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RESEARCH ARTICLE

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Efficacy of Persian medicine herbal formulations (capsules and decoction) compared to standard care in patients with COVID-19, a multicenter open-labeled, randomized, controlled clinical trial

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Persian medicine has recommended clinical experiences and proper herbal remedies for prevention and treatment of microbial infections and respiratory diseases. An open-label, randomized, controlled, multicenter trial was conducted at five hospitals in Tehran and Isfahan provinces of Iran on 358 hospitalized adult patients. A total of 174 patients received standard care and 184 received herbal remedies (polyherbal decoction every 8 hr and two herbal capsules every 12 hr) plus standard care for 7 days. The primary clinical endpoint was the duration of hospital stay, and secondary outcomes were clinical improvement of symptoms based on self-assessment questionnaire. Results demonstrated that these natural decoction and capsules treatment plus routine care significantly decreased duration of hospital dyspnea (3.291 day vs. 6.468 days), accelerated clinical improvement, and decreased symptoms such as dry cough, dyspnea, muscle pain, headache, fatigue, anorexia, chills, runny nose, sputum cough, and vertigo in the treatment group compared with standard-care group. Significant effects of these polyherbal formulations on improving the symptoms of COVID-19 could be incredibly promising for managing this pandemic with acceptable tolerability.

KEYWORDS
coronavirus, COVID-19, herbal medicine, Persian medicine, phytotherapy

1 | INTRODUCTION

Since December 2019, a novel coronavirus disease (COVID-19) has caused outbreak of pneumonia in Wuhan, Hubei province, China (Guan et al., 2020). The rapid spread of COVID-19 was identified as a pandemic and public health emergency of international concern (PHEIC) by the World Health Organization (WHO, 2020) on March 11, 2020 (Huang, Wei, Hu, Wen, & Chen, 2020). Shi et al explained that bats are natural hosts of COVID-19, and full sequence of the COVID-19 genome in an infected patient is 96% similar to coronavirus in bats (Zhou et al., 2020). This strain of coronavirus also belonged to the same family of viruses that lead to Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) (Yang, Islam, Wang, Li, & Chen, 2020). The most common symptoms related to COVID-19 infection are fever, fatigue, loss of appetite, dry cough, and dyspnea, whereas less common symptoms are diarrhea, nausea, vomiting, rhinorrhea, chest pain, congestion, malaise, arthralgia, myalgia, headache, and sore throat (Abebe, Dejenie, Shiferaw, & Malik, 2020). Since the beginning of the spread, more than 57,639,631 confirmed COVID-19 patients have been identified and over 1,373,294 deaths have been globally reported (Up to 20 November) (https://covid19.who.int). The number of infected people in Iran has risen more than 828,377, and the number of related deaths has reached to more than 43,896 (up to 20 November) (https://behdasht.gov.ir/). The National Institutes of Health (2020) published guidelines on the management of patients with COVID-19, use of drugs such as chloroquine or hydroxychloroquine with or without azithromycin, Interleukin-6 inhibitors (sarilumab, tocilizumab, siltuximab), antiviral drugs (ivermectin), RNA-dependent RNA polymerase (remdesivir), corticosteroids (dexamethasone, methylprednisolone), and interferons (alfa, beta) (https://www.covid19treatmentguidelines.nih.gov/). Although, vaccines have been approved, there is not a final solution yet and US Food and Drug Administration (FDA), European Medicines Agency, and WHO are coordinating with industries and scientists to develop new drugs for COVID-19 (Huang et al., 2020). Natural products, their derivatives, and herbal extracts have potential activities in the viral infections therapy (Rosales-Mendoza, 2020). Significant antiviral activity of glycyrrhizin in *Glycyrrhiza glabra* against SARS coronavirus has been confirmed in various studies (Ahmad, Rehman, & Alkharfy, 2020). In this regard, usage of traditional, complementary, and alternative medicine to reach new approach for treatment is promising. Persian medicine is one of the oldest traditional medical system in the world that dates back to more than 7,000 years ago (Soleymani & Zargaran, 2018). Persian medicine has obtained important clinical experiences, as well as efficient and proper herbal formulations based on patients' symptoms on the prohibition and treatment of microbial infections and respiratory diseases (Walsh, 2021; Yingwen, 2021). Thus, it could be an alternative strategy to overcome viral transmission and prevention and treatment of COVID-19. Regarding this strategy, this multicenter open-labeled, randomized,

controlled, clinical study was designed to evaluate the efficacy of three herbal formulations (polyherbal decoction and two capsules) based on Persian medicine in hospitalized patients with COVID-19.

2 | MATERIALS AND METHODS

2.1 | Study design of clinical trial

This is a multicenter open-labeled, randomized, controlled clinical trial and five centers participated in this trial from March 2020 to July 2020 (Table 1). Patients with COVID-19 based on CT scan, oxygen saturation, and RT-PCR test as well as visit of an infectious disease specialist were enrolled in the study.

2.2 | Ethical issues

The protocol was approved by the Research Ethic Committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1399.024). Furthermore, it was registered at the Iranian Registry of Clinical Trials (IRCT) as IRCT20180712040449N2. All patients were aware about study protocols and signed the written informed consent.

2.3 | Formulation of natural remedies

To reach a formulation based on Persian medicine principals, all the monographs (about 1700 monographs) in the book of *Makhzan al-Advieh (the Storehouse of Medicaments)* were studied to find someones most likely to have been influential on COVID-19 based on Persian medicine principals (Aghili khorasani Shirazi, 2006). This book is a comprehensive Persian encyclopedia of *materia medica*, which was written in the 19th century. It is available in a database called Universal Natural Product Resource (UnaProd, 2020) (http://unaprod.com). Initially, a list of 101 diseases and symptoms that resembled COVID-19 infection were selected from Iranian traditional medicine General Ontology (IrGO, 2020) knowledge base (http://ir-go.net). Additionally, a list of 77 drug actions that included those effective on the selected diseases, or associated with reinforcement of the body, and tonifying of lung and its functions were prepared. Subsequently, monographs that were effective on one or more of the selected diseases and actions were extracted via text mining methods in R. Also, scientific names of these herbs were extracted from UnaProd and then searched in PubMed in combination with relevant keywords to find mechanism of actions according to current science. Finally, by meeting Persian medicine and current medical science, two capsules and one decoction were formulated for this study.

In the next step, adequate amount of several plants was purchased from a traditional herbal market in Tehran. These plants were identified and approved by botanists at the Herbarium Center of the School of Pharmacy, Tehran University of Medical Sciences (Table 2).

For preparation of capsule 1, first, rhizome of *Rheum palmatum* L., root of *G. glabra* L., and fruit peel of *Punica granatum* L. were mixed in a ratio of 0.5:1: 1 and pulverized with an electric mill. They were then extracted by maceration using 4 L of 70% of hydroethanolic solution (70:30 vol/vol ethanol: water) every 48 hr for three times. Then, the extract was separated and concentrated using rotary evaporator as much as possible. It was put in a vacuum oven until maximum drying. Afterward, lyophilized powder was prepared via a freeze dryer. The final product was mixed with starch (Merck, Germany) as filler and was packaged in 500-mg capsules. It was determined that every capsule has lyophilized powder of hydroalcoholic extract of one-gram raw material of *G. glabra* and *P. granatum* and 0.5-g raw material of *R. palmatum*, and the rest of each capsule was filled by starch as filler.

To prepare capsule 2, seed of *Nigella sativa* L. was powdered and packaged in 500-mg capsules.

Another remedy was prepared as a polyherbal decoction. Each package contains 7 sachets of a mixture of 10 g of each following powdered herbs (each sachet for one day): *Matricaria chamomilla* L., *Zataria multiflora* Boiss., *G. glabra* L., *Ziziphus jujuba* Mill., *Ficus carica* L., *Urtica dioica* L., *Althaea officinalis* L., and *Nepeta bracteata* Benth. Every day, one sachet was decocted for 1 hr in 900 cc of water and then filtered and used three times a day (each time about 300 cc).

TABLE 1 The centers and number of patients included in this study

Medical center	City, country	Number of patients
Ziaeian Hospital at Tehran University of Medical Sciences	Tehran, Iran	142
Shohada Gomnam Specialty and Subspecialty Hospital at Shahid Beheshti University of Medical Sciences	Tehran, Iran	36
Shohada Pakdasht Specialty and Subspecialty Hospital at Shahid Beheshti University of Medical Sciences	Tehran, Iran	43
Isabn-e-Maryam Hospital at Isfahan University of Medical Sciences,	Isfahan, Iran	99
Shahid Beheshti Hospital at Kashan University of Medical Sciences	Kashan, Iran	64

2.4 | Standardization of formulations

2.4.1 | Total phenolic content

Total phenolic content was determined via spectrophotometer based on the Folin Ciocalteu's method, and absorbance was evaluated against the prepared blank at 765 nm. The calibration curve was plotted using standard gallic acid. The total phenolic content was represented as mg gallic acid per gram of product (Marinova, Ribarova, & Atanassova, 2005).

TABLE 2 Medicinal plants used in three natural products of the study

Herbarium no.	Persian name	Scientific name	Part use
Capsule 1			
PMP-1226	*Rivand*	*Rheum palmatum* L.	Root
PMP-1227	*Shirin Bayan*	*Glycyrrhiza glabra* L.	Rhizome
PMP-1747	*Anar*	*Punica granatum* L.	Fruit peel
Capsule 2			
PMP-1744	*Siah Daneh*	*Nigella sativa* L.	Seed
Herbal decoction			
PMP-1397	*Babooneh*	*Matricaria chamomilla* L.	Flower
PMP-1396	*Avishan*	*Zataria multiflora* Boiss.	Aerial part
PMP-1227	*Shirin Bayan*	*G. glabra* L.	Root
PMP-1745	*Annab*	*Ziziphus jujuba* mill.	Fruit
PMP-1746	*Anjir*	*Ficus carica* L.	Fruit
PMP-1398	*Gazaneh*	*Urtica dioica* L.	Leaf
PMP-579	*Khatmi*	*Althaea officinalis* L.	Flower
PMP-1399	*Zoofa*	*Nepeta bracteata* Benth.	Flower

2.4.2 | Total flavonoid content

Total flavonoid content was estimated according to a colorimetric method, and absorbance was measured at 415 nm against blank. Quercetin was applied as standard to construct the standard curve. Total flavonoid content was expressed as mg quercetin equivalent per gram of product (Beketov, Pakhomov, & Nesterova, 2005).

2.4.3 | Standardization based on main markers via HPLC (high-performance liquid chromatography)

Also, a HPLC method was performed to standardize the formulations based on the content of some main markers in them. The selected markers are Ellagic acid (*P. granatum*) and Emodin (*R. palmatum*) in *Ahmadieh* capsule; Glycyrrhizin (*G. glabra*) and Apigenin (*M. chamomilla*) in decoction; and Thymoquinone (*N. sativa*) in Black Seed capsule.

HPLC analysis was performed using a KNAUER System (Berlin, Germany) equipped with a binary wellchrome K1001, a multiple UV–VIS wavelength PDA (2,800 model), the column configuration consisted of a KNAUER Eurospher RP C18 Column (5 μm, 4.6 × 250 mm I.D.). An isocratic elution with acetonitrile/water (45:55%vol/vol) at a flow rate of 1 ml/min was used for Ellagic acid, Emodin, and Glycyrrhizin, and UV monitoring was carried out at 252, 288 and 250 nm, respectively (Feng et al., 2017; Sabbioni, Ferranti, Bugamelli, Forti, & Raggi, 2006; Zhou, Wu, Li, Zhang, & Hu, 2008). For the qualification of thymoquinone using an isocratic mobile phase of water, methanol, and 2-propanol (50:45:5%vol/vol) at a flow rate of 0.8 ml/min and $\lambda_{max} = 254$ nm (Alemi, Sabouni, Sanjarian, Haghbeen, & Ansari, 2013). Also, an isocratic elution with water (with 0.2% phosphoric acid)/methanol (58:42%vol/vol) at a flow rate of 1 ml/min, and $\lambda_{max} = 339$ nm was used for apigenin. All solutions were filtered through a 0.45 mm filter prior to injection. The content of these markers is obtained based on standard samples and calibration curves for each one.

2.5 | Clinical evaluation

2.5.1 | Sample size

A Cox regression of the log hazard ratio on a covariate with a standard deviation of 0.4 based on a sample of 115 observations in each group achieves 80% power at a $\beta = .2$, $\alpha = .05$ significance level to detect a regression coefficient equal to $-.69$. The sample size for an anticipated event rate of 0.9 was estimated to be about 115 people. Finally, assuming loss to follow up 0.05, sample size was calculated 182 patients in each group.

2.5.2 | Patients and intervention

After explaining the study procedure to eligible patients and obtaining their informed consent, 358 hospitalized patients were selected (161 women and 197 men) who were positive on RT-PCR, had pneumonia confirmed by chest imaging and had an oxygen saturation of 93% or lower on room air.

The patients were randomly assigned into two groups of treatment and control by a third person through a computer program with block randomization method with four size blocks. The random sample number is generated and each patient will be assigned a number. As many as 174 patients received routine interventions according to the instructions of the Iranian Ministry of Health (2020) such as azithromycin, hydroxychloroquine, KALETRA® (lopinavir/ritonavir), and 184 received herbal remedies (decoction every 8 hr and capsules every 12 hr) plus routine interventions for 7 days. Demographic information of the patients is explained in more details at baseline in Table 3. Patients were assessed on days 0, 3, and 7 by physicians who were specialists in Persian medicine.

2.5.3 | Inclusion and exclusion criteria

Inclusion criteria are age range of 18 to 75 years in both genders with one or more of the following symptoms: acute respiratory disease (ARI); RR > 30; oxygen saturation < 93%; pulmonary infiltration in

TABLE 3 Characteristic details of the included patients at baseline

Characteristics	Treatment ($n =$)	Control ($n =$)	p value
Age, $M \pm SD$ (years)	48.72 ± 14.863	50.79 ± 15.878	>.05
Gender (case [%])			>.05
Male	106 (58.1%)	91 (57.7%)	
Female	76 (41.9%)	85 (48.3%)	

chest x-ray; absence of intubation; and lack of any serious concomitant disease of the heart, brain and lungs, and metabolic disorders.

Exclusion criteria are pregnancy and lactation; any history of allergy to any of the herbal product components; inability to take a drug per-oral; need for intubation; any condition that precludes continuance of medical intervention based on the judgment of a physician; nausea and vomiting and oral intolerance; resistant hypoxemia; reduced level of consciousness; hemodynamic instability; hypercapnia; and respiratory fatigue.

2.5.4 | Outcomes

The primary clinical endpoint was duration of hospital stay from the start of treatment to live discharge from the hospital. Definition of clinical improvement was fever ≤36.6° oral or ≤37.2° from the armpit; number of breaths ≤24 in room temperature; oxygen saturation of on room air >94% in room temperature; and lack of cough or mild cough. Secondary outcomes were reduction of chest pain, dry cough, fatigue, muscle pain, nausea, fever, cramp, chills, diarrhea, anorexia, dyspnea, sputum cough, vertigo, and runny nose. These clinical outcomes were assessed based on a self-assessment questionnaire. This questionnaire consisted of 17 questions about clinical symptoms and response to each question was scored from zero to four. Safety outcomes including possible side effects that occurred during treatment and premature discontinuation of treatment were evaluated at each visit based on Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. 2017.

2.5.5 | Statistical analysis

After data collection, all 358 participants who completed the study were included in the statistical analysis. Cox regression was used for comparing primary outcome (hospital stay variable) between two groups. For the others, because of the type of other outcome variables, the ordinal logistic regression, GEE test was employed. In final steps of data analysis, time * group interactions were evaluated and discussed. *p* value of less than .05 was considered statistically significant. IBM SPSS statistics version 25 software was utilized for the statistical analysis. Primary plan of analysis was to perform intention-to-treat analysis; however, due to the lack of protocol deviation, the samples were analyzed in their own group.

3 | RESULTS

3.1 | Standardization of formulations

3.1.1 | Total phenol and flavonoid contents of the preparations

The total amounts of phenol of the decoction, capsule 1 and capsule 2 were 35.57 ± 0.64 mg galic acid equivalent (GAE)/g, 15.44 ± 0.34 mg galic acid equivalent (GAE)/g, and 4.52 ± 0.14 mg galic acid equivalent (GAE)/g, respectively. The total amounts of flavonoid of the decoction, capsule 1 and capsule 2 were 11.21 ± 0.58 mg quercetin equivalent (QE)/g, 7.81 ± 0.81 mg quercetin equivalent (QE)/g, and 3. 65 ± 0.18 mg quercetin equivalent (QE)/g, respectively.

3.1.2 | The content of main markers in formulations via HPLC

The HPLC chromatograms of ellagic acid, emodin, glycyrrhizin, apigenin, and thymoquinone with retention time of 35.937, 14.80, 22.40, 8.60, and 24.657 min, respectively, are presented in Figure 1. The amount of ellagic acid and emodin in *Ahmadieh capsule* was quantified 3.274 and 0.119 μg/mg, respectively. Also, glycyrrhizin and apigenin in herbal decoction were measured 29.505 and 0.168 μg/ml, respectively, and thymoquinone in Black Seed capsule was quantified 4.33 μg/mg, by using calibration curves.

3.2 | Clinical evaluation of remedies versus placebo in COVID-19 patients

3.2.1 | Patients

Registration of patients is displayed in the CONSORT flow diagram (Figure 2). The mean age of study patients was 49.74 ± 15.384 years; sex distribution was 106 (58.1%) men versus 76 (41.9%) women in the intervention group; and 91 (51.7%) versus 85 (48.3%) in the placebo group. Among a total number of 381 patients who underwent randomization, 358 patients completed the therapeutic protocol; 184 patients were assigned to receive decoction and capsules plus routine interventions; and 174 patients routine care alone. Eight patients in the intervention group and 15 patients in the standard care group were excluded. Four patients in intervention group were excluded because they could not tolerate taste of decoction. Two patients in the intervention group and five patients in standard care group were excluded from the study due to lower level of consciousness and transfer to the ICU. Six patients (2 in intervention group and 4 in standard care group) were expired. Six patients in standard care group were discharged from the hospital with personal consent and did not continue the treatment.

3.2.2 | Efficacy evaluation

Primary endpoint

Significant statistical differences were detected in terms of duration of hospital stay between the two groups ($p < .001$, hazard ratio = 0.3). Patients in the treatment group had a shorter stay in the hospital than those in the standard-care group (median, 3.291 days vs. 6.468 days, respectively).

Secondary outcome

Seven days after the onset of interventions, fever reduction was statistically significant in treatment group compared with standard-care group ($p = .001$; odds ratio, OR = 2.988; 95% CI, 1.534–5.817). This

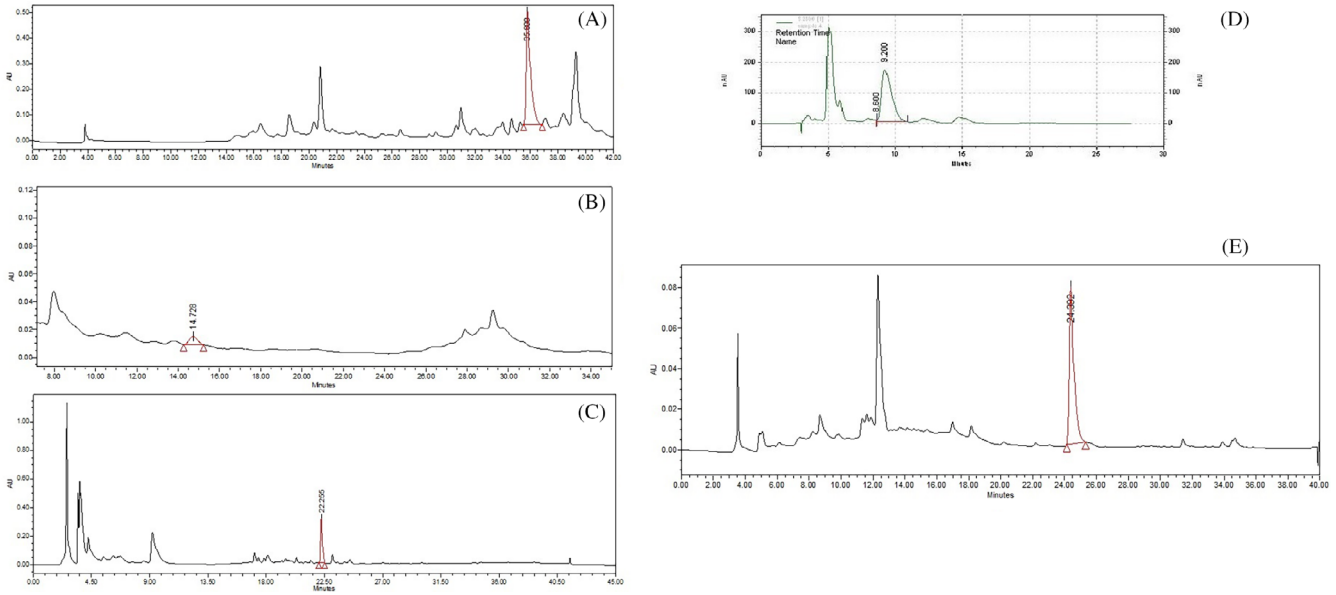

FIGURE 1 HPLC chromatograms of ellagic acid (a), emodin (b), glycyrrhizin (c), apigenin (d) thymoquinone (e) in formulations

indicates that the rate of fever reduction in the treatment group was about three times the standard group. Also, there were significant differences and clinical improvement for other outcomes such as dry cough ($p < .001$; OR = 1.159; 95% CI, 1.076–1.248), dyspnea ($p < .001$; OR = 1.159; 95% CI, 1.076–1.247), muscle pain ($p < .001$; OR = 1.277; 95% CI, 1.180–1.381), headache ($p < .001$; OR = 1.224; 95% CI, 1.127–1.329), fatigue ($p < .001$; OR = 1.137; 95% CI, 1.064–1.216), anorexia ($p < .001$; OR = 1.213; 95% CI, 1.123–1.310), chills ($p < .001$; OR = 1.276; 95% CI, 1.156–1.407), runny nose ($p = .020$; OR = 1.394; 95% CI, 1.054–1.842), sputum cough ($p = .003$; OR = 1.125; 95% CI, 1.040–1.217), and vertigo ($p = .042$; OR = 1.097; 95% CI, 1.003–1.199) in the treatment group compared with standard-care group (Table 4, Figures 3 and 4). However, the decrease in chest pain, laryngeal pain, sore throat, diarrhea, and cramp were not significant at day 7 between the two groups (Table 4 and Figure 5). Eighty-six patients in the treatment group and 89 in the standard care group reported gastrointestinal adverse events including nausea and diarrhea between days 2 and 4.

4 | DISCUSSION

This multicenter open-labeled, randomized, controlled clinical trial found that polyherbal Persian medicine formulations (decoction and two capsules) treatment together with standard supportive care was associated with significant shortened average length of hospital stay and improved symptoms in the patients with COVID-19. This clinical research demonstrates that integrative therapy by combining Persian medicine and current medicine for COVID-19 is significantly better at shortening the average length of hospital stay and clinical improvement in COVID-19 patients than treatments using current medicine alone.

Major biological features of traditional remedies in this research (decoction and capsules) include anti-inflammatory, antioxidant, antiviral, mucolytic, bronchodilator, antitussive, immunomodulatory, and anti-SARS-CoV activities.

G. glabra known as liquorice is a perennial plant native to the Mediterranean region, central, and southwest Asia. The main component of the root of this plant is a triterpenoid saponin called glycyrrhizic acid or glycyrrhizin which is used in the pharmaceutical and food industries (Parvaiz et al., 2014). Clinical and experimental studies have demonstrated varied therapeutic properties for this plant such as anti-inflammatory, antiviral (Sabouri Ghannad, 2014) antimicrobial, antioxidant, and immune system enhancer activities and also positive effects in lung diseases (Sultan, Buttxs, Qayyum, & Suleria, 2014). Licorice and glycyrrhizin have also been markedly effective against SARS- CoV (Cinatl et al., 2003; Parvaiz et al., 2014), hepatitis C (Miyake et al., 2002) and upper respiratory tract infection (Yanagawa, Ogura, Fujimoto, Shono, & Okuda, 2004). β-glycyrrhizic acid is a potent anti-inflammatory compound in licorice that controls inflammation by inhibiting glucocorticoid accumulation and ROS production by neutrophils as strong mediators of tissue inflammation (Parvaiz et al., 2014). In a randomized trial, adding licorice (capsule 500 mg twice daily) to the long-acting beta-agonist regimen in chronic stable moderate bronchial asthmatic patients significantly improved Forced Vital Capacity (FVC) % and Forced Expiratory Volume1 (FEV1) (Sadek, Tawfik, Hussein, & Abdelhakeem, 2019). A molecular docking study has demonstrated that glycyrrhizic acid have high binding affinity of −8.0 Kcal/mol and strong inhibitors for M_{pro} of SARS-CoV2 (Srivastava, Yadav, & Sarkar, 2020).

Main pharmacological properties of *N. sativa* and its chemical constituents are antiviral (Salem & Hossain, 2000), anti-inflammatory, immunomodulatory (Forouzanfar, Bazzaz, & Hosseinzadeh, 2014), and

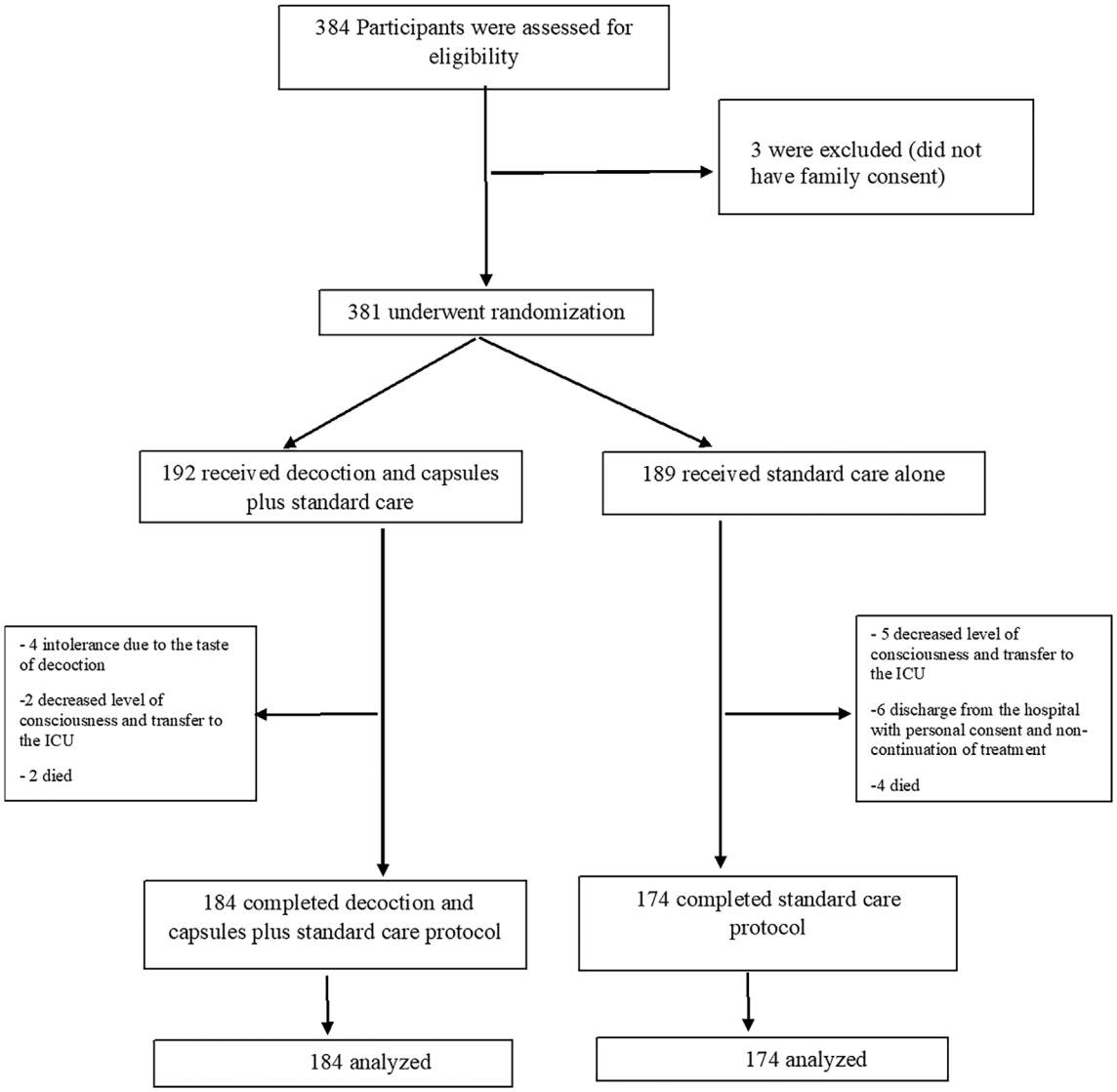

FIGURE 2 CONSORT flow diagram of open-label, randomized, controlled, multicenter clinical trial for COVID-19 patients

anti-cough (Hosseinzadeh, Eskandari, & Ziaee, 2008) effects. There are several preclinical studies that describe the multifaceted effects of *N. sativa* in animal or cellular models of asthma, including bronchodilation, antihistamines, anti-inflammatory, anti-leukotriene, and immunomodulatory effects (Koshak, Koshak, & Heinrich, 2017). Potential efficacy of *N. sativa* on asthma outcomes and biomarkers such as reduction of blood eosinophilia (Koshak et al., 2017) and increase in serum INF-γ cytokine (Salem et al., 2017), improvement in ACT and PFT scores (Ameen et al., 2011), clinical symptoms, and pulmonary function test in adult asthmatics were confirmed in several clinical studies (Boskabady, Javan, Sajady, & Rakhshandeh, 2007; Kardani, Fitri, Barlianto, Olivianto, & Kusuma, 2013). Several in silico studies have demonstrated that some chemical constituents of *N sativa*, such as thymoquinone, thymohydroquinone, hederagenin, α-hederin, and nigelledine, had affinity with SARS-CoV-2 enzymes and proteins and may potentially inhibit virus replication and attachment to host cell receptors (Koshak & Koshak, 2020).

There is 2.6% of essential oil in *Zinnia multiflora* that mainly contains phenolic compounds (20–80%) such as thymol and carvacrol (Shayeganmehr, Vasfi Marandi, Karimi, Barin, & Ghalyanchilangeroudi, 2018). The effects of *Z. multiflora* against Herpes simplex type 1 have been proven in all stages of the disease (Arabzadeh, Ansari-Dogaheh, Sharififar, Shakibaie, & Heidarbeigi, 2013). Phenolic compounds in this plant have been demonstrated to inhibit viral replication by preventing RNA or protein synthesis and limiting virus entry into host cells by impairing haemagglutinin activity (Hamauzu, Yasui, Inno, Kume, & Omanyuda, 2005). In a study conducted by Kianmehr, et al, *Z. multiflora* extract lowered the gene expression of inflammatory cytokines (IL-4, IL-17, TGF-β) and raised anti-inflammatory cytokines (IFN-γ) and the number of FOXP3 in splenocytes, which suppressed Th2 and Th17 cells in mouse model of allergic asthma (Kianmehr et al., 2017). In a double-blind randomized study in 40 asthmatic patients, *Z. multiflora* and its constituent, carvacrol, improved FEV1% while reduced wheezing and plasma level of NO^{2-} (Alavinezhad, Hedayati, & Boskabady, 2017). The effect of this plant on serum cytokine levels and

TABLE 4 Statistical analysis of outcomes in treatment group compared with standard-care group

Parameter	Analytical tests						
	β	*SE*	Wald Chi-Square	*p* value	Odds ratio	CI-lower	CI-upper
Fever	1.094	0.3399	10.365	.001	2.988	1.534	5.817
Dry cough	.148	0.0379	15.175	<.001	1.159	1.076	1.248
Dyspnea	.147	0.0376	15.370	<.001	1.159	1.076	1.247
Muscle pain	.244	0.0402	36.939	<.001	1.277	1.180	1.381
Headache	.202	0.0420	23.154	<.001	1.224	1.127	1.329
Fatigue	.129	0.0339	14.436	<.001	1.137	1.064	1.216
Anorexia	.193	0.0392	24.233	<.001	1.213	1.123	1.310
Chills	.243	0.0501	23.553	<.001	1.276	1.156	1.407
Runny nose	.332	0.1425	5.424	.020	1.394	1.054	1.842
Sputum cough	.118	0.0402	8.626	.003	1.125	1.040	1.217
Vertigo	.092	0.0455	4.127	.042	1.097	1.003	1.199
Chest pain	.121	0.0433	7.774	.005	1.128	1.037	1.229
Laryngeal pain	.186	0.0990	3.528	.060	1.204	0.992	1.462
Sore throat	.104	0.0589	3.119	.077	1.110	0.989	1.245
Diarrhea	.112	0.0648	3.000	.083	1.119	0.985	1.270
Cramp	.016	0.0451	0.121	.728	1.016	0.930	1.110

pulmonary function tests (PFT) in sulfur mustard-induced lung disorders was evaluated in a randomized double-blind clinical trial. The results show that 2 months of cure with *Z. multiflora* decreased inflammation (IL-2, IL-6, IL-8), while it increased anti-inflammatory cytokines (IL-10, IFN-γ) and improved PFT indices in sulfur mustard-exposed patients (Khazdair, Ghorani, Alavinezhad, & Boskabady, 2020).

Major constituents of the flowers of *M. chamomilla*, once called chamomile, include flavonoids (apigenin, luteolin, and quercetin) and essential oils (chamazulene and α-bisabolol) (Gupta, Mittal, Bansal, Khokra, & Kaushik, 2010). Several studies showed that chamomile possessed strong anti-inflammatory activity. The freeze-dried extracts of chamomile repressed leukocyte infiltration and inflammatory effect (Al-Hindawi, Al-Deen, Nabi, & Ismail, 1989). Efficacy of α-bisabolol on the inflammatory response was evaluated by affecting on leukocyte activity and NO production in systemic infection experimental model in mice (Cavalcante et al., 2020). Immunomodulatory effects of chamomile heteropolysaccharides are attributed to the activation of immunoregulation cells of peripheral blood, initiation of immunostimulatory effects of erythrocytes (macrocytes), and heightened sensitivity of helper cells (Gupta et al., 2010). Also, using chamomile essential oil topically improved patients with genital herpes (Koch, Reichling, Schneele, & Schnitzler, 2008). According to various studies in folk medicine of different countries, chamomile is used to treat respiratory diseases such as treatment of influenza, colds, and cough (Kültür, 2007). In a double-blind randomized clinical trial on 45 children aged 7–12 years with asthma, a mixture of *M. chamomilla*, *A. officinalis*, *G. glabra*, *Z. jujuba*, *Adiantum capillus-veneris* L., and *H. officinalis* given to the drug group for 5 days significantly reduced the severity of cough, nighttime awakenings, and viral respiratory infection compared with placebo (Javid et al., 2019).

As a deciduous shrub, *P. granatum* (pomegranate) has been widely used as a traditional medicine (Akbarpour, Hemmati, & Sharifani, 2009; Shaygannia, Bahmani, Zamanzad, & Rafieian-Kopaei, 2016). Pomegranate contains polyphenolic compounds, sugars, fatty acids, aromatic compounds, amino acids, tocopherols, sterols, terpenoids, alkaloids, anthocyanins, alginic acid, etc. (Gil, Tomás-Barberán, Hess-Pierce, Holcroft, & Kader, 2000). Medicine pomegranate polyphenolic compounds, by suppressing influenza virus RNA replication, showed virus suppression and synergistic effects with oseltamivir (Haidari, Ali, Casscells III, & Madjid, 2009). Also, in various studies, the immunomodulatory effects of pomegranate have been revealed, such as the growth stimulant effects of polysaccharides isolated from pomegranate on lymphocytes (Joseph, Aravind, Varghese, Mini, & Sreelekha, 2012). In a study of ethnomedicine in Pakistan, it was regarded as an effective plant for respiratory problems, especially cough and fever caused by colds (Aziz et al., 2016). Therapeutic effects of pomegranate juice in various inflammatory diseases such as rheumatoid arthritis, IBD, and in animal models of respiratory diseases, suggesting its usage in the treatment of chronic inflammatory diseases (Danesi & Ferguson, 2017). Moreover, pomegranate extract has demonstrated anti-inflammatory activity in an experimental model of acute lung injury (LPS-initiated) by decreasing myeloperoxidase in the lungs of mice due to its compounds such as alginic acid and epigallocatechin gallate (Cornélio Favarin, Robison de Oliveira, Jose Freire de Oliveira, & de Paula Rogerio, 2013). Furthermore, a computational study exhibited that polyphenols of pomegranate peel extracts, punicalin, and punicalagin had potential inhibitors of SARS-CoV-2 virus internalization by significant interactions with protein targets including SARS-CoV-2 spike glycoprotein, angiotensin-converting enzyme 2, furin, and transmembrane serine protease 2 (Suručić et al., 2020).

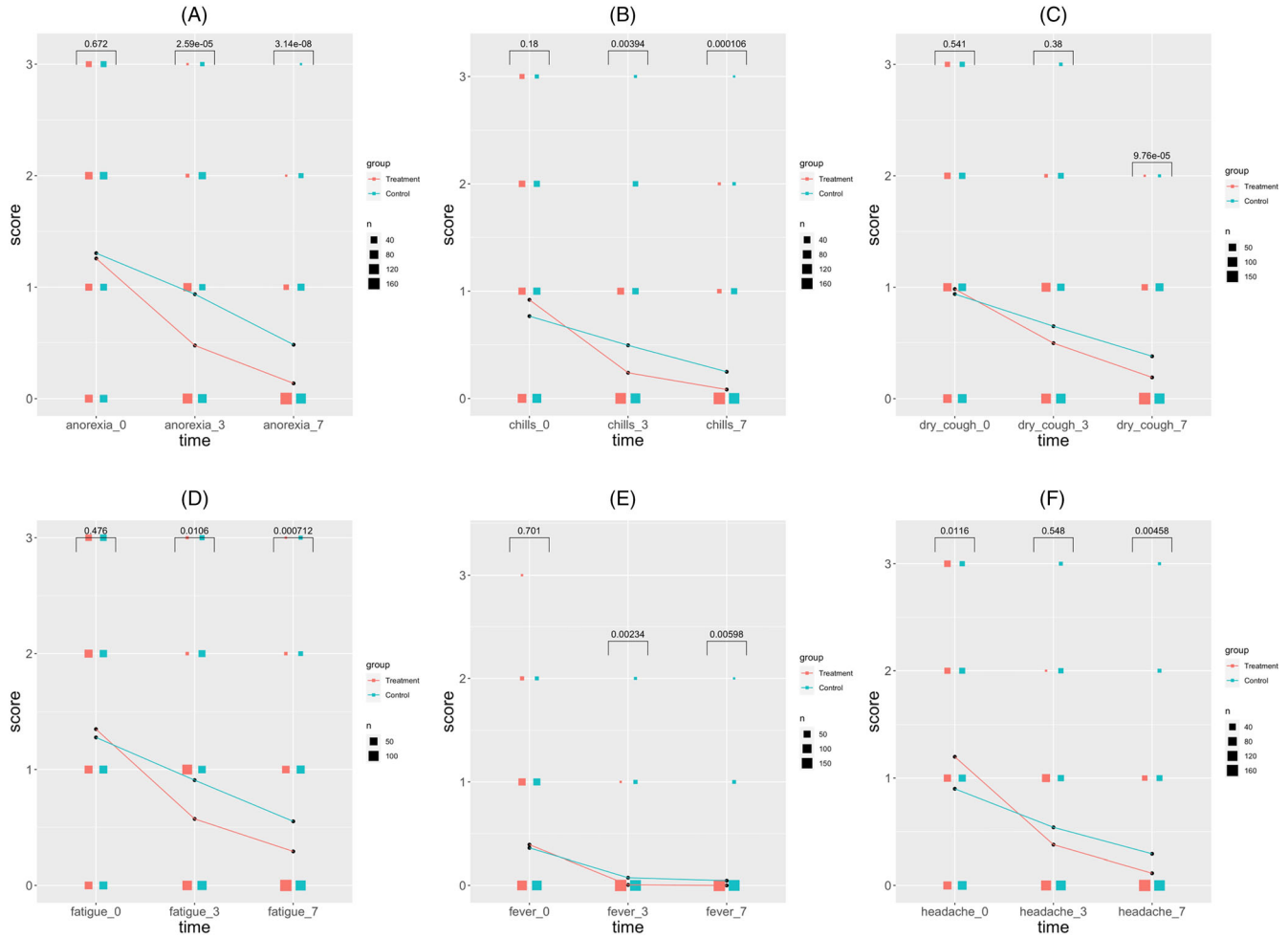

FIGURE 3 Comparison of improvement of secondary outcomes including (a) anorexia, (b) chills, (c) dry cough, (d) fatigue, (e) fever, (f) headache in two groups on days 0, 3, 7

Chinese rhubarb or rhizomes of *R. palmatum* contain anthraquinones (rhein, emodin), tannins (catechins), flavonoids, and naphthohydroquinones as the most important active compounds. Chinese rhubarb has an antivirus activity on both RNA and DNA viruses such as simple herpes virus, hepatitis B virus, influenza virus A, influenza virus B, and SARS coronavirus (Xu, Li, & Cong, 2005). Luo et al. in 2009, demonstrated that hydroethanolic extract of 70% Chinese rhubarb can strongly function against SARS-CoV 3CL protease (Luo et al., 2009). In another study, anthraquinone emodin and kaempferole glycosides in Chinese rhubarb considerably reduced the symptoms of SARS-CoV by inhibiting 3a-channels (Schwarz et al., 2012). Moreover, with block SARS-CoV spike protein and angiotensin-converting enzyme 2 (ACE-2) in a dose-dependent manner, emodin showed anti SARS-CoV activity (Ho, Wu, Chen, Li, & Hsiang, 2007). In another study conducted by Song et al. in 2018, emodin effectively subsided airway inflammation and activated macrophages in murine asthma model (Song et al., 2018).

Fruits of Jujube or *Z. jujuba* contain various components including phenolic acid (coumaric acid, cinnamic acid and caffeic acid), flavonoids (quercetin and rutin), triterpenic acids, polysaccharides, carotene, alpha tocopherol, and saponin (Gao, Wu, & Wang, 2013). Triterpenic acids isolated from jujube aqueous extract have shown inhibitory effects on inflammatory cells such as proliferation of splenocytes stimulated by prostratin and nitric oxide that is produced by macrophages (Yu et al., 2012). Another study showed a strong protective role of jujube fruits against acute and chronic inflammatory reactions in rats by reducing nitric oxide expression (Goyal, Sharma, & Singh, 2011). In this study, polysaccharides significantly raised spleen indexes, improved serum hemolysin formation, increased phagocytic activity of macrophages, and inhibited edema in mice (Zou, Chen, Sun-Waterhouse, Zhang, & Li, 2018). The antiasthmatic activity of jujube fruits is evaluated in a model of asthma induced in rats by ovalbumin. Jujube ethanolic extract and Jujuboside B (saponin in the fruit) showed strong antispasmodic activity by various mechanisms such as clonidine-induced mast cell degranulation, inhibition of clonidine-induced catalepsy, inhibition of leukocytosis and eosinophilia, reduction of bronchoalveolar inflammatory cells, and weakening the expression of T-helper type 2 cytokines (Ninave & Patil, 2019).

The *F. carica* or fig tree was possibly the first internationally cultivated herb during the Neolithic revolution. Dried fig contains water, protein, fat, carbohydrates, calcium, phosphorus, iron, sodium,

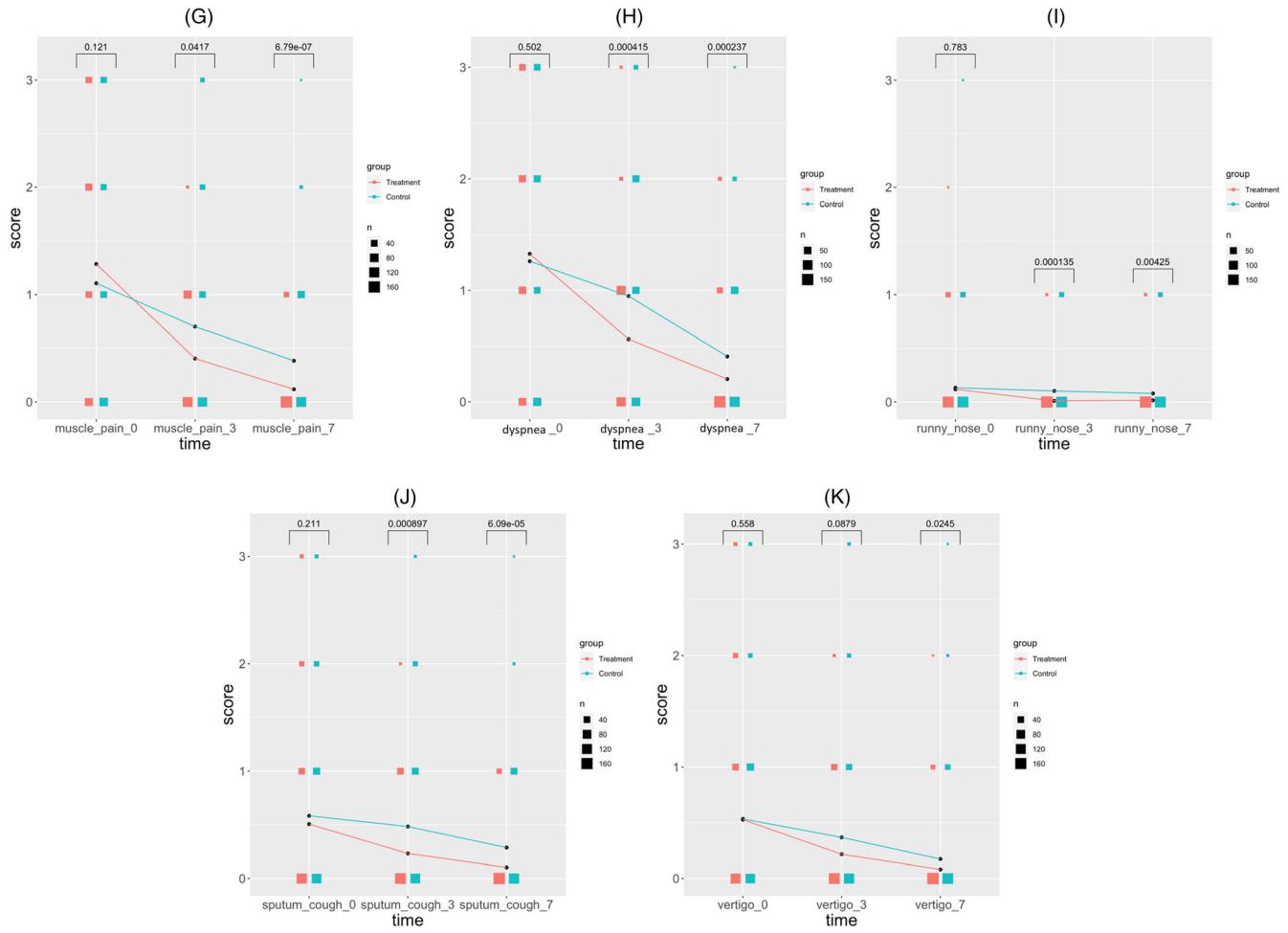

FIGURE 4 Comparison of improvement of secondary outcomes including (g) muscle pain, (h) dyspnea, (i) runny nose, (j) sputum cough, and (k) vertigo in two groups on days 0, 3, 7

potassium, vitamin A, thiamine (B1), riboflavin (B2), and niacin (B3) (Ahmad, Bhatti, Khaliq, Irshad, & Madni, 2013). The hexanic and hexane–ethyl acetate extracts of fig extract showed antiviral activities and prevented multiplication of viruses via inhibiting virus replication, cell uptake and penetration, and intracellular inhibition (Lazreg Aref et al., 2011). In an animal study, fig latex significantly reduced caprine herpesvirus1 (Camero et al., 2016). The anti-inflammatory effects of figs were demonstrated by hampering the inflammatory pathway NF-κB/IL-6/STAT3 in cellular and animal models (Lu et al., 2018). Another study showed the anti-inflammatory effect of isoflavones isolated from fig fruit by hindering nitric oxide production (Liu et al., 2019). In an ethnobotany study in the region of Morako, fig fruit was regarded effective in the treatment of respiratory diseases (Fatiha et al., 2017).

Urtica dioica (stinging nettle) is an herbaceous perennial flowering herb, that is, native to Eurasia. Nettles are a very nutritious food and high in minerals (particularly iron), vitamin C and pro-vitamin A. A red substance called urticin is extracted from the aerial parts of this plant (Dhouibi et al., 2020). Anti-inflammatory effect of nettle was similar to indomethacin by inhibition of lipoxygenase, cyclooxygenase, and cytokine production (Chrubasik, Roufogalis, Wagner, & Chrubasik, 2007). Strong nettle antiviral activity was shown to inhibit replication of HIV (HIV-l and HIV-2) and cytomegalovirus, as well as respiratory syncytial virus replication (RSV) (Flores-Ocelotl et al., 2018). Immunomodulatory effect of aerial parts of nettle and some of its main components such as isorhamnethol-3-*O*-glucoside, kaempferol-3-0-rutinoside, and quercetol-3-0-rutinoside on neutrophils were demonstrated by Akbay, Basaran, Undeger, and Basaran (2003). Nettle extract significantly prevented eosinophilia, leucocytes, and lymphocytes levels in serum and effectively suppressed inflammatory cells in the asthmatic rat model. Also, lipid peroxidation generated by allergen was significantly reduced in lung tissue (Zemmouri et al., 2017). Lectins (plant agglutinins) isolated from the nettle possess antiviral effects with binding capacity on coronavirus envelope glycans as SARS-CoV spike protein contains 12 *N*-glycosylation sites (Orhan & Deniz, 2020).

Nepeta sp. belongs to the Lamiaceae family that is composed of about 300 species that are native to central and southern Asia and Europe. There are 75 species of this genus in Iran, about 53% of which are endemic (Sefidkon & Jamzad, 2007). Flowers contain phenols, flavonoids, terpenoids (iridoids and diterpenes), flavanones,

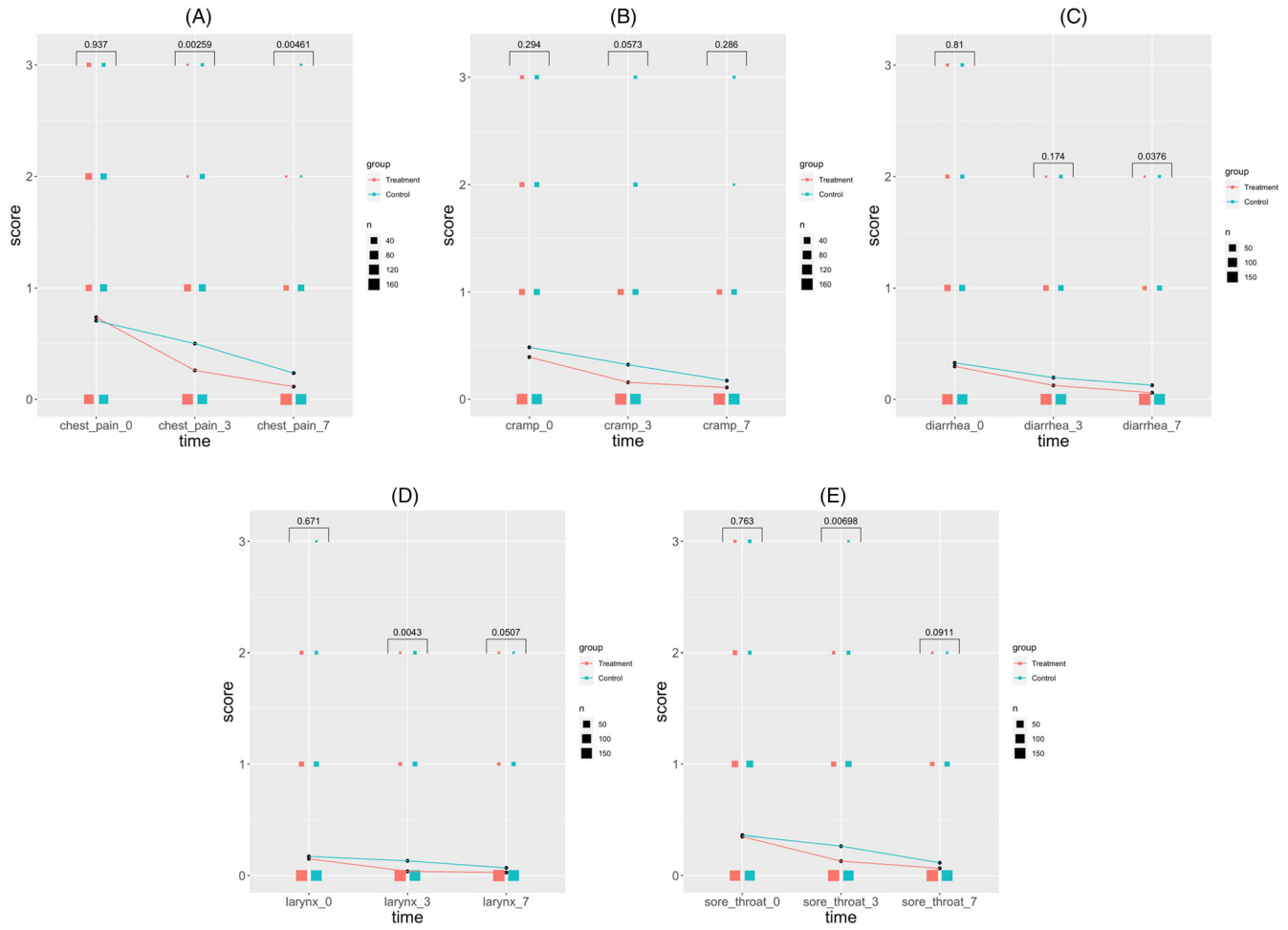

FIGURE 5 Comparison of secondary outcomes including (a) chest pain, (b) cramp, (c) diarrhea, (d) laryngeal pain, and (e) sore throat in two groups on days 0, 3, 7

glycosides, sterols, carbohydrates, and proteins (Naghibi, Mosadegh, Mohammadi, & Ghorbani, 2005; Siddiqui, Rauf, Latif, & Mahmood, 2017). *N. bracteate* improved lung pathology, by reducing basophils, eosinophil, and neutrophil infiltration, inhibition of Th17 cytokine response, increasing IL-10, and reduction of TGF-β level in asthmatic mice model (Wang et al., 2016). In a randomized double-blind clinical trial, effect of *N. bracteate* syrup was evaluated on allergic rhinitis symptoms (itchy nose, sneezing, nasal obstruction, rhinorrhea, and ocular symptoms). Results demonstrated that *N. bracteate* syrup significantly reduced allergic rhinitis symptoms after 4 weeks (Hajiheydari et al., 2017). In a triple-blinded, randomized clinical trial on patients with chronic obstructive pulmonary disease (COPD), significant improvement in the CAT score (COPD Assessment Test), FEV1, and FEV1/FVC ratio was demonstrated in *N. bracteate* syrup group compared to the placebo group after four weeks (Abdolahinia, Naseri, Eslaminejad, Ghaffari, & Velayati, 2018). Another clinical study on productive cough demonstrated that *N. bracteata* have anti-allergic properties and significantly decrease eosinophil and erythrocyte sedimentation rate (Sehar, Alam, Arfin, Ahmad, & Goswami, 2015).

Althaea officinalis (common marshmallow) is native to Asia, United States of America, and Europe that contained mucilage, pectins, mono-, and di-saccharide, flavonoids (pcoumaric acid, kaempferol, caffeic, quercitrin, and hypolaetin-8-glucoside), tannins, scopoletin, asparagine, phytosterols, and coumarins (Al-Snafi, 2013; Gudej, 1990). Mucilage polysaccharides of marshmallow administered intraperitoneally to mice revealed anti-inflammatory activity by enhancing phagocytic activity of macrophages in the carbon-clearance test (Naqvi, Khan, & Vohora, 1991). In another study, hypolaetin 8-glucoside (flavonoid in marshmallow) repressed the acute phase of adjuvant carrageenan-induced inflammation, more even than phenylbutazone (Al-Snafi, 2013). Marshmallow polysaccharides that contain the highest proportion of the uronic acid component, displayed statistically significant cough-repressing activity than non-narcotic drugs applied in clinical practice to treat coughing (Sutovska, Nosalova, Franova, & Kardosova, 2007). Also, combination of the extracts of *Zingiber officinale* and *A. officinalis* diminished severity of acute bronchitis-induced coughs (Roohi Broujeni, Ganji, & Roohi Broujeni, 2009). In a double-blind clinical study, the effect of marshmallow on cough associated with angiotensin-converting enzyme

inhibitors was evaluated. Sixty patients received marshmallow (40 mg, three times daily, for four weeks). The severity of the cough in the group that has been treated by marshmallow had a significant reduction. Eight patients in the marshmallow group demonstrated almost complete cough abolition (Rouhi & Ganji, 2007).

Treatment strategies for treating COVID-19 patients include corticosteroids, a combination of wide-ranging antiviral medicines, healing plasma, some antibiotics, and supportive care (Jahan & Onay, 2020). Moreover, lopinavir–ritonavir treatment beyond standard care was not efficient for hospitalized adult patients with severe COVID-19 (Cao et al., 2020). Also, intravenous remdesivir did not significantly improve mortality, time to clearance of virus, and clinical improvement in patients with serious COVID-19 compared with placebo (Wang et al., 2020). Thus, any supplements or treatments that can help alleviate symptoms and enhance tolerance against COVID-19, even using traditional medicinal knowledge seem promising. Medicinal herbs used in this study might not be regarded a complete treatment, but the results show that they can be beneficial for the patients in this critical situation. Open-label design of this study due to the COVID-19 pandemic was main limitation of this study.

5 | CONCLUSION

The present study demonstrated that these natural decoction and capsules treatment plus routine care significantly decreased duration of hospital stay, accelerate clinical improvement, and alleviated symptoms such as fever, dry cough, anorexia, muscle pain, and runny nose. These herbal formulations are well tolerated by patients. Hence, these herbal formulations can be considered as a potential natural remedy based on Persian medicine for patients with COVID-19. Notably, medicinal herbs in Persian medicine have antifever, bronchodilator, and antiasthma features, strengthen the body, and invigorate lungs. They have been commonly used for thousands of years for treating various infections. As a result of irrepressible epidemic of COVID-19 and unavailability of approved medications, traditional, complementary, and alternative treatments could be incredibly promising for managing this pandemic via attenuating the severity of infection caused by SARS-CoV-2.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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