Finally, we did not assess the individual effects of AGP mixture components.

Conclusion

In conclusion, this is the first randomized controlled trial assessing the beneficial effects of almond porridge, grape extract, and pea syrup in improving fatigue severity and clinical symptoms in patients with COVID-19 with high levels of fatigue. The current study found AGP mixture is effective in reducing fatigue severity in the long-term but not in the short-term, with no side effects. Further studies with larger sample sizes are required to determine the effects of AGP mixture in chronic fatigue post-COVID-19.

References

1. Covid W. Dashboard.
2. Bennett S, Tafuro J, Mayer J, Darlington D, Wong CW, Muntean EA, et al. Clinical features and outcomes of adults with coronavirus disease 2019: A systematic review and pooled analysis of the literature. Int J Clin Pract. 2021;75(3):e13725.
3. Hasani H, Mardi S, Shakerian S, Taherzadeh-Ghahfarokhi N, Mardi P. The novel coronavirus disease (COVID-19): a PRISMA systematic review and meta-analysis of clinical and paraclinical characteristics. BioMed Research International. 2020;2020.
4. Salamanna F, Veronesi F, Martini L, Landini MP, Fini M. Post-COVID-19 Syndrome: The Persistent Symptoms at the Post-viral Stage of the Disease. A Systematic Review of the Current Data. Front Med (Lausanne). 2021;8:653516.
5. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. The Lancet Psychiatry. 2020;7(7):611-27.
6. Perrin R, Riste L, Hann M, Walther A, Mukherjee A, Heald A. Into the looking glass: Post-viral syndrome post COVID-19. Medical hypotheses. 2020;144:110055.
7. Islam MF, Cotler J, Jason LA. Post-viral fatigue and COVID-19: lessons from past epidemics. Fatigue: Biomedicine, Health & Behavior. 2020;8(2):61-9.
8. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. The Lancet. 2021;397(10270):220-32.
9. Simani L, Ramezani M, Darazam IA, Sagharichi M, Aalipour MA, Ghorbani F, et al. Prevalence and correlates of chronic fatigue syndrome and post-traumatic stress disorder after the outbreak of the COVID-19. Journal of neurovirology. 2021;27(1):154-9.
10. Goërtz YM, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FV, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ open research. 2020;6(4).
11. Boscolo-Rizzo P, Guida F, Polesel J, Marcuzzo AV, Capriotti V, D'Alessandro A, et al. Sequelae in adults at 12 months after mild-to-moderate coronavirus disease 2019 (COVID-19). Int Forum Allergy Rhinol. 2021;11(12):1685-8.
12. Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. BMC Neurol. 2011;11:37.
13. Lam MH-B, Wing Y-K, Yu MW-M, Leung C-M, Ma RC, Kong AP, et al. Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. Archives of internal medicine. 2009;169(22):2142-7.
14. Morroy G, Keijmel SP, Delsing CE, Bleijenberg G, Langendam M, Timen A, et al. Fatigue following acute Q-fever: a systematic literature review. PloS one. 2016;11(5):e0155884.
15. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. The Lancet infectious diseases. 2020;20(5):533-4.
16. Kuut TA, Müller F, Aldenkamp A, Assmann-Schuilwerve E, Braamse A, Geerlings SE, et al. A randomised controlled trial testing the efficacy of Fit after COVID, a cognitive behavioural therapy targeting severe post-infectious fatigue following COVID-19 (ReCOVer): study protocol. Trials. 2021;22(1):867.
17. Hulme K, Hudson JL, Rojczyk P, Little P, Moss-Morris R. Biopsychosocial risk factors of persistent fatigue

after acute infection: a systematic review to inform interventions. Journal of psychosomatic research. 2017;99:120-9.
18. Korenromp IH, Meeus M, Bleijenbergh G. Nederlandstalige definitie van chronische vermoeidheid. NEDERLANDSCH TIJDSCHRIFT VOOR GENEESKUNDE. 2012;156(16).
19. Nakatomi Y, Mizuno K, Ishii A, Wada Y, Tanaka M, Tazawa S, et al. Neuroinflammation in patients with chronic fatigue syndrome/myalgic encephalomyelitis: an 11C-(R)-PK11195 PET study. Journal of Nuclear Medicine. 2014;55(6):945-50.
20. Rasa S, Nora-Krukle Z, Henning N, Eliassen E, Shikova E, Harrer T, et al. Chronic viral infections in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Journal of translational medicine. 2018;16(1):1-25.
21. Mackay A. A Paradigm for Post-Covid-19 Fatigue Syndrome Analogous to ME/CFS. Front Neurol. 2021;12:701419.
22. Jeon S-R, Kang JW, Ang L, Lee HW, Lee MS, Kim T-H. Complementary and alternative medicine (CAM) interventions for COVID-19: An overview of systematic reviews. Integrative Medicine Research. 2022;11(3):100842.
23. Pownall TL, Udenigwe CC, Aluko RE. Amino acid composition and antioxidant properties of pea seed (Pisum sativum L.) enzymatic protein hydrolysate fractions. J Agric Food Chem. 2010;58(8):4712-8.
24. Liu Q, Tang GY, Zhao CN, Feng XL, Xu XY, Cao SY, et al. Comparison of Antioxidant Activities of Different Grape Varieties. Molecules. 2018;23(10).
25. Chen CO, Milbury PE, Blumberg JB. Polyphenols in Almond Skins after Blanching Modulate Plasma Biomarkers of Oxidative Stress in Healthy Humans. Antioxidants (Basel). 2019;8(4).
26. Carlson RV, Boyd KM, Webb DJ. The revision of the Declaration of Helsinki: past, present and future. Br J Clin Pharmacol. 2004;57(6):695-713.
27. Jasbi M, Sadeghi Bahmani D, Karami G, Omidbeygi M, Peyravi M, Panahi A, et al. Influence of adjuvant mindfulness-based cognitive therapy (MBCT) on symptoms of post-traumatic stress disorder (PTSD) in veterans – results from a randomized control study. Cognitive Behaviour Therapy. 2018;47(5):431-46.
28. Ang L, Song E, Hu XY, Lee HW, Chen Y, Lee MS. Herbal Medicine Intervention for the Treatment of COVID-19: A Living Systematic Review and Cumulative Meta-Analysis. Front Pharmacol. 2022;13:906764.
29. Duan C, Xia W, Zheng C, Sun G, Li Z, Li Q. Clinical observation on Jinhua Qinggan granule combined with conventional western medicine therapy in treating mild cases of coronavirus disease 2019. J Tradit Chin Med. 2020;61(17):1473-7.
30. SUN H-m, Xu F, ZHANG L, WEI C, CHEN J-y, WANG Q-x, et al. Study on clinical efficacy of Lianhua Qingke granule in treatment of mild and ordinary COVID-19. Chinese Journal of Experimental Traditional Medical Formulae. 2020:29-34.
31. Wang J-b, Wang Z-x, Jing J, Zhao P, Dong J-h, Zhou Y-f, et al. Exploring an Integrative Therapy for Treating COVID-19: A Randomized Controlled Trial. Chinese Journal of Integrative Medicine. 2020;26(9):648-55.
32. Xiong W-z, Wang G, Du J, Ai W. Efficacy of herbal medicine (Xuanfei Baidu decoction) combined with conventional drug in treating COVID-19: A pilot randomized clinical trial. Integrative medicine research. 2020;9(3):100489.
33. Zhang Y, Lei L, Xu Y, Wei D, Hu F. Clinical efficacy of Jinyinhua oral liquid in the treatment of 80 patients with coronavirus disease 2019. China Pharmaceuticals. 2020;29(9):23-6.
34. Poenaru S, Abdallah SJ, Corrales-Medina V, Cowan J. COVID-19 and post-infectious myalgic encephalomyelitis/chronic fatigue syndrome: a narrative review. Therapeutic advances in infectious disease. 2021;8:20499361211009385.
35. Rudroff T, Fietsam AC, Deters JR, Bryant AD, Kamholz J. Post-COVID-19 fatigue: potential contributing factors. Brain sciences. 2020;10(12):1012.
36. Vaziri-harami R, Delkash P. Can l-carnitine reduce post-COVID-19 fatigue? Annals of Medicine and Surgery. 2022;73:103145.
37. Virgens IP, Santana NM, Lima SC, Fayh AP. Can COVID-19 be a risk for cachexia for patients during intensive care? Narrative review and nutritional recommendations. British Journal of Nutrition. 2021;126(4):552-60.
38. Gaber T. Assessment and management of post-COVID fatigue. Progress in Neurology and Psychiatry. 2021;25(1):36-9.
39. Mackay A. A paradigm for post-Covid-19 fatigue syndrome analogous to ME/CFS. Frontiers in Neurology. 2021:1334.
40. HOSSEINZADEH M, MOAYEDI A, Chodar Moghadas H, REZAEI K. Nutritional, Anti-Nutritional, and Antioxidant Properties of Several Wild Almond Species from Iran. JOURNAL OF AGRICULTURAL SCIENCE AND TECHNOLOGY (JAST). 2019;21(2 #M00521):-.
41. Nile SH, Kim SH, Ko EY, Park SW. Polyphenolic Contents and Antioxidant Properties of Different Grape (V. vinifera, V. labrusca, and V. hybrid) Cultivars. BioMed Research International. 2013;2013:718065.

42. Kumari T, Deka SC. Potential health benefits of garden pea seeds and pods: A review. Legume Science. 2021;3(2):e82.

Table 1. Baseline characteristics of the patients in two trial groups

	Intervention group (n=75)	**Placebo group (n=71)**	**P-value**
Age [years; mean (SD)]	48.05 (13.2)	47.58 (14.5)	0.836[a]
Sex [n (%)]			0.828[b]
• **Male**	53 (70.7%)	49 (69%)	
• **Female**	22 (29.3%)	22 (31%)	
Hospital stay [days; mean (SD)]	6.59 (1.2)	7.04 (1.6)	0.142[c]

P-value of <0.05 was considered statistically significant.
SD: standard deviation
[a] Independent T-test
[b] Chi-square test
[c] Mann–Whitney U test

Table 2. Comparison of FAS scores between the two trial groups

FAS	Intervention group (n=75)	Placebo group (n=71)	P-value
Baseline	40.43 (4.16)	40.37 (4.18)	0.930[a]
After discharge	31.71 (3.00)	32.58 (3.74)	0.081[b]
3 months after discharge	20.80 (3.70)	23.86 (3.62)	**<0.001**[b]
6 months after discharge	14.65 (3.19)	17.63 (3.80)	**<0.001**[a]
Change from baseline to discharge	8.72 (4.29)	7.79 (3.24)	0.265[b]
Change from baseline to month 3	19.63 (4.50)	16.51 (3.78)	**<0.001**[a]
Change from baseline to month 6	25.77 (4.58)	22.73 (5.21)	**<0.001**[a]

P-value of < 0.05 was considered statistically significant; Data are shown as mean (standard deviation).

[a] Independent T-test

[b] Mann–Whitney U test

Table 3. Comparison vital signs and clinical symptoms in trial groups

	Time points/periods	Intervention group (n=75)	Placebo group (n=71)	P-value
Temperature	Baseline	38.07 (0.47)	38.05 (0.49)	0.789 [a]
	Discharge	37.31 (0.11)	37.32 (0.14)	0.977 [c]
O_2	Baseline	89.59 (2.61)	90.08 (2.95)	0.281 [a]
	Discharge	96.28 (1.28)	96.62 (1.42)	0.227 [c]
Cough	Baseline	75 (100%)	67 (94.4%)	0.053[d]
	Discharge	65 (86.7%)	63 (88.7%)	0.704 [b]
	Discharge in days	6.20 (1.34)	6.21 (2.07)	0.213 [c]
Productive cough	Baseline	51 (68.0%)	48 (67.6%)	0.959 [b]
	Discharge	8 (8.0%)	9 (12.7%)	0.351 [b]
	Discharge in days	1.89 (2.11)	2.15 (2.32)	0.602 [c]
Diarrhea	Baseline	27 (36%)	25 (35.2%)	0.921 [b]
	Discharge	20 (26.7%)	17 (23.9%)	0.705 [b]
	Discharge in days	1.21 (2.01)	1.85 (3.02)	0.670 [c]
Headache	Baseline	1.39 (1.48)	1.06 (1.16)	0.278 [c]
	Discharge	0.29 (0.49)	0.30 (0.49)	0.980 [c]
	Discharge in days	1.47 (1.99)	2.14 (2.65)	0.375 [c]
Musculoskeletal pain	Baseline	3.33 (1.34)	3.13 (1.45)	0.406 [c]
	Discharge	2.00 (0.97)	1.85 (1.15)	0.454 [c]
	Discharge in days	6.24 (1.28)	6.68 (1.61)	0.167 [c]

P-value of < 0.05 was considered statistically significant; Data are shown as mean (standard deviation) or frequency (%).

[a] Independent T-test

[b] Chi-square test

[c] Mann–Whitney U test

[d] Fisher's exact test

Table 4. Comparison of laboratory parameters between the two trial groups

	Time points/periods	Intervention group (n=75)	Placebo group (n=71)	P-value
CRP (mg/l)	Baseline	57.07 (38.13)	56.32 (38.36)	0.481[b]
	Discharge	12.69 (3.38)	15.04 (6.71)	**0.021**[a]
ESR (mm/h)	Baseline	52.27 (13.60)	52.80 (13.0.)	0.809[a]
	Discharge	22.28 (4.47)	22.51 (4.63)	0.764[a]
WBC (n/ul)	Baseline	7610.7 (1834.1)	7747.9 (1597.8)	0.695[a]
	Discharge	5236.0 (804.1)	5287.3 (770.3)	0.582[b]
Neutrophil (%)	Baseline	62.24 (5.04)	61.37 (4.80)	0.286[a]
	Discharge	62.20 (3.70)	61.37 (3.59)	0.170[a]
Lymphocyte (%)	Baseline	31.64 (7.55)	31.10 (7.59)	0.623[b]
	Discharge	30.04 (4.23)	30.17 (4.34)	0.783[b]
Hemoglobin (g/dl)	Baseline	15.50 (0.59)	15.17 (0.61)	0.776[a]
	Discharge	15.22 (0.67)	15.18 (0.68)	0.697[a]
Platelet (n/ul)	Baseline	205600 (53619)	200282 (44295)	0.920[b]
	Discharge	235400 (49455)	228451 (47007)	0.386[a]
AST (u/l)	Baseline	30.09 (11.95)	30.56 (11.34)	0.808[a]
	Discharge	27.07 (9.70)	27.51 (9.86)	0.786[a]
ALT (u/l)	Baseline	29.60 (9.61)	29.70 (10.07)	0.949[a]
	Discharge	26.83 (9.60)	26.45 (9.79)	0.870[a]
Creatinine (mg/dl)	Baseline	1.20 (0.54)	1.19 (0.48)	0.641[b]
	Discharge	1.08 (0.25)	1.07 (0.25)	0.842[b]
LDH (iu/l)	Baseline	500.80 (357.27)	497.39 (354.11)	0.810[b]
	Discharge	167.73 (34.08)	164.58 (34.69)	0.431[b]
Albumin (g/dl)	Baseline	4.61 (0.44)	4.61 (0.46)	0.993[a]
	Discharge	4.65 (0.45)	4.66 (0.46)	0.909[a]

P-value of < 0.05 was considered statistically significant; Data are shown as mean (standard deviation).

[a] Independent T-test

[b] Mann–Whitney U test

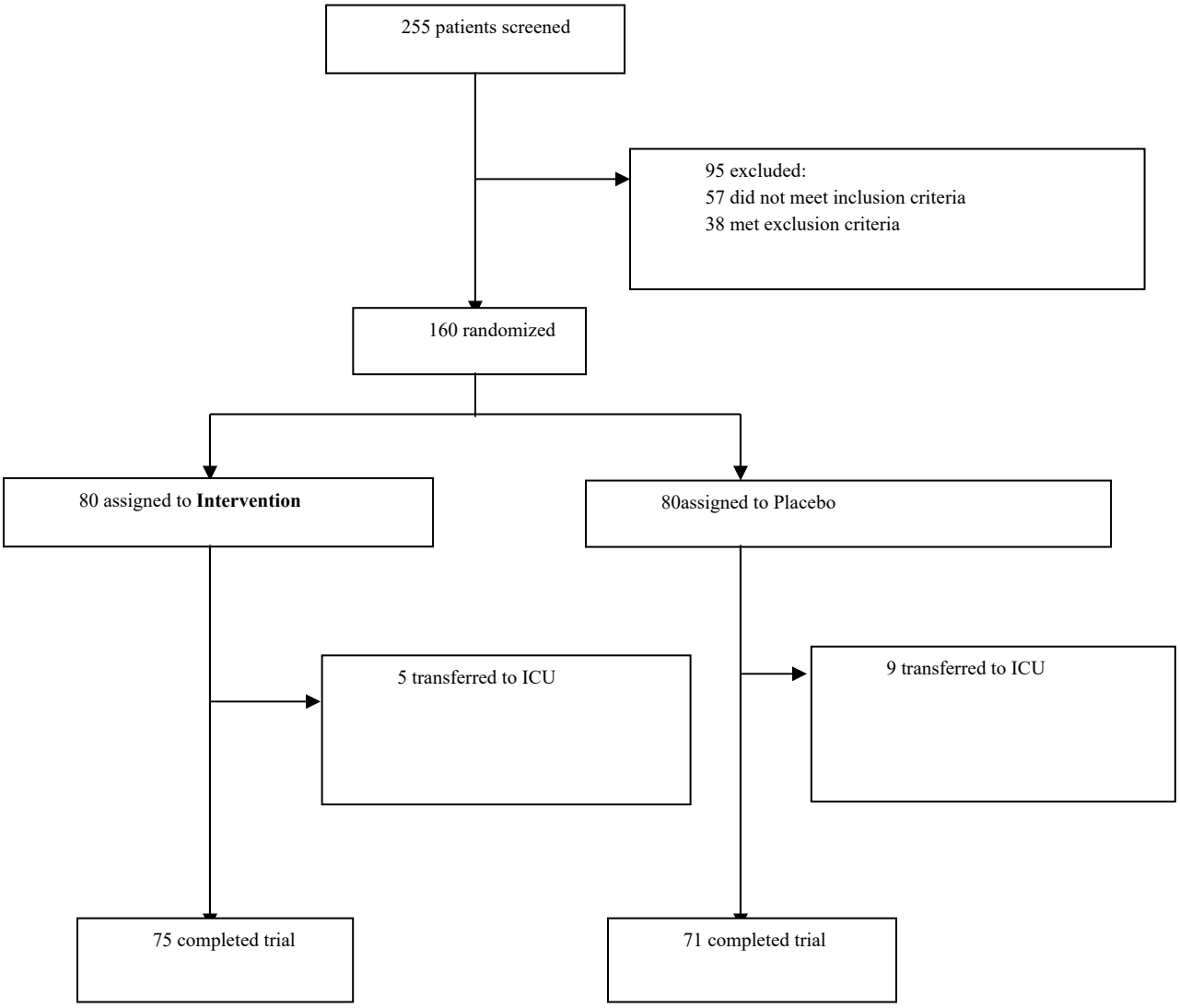

Figure 1. Flow diagram of the study

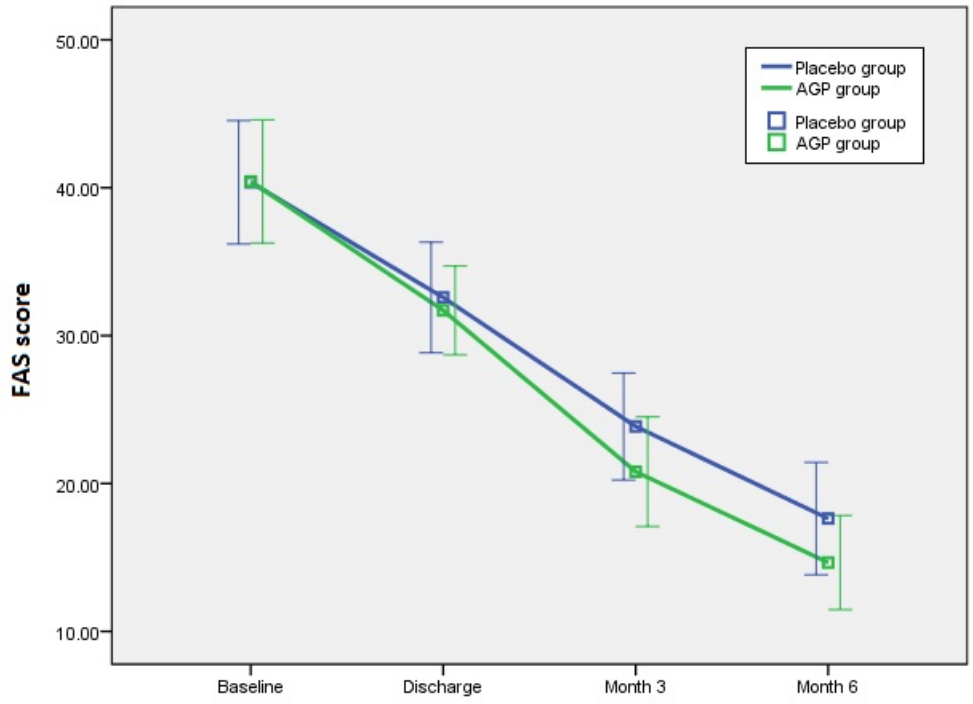

Figure 2. Comparison of FAS scores [mean (standard deviation)] between the AGP and placebo groups

.