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Research article

Herbal medicines for long COVID: A phase 2 pilot clinical study

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ABSTRACT

Background: Infections of Coronavirus Disease-2019 (COVID-19) can cause long-term effects known as long COVID. This pilot study aimed to evaluate the feasibility of a clinical study as well as the efficacy and safety of traditional East Asian herbal medicines in alleviating fatigue and cognitive dysfunction in patients with long COVID.

Methods: This prospective pilot study investigated the use of three types of herbal medicines, Bojungikgi-tang (BIT), Kyungok-go (KOG), and Cheonwangbosim-dan (CBD), for a 12-week period as potential treatments for fatigue and cognitive dysfunction in patients with long COVID. Forty-five patients with long COVID were recruited, and one of three drugs was given based on the patient's symptoms and pattern identification. The effect of herbal medications on fatigue and cognitive function outcomes was assessed over a 36-week period, with patient adherence closely monitored.

Results: After 12 weeks of herbal drug administration, fatigue symptoms improved significantly across all groups, with treatment success rates of 80 %, 53.33 %, and 46.67 % in the BIT, KOG, and CBD groups, respectively. However, cognitive dysfunction symptoms showed less improvement, with treatment success rates of 40 %, 46.67 %, and 13.33 % in the BIT, KOG, and CBD groups, respectively. All adverse events reported were mild and unrelated to the medication. The study design was found to be feasible with high medication adherence.

Conclusions: This study demonstrated the feasibility of conducting a clinical trial with three herbal medicines to treat long COVID symptoms like fatigue and cognitive dysfunction.

Abbreviations: AEs, Adverse events; BDI, Beck's Depression Inventory; BIT, Bojungikgi-tang; CAM, Complementary and alternative medicine; CFQ, Cognitive Failure Questionnaire; CBD, Cheonwangbosim; ChFS, Chalder Fatigue Scale; CIS, Checklist Individual Strength; COVID, Coronavirus disease; COVID-19, coronavirus infectious disease 2019; K-BNT-15, Korean-Boston Naming Test-15; KM, Korean Medicine; MFDS, The Ministry of Food and Drug Safety; KOG, Kyungok-go; PSQI-K, the Korean version of Pittsburgh Sleep Quality Index; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; VAS, Visual Analog Scale; WAIS, Digit Span Test in Korean-Wechsler Adult Intelligence Scale.

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1. Introduction

Although a significant number of patients have reported persistent symptoms following acute coronavirus disease 2019 (COVID-19), a global consensus on terminologies and definitions has yet to be established. The definition of long COVID, also known as chronic or postacute sequelae of SARS-CoV-2 infection (PASC) is not well defined, and different countries and institutions use different terms or definitions. According to the World Health Organization, post-COVID-19 conditions are defined as symptoms that usually occur within three months of the onset of COVID-19 symptoms, persist for at least two months, and are not explained by other alternative diagnoses [1]. In South Korea, chronic COVID-19 syndrome (long COVID) is defined as the persistence of one or more symptoms or signs that cannot be explained by another disease after 12 weeks of COVID-19 diagnosis [2]. These symptoms are diverse and can affect various systems, commonly including fatigue, shortness of breath, cough, chest pain, joint pain, muscle aches, cognitive dysfunction (cognitive difficulties), headache, heart palpitations, sleep disturbances, depression, anxiety, and loss of taste or smell. A meta-analysis of 41 studies found that the global combined prevalence of long COVID was 43 %, with fatigue, memory problems, and dyspnea being the most common symptoms [3]. Similarly, other studies have found that fatigue and cognitive impairment are the most common and frequently reported long COVID symptoms [4,5]. In addition, unlike other common symptoms of long COVID, such as dyspnea and depression, there are currently no established and effective treatments for these conditions [6]. It is important to note that the prevalence of long COVID can vary based on factors such as the definition of long COVID used in the study, the population being studied, and the follow-up duration.

Several risk factors appear to be associated with long COVID, including female gender, ethnic minority status, socioeconomic deprivation, smoking, obesity, and comorbidities [7]. Data from the United States, 153,543 adults, including 19,985 with long COVID, revealed that 14 % of adults aged 18–84 (35.11 million) and 15.5 % of adults at the working age of 18–64 (30.65 million) had long COVID by November 2022 [8]. In addition, approximately 27.7 million adults and 24.2 million adults at the working age may experience adverse socioeconomic and mental health outcomes due to long COVID. Furthermore, the estimated annual earnings loss among working-age adults was $175 billion. These findings highlight the significant public health and economic impact of long COVID, underscoring the need for further investigation and intervention [8].

Despite the significant impacts of long COVID, there is currently a lack of treatment methods supported by concrete evidence. There are several approaches available to manage symptoms and improve overall well-being in individuals with long COVID. For fatigue in patients with long COVID-19, treatment options include medications, alternative medicine, cognitive behavioral therapy, and exercise therapy. However, studies evaluating the effectiveness of these interventions are limited and lack high-quality evidence [9]. Currently, numerous clinical trials are actively evaluating the effectiveness of various interventions to treat the diverse symptoms of long COVID [10]. However, these trials primarily focus on antiviral agents, cardiac agents, anti-inflammatory agents, and respiratory agents. There is a notable lack of studies addressing the fatigue and cognitive decline that long COVID patients commonly report [11]. To date, the treatment strategies for various post-COVID-19 syndromes are inadequate. However, traditional medicine has been identified as a potential solution due to its ability to relieve symptoms, improve organic injuries, and affect immune function [12]. According to a previous study, a significant number of patients with post-COVID-19 syndrome who were identified with particular syndromes, such as Lung and Spleen Qi Deficiency and Qi and Yin Deficiency, in traditional East Asian medicine showed improvement in symptoms after treatment [13]. Furthermore, randomized controlled trials have suggested that traditional medicine can improve fatigue in post-COVID-19 patients [14]. However, these pieces of evidence appear to be insufficient for complementary and alternative medicine (CAM). There is a lack of published studies regarding the effectiveness and safety of CAM interventions for long COVID [15], highlighting the need for more clinical studies in this area.

According to reports, Korean medicine (KM) doctors consider Qi Deficiency as a major cause of chronic fatigue syndrome and prioritize prescribing Bojungikgi-tang (BIT; Bu-zhong-yi-qi-tang in China or Hochu-ekki-to in Japan) as a treatment [16]. In Japan, Bojungikgi-tang is also frequently used to treat fatigue associated with long COVID [17]. During the pandemic period, the most commonly prescribed herbal medicine in South Korea for fatigue, weakness, and dry cough was Kyungok-go (KOG; Qiong-yu-gao in China or Kei-gyoku-kou in Japan) [18]. Furthermore, Cheonwangbosim-dan (CBD; Tian-wang-bu-xin-dan in China or Tenn-o-ho-sin-tan in Japan) has the potential to improve or treat physical and mental illnesses, such as cognitive dysfunction, neurosis, insomnia, and cardiac malfunction-induced disease [19]. Therefore, these herbal medicines are considered potentially useful in alleviating long COVID symptoms. It is necessary to establish clinical evidence for these herbal medicines, not only to develop traditional medical treatment strategies for long COVID but also to provide them to the growing number of patients.

This was a phase 2 preliminary clinical trial that aimed to evaluate the safety and efficacy of frequently used herbal medicines in patients experiencing fatigue or cognitive dysfunction associated with long COVID. The research objectives were to assess the feasibility of the intervention and gather evidence for future large-scale studies.

2. Materials and methods

2.1. Trial design

This was a prospective pilot study conducted at Kyung Hee University Korean Medicine Hospital in Seoul, Republic of Korea, with the aim of testing the feasibility and acceptability of using selected herbal medicines in patients experiencing fatigue or cognitive dysfunction after COVID-19. This study was approved by the Institutional Review Board of Kyung Hee University KM Hospital (KOMCIRB 2020-12-002-001). The protocol of this study was published as a protocol paper [20] and registered at cris. nih.go.kr (KCT0006252) prior to the start of the clinical trial.

2.2. Participants

Patients with fatigue or cognitive symptoms were recruited for this study. Each patient was prescribed three KM herbal medications based on syndrome differentiation and symptom type. Since this clinical trial did not include a control group, randomization, allocation concealment, and blinding were not implemented. Patients had monthly visits for a 12-week medication period, and their symptoms and blood biochemistry were assessed up to 36 weeks after participation. The enrollment, intervention, and assessment schedules are summarized in Table 1.

This study included individuals over the age of 19 who had recovered from COVID-19, reported persistent fatigue or cognitive dysfunction for more than four weeks after their diagnosis but not before, achieved a total score of more than 76 points on the Checklist Individual Strength (CIS), had no overall cognitive function issues, and could provide written informed consent. However, individuals with conditions that could potentially cause fatigue or cognitive dysfunction or interfere with drug intake or absorption as well as those with other allergic, hepatic, or nephrotic diseases, were excluded from the study. All participants provided written informed consent prior to participating in this study. All of the entry criteria are listed in Table S1.

2.3. Intervention

The KM syndrome differentiation was conducted by a Korean Medicine doctor specializing in internal medicine specialist, with over 10 years of clinical experience. Patients were classified into either the fatigue or cognitive dysfunction group based on the primary symptoms observed after COVID-19. Subsequently, they were assigned to the appropriate herbal medicine intervention group according to their specific sub-syndrome differentiation pattern. The criteria for syndrome differentiation can be found in Table 2. Based on syndrome differentiation, three different herbal medications were prescribed to each patient for 12 weeks. Among patients with fatigue, the pattern/syndrome of Lung-Spleen Qi Deficiency group received BIT (Kolmar Pharma, Seoul, Korea) as one sachet (3.75 g) twice a day before or in between meals. In addition, the syndrome of Dual Deficiency of Qi and Yin group received KOG (KBPharm,

Table 1
Schedule summary.

Visit	0	1	2	3	4	5	6	UV *
Week	−7	1	5	9	13	25	37	–
Visit Window (±Days)	–	2	±7	±7	±7	±7	±7	–
Informed consent for the study	●							
Demographic information	●							
Participation in other clinical trials	●							
Medical history	●							
Confirmation of diagnosis of COVID-19 infection	●							
Medication history	●							
Vital signs	●	●	●	●	●	●	●	●
Electrocardiogram	●				●			●
Laboratory test	●				●			●
Blood collection for immune response and metabolite analysis	●				●	●	●	●
Pregnancy **	●							
Evaluation of fatigue or cognitive dysfunction	●							
CIS	●		●	●	●	●	●	●
VAS (0–100) score for fatigue or cognitive dysfunction	●		●	●	●	●	●	●
Inclusion/exclusion criteria	●							
KM syndrome differentiation		●						
Prescription of herbal medicine ***		●	●	●				
Drug adherence			●	●	●			●
Check for combination therapy			●	●	●	●	●	●
ChFS		●	●	●	●	●	●	●
EQ-5D-5L		●	●	●	●	●	●	●
PSQI-K		●	●	●	●	●	●	●
K-MoCA		●	●	●	●	●	●	●
CFQ		●					●	●
BDI		●	●	●	●	●	●	●
Digit span test in K-WAIS (DF, DB, and DF-DB)		●			●	●	●	
K-BNT-15		●			●	●	●	
Adverse events check		●	●	●	●	●	●	●

●, check on visit * UV, unscheduled visit, ** only fertile women, *** Evaluation for the continuation of herbal medicine administration at 5th and 9th weeks.

Abbreviations: COVID-19, coronavirus infectious disease 2019; CIS, Checklist Individual Strength; VAS, Visual Analog Scale; KM, Korean Medicine; ChFS, Chalder Fatigue Scale; EQ-5D-5L, Standardized 5-level EuroQol 5-Dimensional Questionnaire; PSQI-K, the Korean version of Pittsburgh Sleep Quality Index; K-MoCA, Korean–Montreal Cognitive Assessment scale for cognitive function; CFQ, Cognitive Failure Questionnaire; BDI, Beck's Depression Inventory; K-WAIS, Digit Span Test in Korean-Wechsler Adult Intelligence Scale; DF, Digit Span Forward; DB, Digit Span Backward; K-BNT-15, Korean-Boston Naming Test-15.

Incheon, Korea) as one sachet (20 g) twice a day in the morning and evening before or in between meals. Furthermore, the cognitive dysfunction group received CBD (Hanpoong Pharm, Seoul, Korea) as one sachet (3.0 g) once a day in between meals. All medications and their respective dosages were approved by the Ministry of Food and Drug Safety (MFDS). All medication ingredients are detailed in Table 3.

2.4. Outcome measures

The primary endpoint of this study was to determine the treatment success rate after 12 weeks of herbal medication for fatigue and cognitive dysfunction in patients who had recovered from COVID-19. The fatigue or cognitive dysfunction was assessed before and 13 weeks after the administration of herbal medicines using a Visual Analog Scale (VAS) score ranging from 0 to 100. A change in VAS score between before and after treatment greater than 15 points was defined as treatment success. The secondary endpoints included evaluating medication adherence and utilizing CIS [21], VAS for fatigue and cognitive dysfunction, Chalder Fatigue Scale (ChFS) and Subscale [22], Korean–Montreal Cognitive Assessment scale for cognitive function [23], Cognitive Failure Questionnaire for cognitive function [24], Digit Span Test in the Korean–Wechsler Adult Intelligence Scale for assessing changes in cognitive dysfunction [25], EQ-5D-5L for health-related quality of life [26], Pittsburgh Sleep Quality Index-K [27], Beck's Depression Inventory [28], and Korean–Boston Naming Test-15 for measuring language proficiency in cognitive impairments [29]. During the 12-week treatment period, patients had monthly visits. Following that, they had follow-up visits every 12 weeks over a total period of 24 weeks for outcome assessment.

To evaluate the study's feasibility, the patient recruitment rate was calculated as the ratio of the number of recruited patients during the study period to the length of the enrollment period in months. Dropout reasons were documented, and the dropout rate was calculated and compared for all study patients as well as for each intervention group.

The safety of the drugs was evaluated by monitoring the incidence of adverse events (AEs). AEs referred to all harmful and unintended symptoms of signs, including abnormal laboratory test results in patients received herbal medicine, without necessarily having a causal relationship. At Weeks 0 and 13, laboratory investigations, including blood chemistry, were performed, and an electrocardiogram was assessed. Laboratory tests determined the levels of red blood cells, hemoglobin, hematocrit, platelets, white blood cells, fasting blood sugar, BUN, creatinine, AST, ALT, and blood electrolytes (Na, K, Cl). AEs were assessed at all in-person visits occurring at 1, 5, 9, 13, 25, and 37 weeks. Detailed research methodology can be found in the previously published protocol paper [20].

2.5. Statistical analysis

To assess the feasibility of the study design, the subject recruitment rate, dropout rate, and dropout reasons were analyzed. Since this trial was conducted as a pilot study, the sample size was not calculated beforehand. The dropout rate was calculated for all participants and for each herbal medication group, and the dropout reasons were also assessed. For continuous variables used to assess the potential clinical effectiveness of the herbal medications, descriptive statistics such as standard deviation, median, minimum, and maximum values were presented for each time point. Statistical analysis was conducted on an intention-to-treat basis, and the last observation carried forward analysis was employed to handle missing data while evaluating effectiveness. An analysis of covariance (ANCOVA) was used to compare the different herbal medication groups ($p < 0.05$). In cases where the basic assumptions of ANCOVA, such as normality and equal variance of data, were violated, the Kruskal–Wallis test was used. The statistical analysis was conducted using the R software (R 4.1.2, The R Foundation, www.r-project.org, accessed on August 9, 2022). A full analysis set was used to analyze variables for effectiveness evaluation, while data for safety evaluation were analyzed using the safety set. All statistical tests, unless otherwise specified, were two-sided with a significance level of 5 %.

Table 2
KM syndrome differentiation for allocation to treatment group.

	Fatigue		Cognitive Dysfunction
Code	BIT	KOG	CBD
Syndrome differentiation classification	Lung-Spleen Qi Deficiency	Dual Deficiency of Qi and Yin	Heart Yin Deficiency Heat
Symptom	Fatigue, appetite loss, cold sweat, shortness of breath, chest tightness, anxiety and others	Fatigue, dry cough and others	Forgetfulness, fever, insomnia, heart palpitation, stomatitis, tongue needles and others
Tongue diagnosis	Pale tongue, thin white fur	Dry mouth, dry tongue	Red tongue and low tongue coated
Pulse diagnosis	Vacuous, large, weak pulse or surging, large pulse	Fine pulse or vacuous, weak pulse	Fine, rapid pulse
Urine/feces	Hard bound stool/sloppy stool	Dry stool	Hard bound stool/sloppy stool

Abbreviations: KM, Korean Medicine; BIT, Bojungikgi-tang; KOG, Kyungok-go; CBD, Cheonwangbosim-dan.

Table 3
Composition of Bojungikgi-tang, Kyungok-go and Cheonwangbosim-dan.

Fomula /Product name	Composition		Manufacturer /License Code	Group /KM syndrome differentiation
Bojungikgi-tang (BIT)[a]	*Panax ginseng* C. A. Meyer	4.0 g	Kyungbang	Fatigue
Kracie Bojungikgi-tang Extract Fine Granule	*Atractylodes japonica* Koidzumi	4.0 g	Pharmaceutical Co.,Ltd	lung-spleen qi deficiency
	Astragalus membranaceus Bunge	4.0 g	201507212	
	Angelica gigas Nakai	3.0 g		
	Zizyphus jujuba Miller var. inermis Rehder	2.0 g		
	Bupleurum falcatum Linné	2.0 g		
	Citrus unshiu Markovich	2.0 g		
	Glycyrrhiza uralensis Fischer	1.5 g		
	Cimicifuga heracleifolia Komarov	1.0 g		
	Zingiber officinale Roscoe	0.5 g		
Kyungok-go (KOG)[b]	*Rehmannia glutinosa* Liboschitz ex Steudel	15.96 g	Kyungbang	Fatigue
Kyungbang Kyungok-go	*Panax ginseng* C. A. Meyer	4.96 g	Pharmaceutical Co.,Ltd	dual deficiency of qi and yin
	Poria cocos Wolf	2.48 g	201708619	
	Mel Honey	16.6 g		
Cheonwangbosim-dan (CBD)[c]	*Rehmannia glutinosa* Liboschitz ex Steudel	0.5 g	Hanpoong	Cognitive dysfunction
Soonsimhwan	*Panax ginseng* C. A. Meyer	0.0625 g	Pharmaceutical Co.,Ltd	heart yin deficiency
	Scrophularia buergeriana Miquel	0.0625 g	200100075	
	Salvia miltiorrhiza Bunge	0.0625 g		
	Polygala tenuifolia Willdenow	0.0625 g		
	Platycodon grandiflorum A. De Candolle	0.0625 g		
	Poria cocos Wolf	0.0625 g		
	Schisandra chinensis (Turcz.) Baillon	0.125 g		
	Angelica gigas Nakai	0.125 g		
	Asparagus cochinchinensis Merrill	0.125 g		
	Liriope platyphylla Wang et Tang	0.125 g		
	Thuja orientalis Linné	0.125 g		
	Zizyphus jujuba Miller var. spinosa Hu ex H. F. Chou	0.125 g		
	Coptis japonica Makino	0.25 mg		

*The dosage of each composition in the medicine is listed based on the raw material equivalent corresponding to a daily dose disclosed by the KFDA. Detailed information is provided at the address below.
https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetailCache?cacheSeq = 201507212aupdateTs2024-06-01 %2002:54:41.0b
https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetailCache?cacheSeq = 201708619aupdateTs2024-06-01 %2003:05:22.0b
https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetailCache?cacheSeq = 200100075aupdateTs2024-06-01 %2003:11:25.0b

[a] This medicine (daily dose of 7.5 g) contains 6400 mg of Bojungikgi-tang Extract. The composition of medicinal herbs within 6400 mg of Bojungikgi-tang Extract is shown in the table.

[b] The composition of the medicinal herbs in this medicine (daily dose of 40 g) is shown in the table.

[c] The composition of the medicinal herb in this medicine (daily dose of 3 g) is shown in the table. This medicine contains the following excipients: Arabic gum, corn starch, polyethylene glycol 6000, Tabshield Brown (11B1422), and hydroxypropyl cellulose.

3. Results

3.1. Participants

A total of 49 potential participants were screened, with 45 included in the study. A flow chart of patients enrolled in this study is depicted in Figs. 1 and 2.

3.2. Baseline characteristics

Herbal drugs for fatigue symptoms (BIT and KOG) and cognitive dysfunction (CBD) were prescribed to patients based on their symptoms and pattern identification diagnosis. Patients in the CBD group were older (average age: 51.33 years) than those in the fatigue herbal drug groups (BIT and KOG). The average duration of symptoms was 89.47 days in the BIT group, 114.8 days in the KOG group, and 119.13 days in the CBD group. The body mass index, educational level, and occupational status were comparable among the groups. When the National Early Warning Score (NEWS) was considered, the KOG and CBD groups showed a more severe status during the acute COVID-19, with fatigue symptoms being more severe in the BIT and KOG groups and cognitive dysfunction symptoms being more severe in the CBD group (Table 4).

3.3. Feasibility assessment

Between August 2021 and July 2022, the targeted recruitment of 45 participants was successfully completed. The number of subjects recruited over 12 months was 45, and the recruitment rate was 4 participants/month. Among the included participants, 14

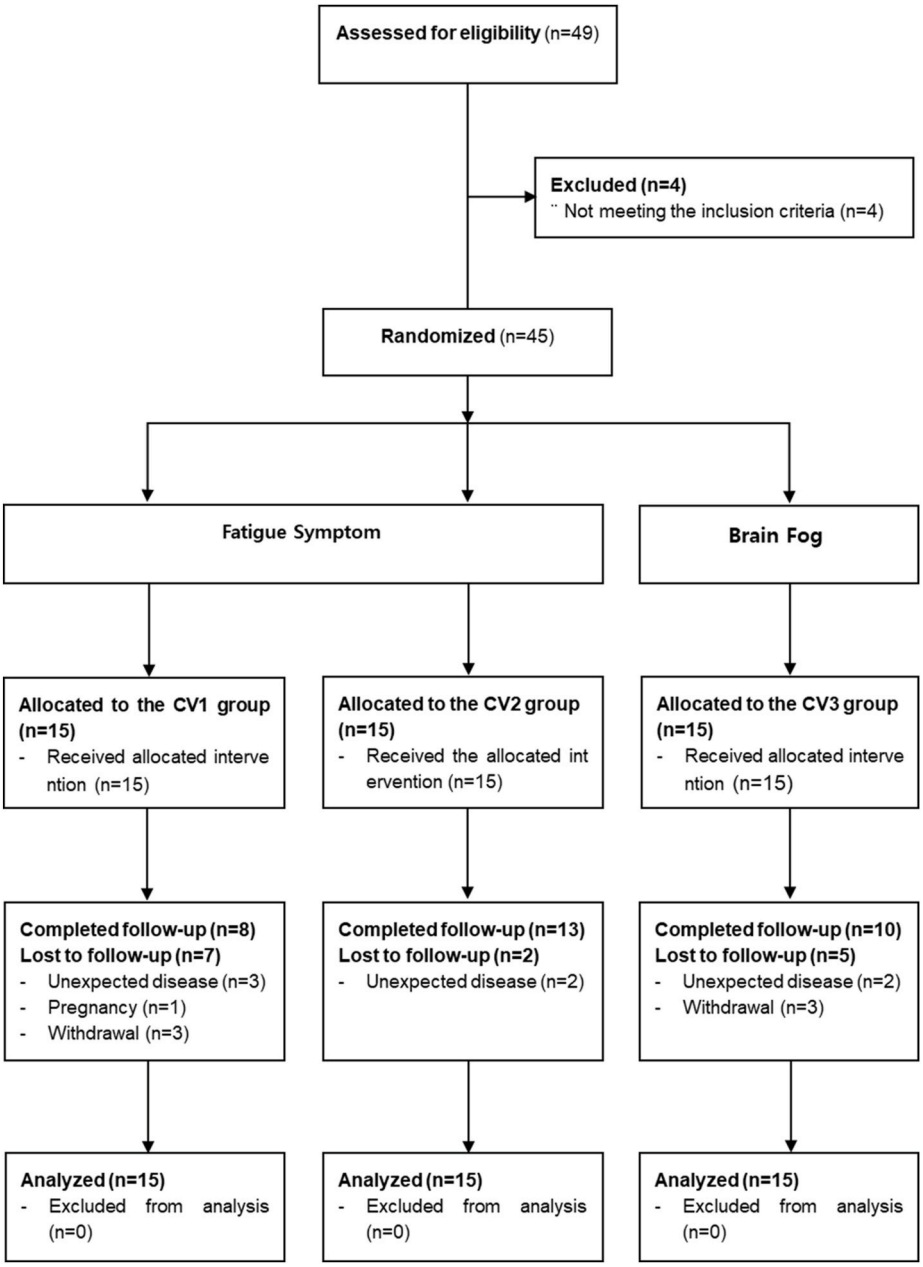

Fig. 1. Flow chart for the study subjects.

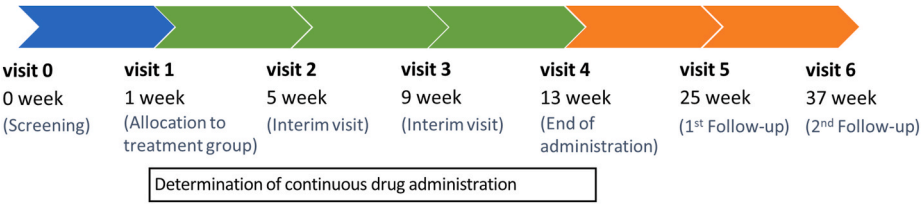

Fig. 2. Timeline for the study subjects.

Table 4
Baseline characteristics.

		BIT (n = 15)	KOG (n = 15)	CBD (n = 15)	P-value
Age[a]		43.80 ± 14.31	45.33 ± 12.57	51.33 ± 15.71	0.3656
Sex (M/F)[b]		9/6	8/7	6/9	0.6548
Body mass index[a]		24.21 ± 3.56	23.17 ± 3.67	23.41 ± 3.07	0.8233
Final level of education[b]					
	Less than elementary school	0	0	0	0.1742
	Elementary school	0	0	0	
	Middle school	0	0	0	
	High school	2 (13.33 %)	5 (33.33 %)	7 (46.67 %)	
	University or college	13 (86.67 %)	10 (66.67 %)	8 (53.33 %)	
Occupation[b]					
	Physical labor	0	1(6.67 %)	6(40.00 %)	0.6692
	Non-physical labor	10 (66.67 %)	11(73.33 %)	8(53.33 %)	
	Others (unemployed, etc)	5 (33.33 %)	3(20.00 %)	1(6.67 %)	
Time duration since initial infection of COVID-19 (days)[a]		8.87 ± 3.46	10.53 ± 4.61	10.20 ± 8.08	0.3310
NEWS[a]		1.00 ± 2.54	2.47 ± 4.26	2.07 ± 4.03	0.3540
Symptom durations					
	Fatigue (days)	89.47 ± 33.25	114.80 ± 92.11	–	
	Cognitive dysfunction (days)	–	–	119.13 ± 97.95	
Baseline CIS score[a]		100.60 ± 10.66	96.60 ± 15.36	105.4 ± 17.93	0.3331
Baseline VAS for fatigue symptom[a]		76.87 ± 14.58	73.27 ± 9.05	70.33 ± 20.34	0.4900
Baseline VAS for cognitive dysfunction[a]		49.27 ± 24.86	40.60 ± 26.08	62.00 ± 24.65	0.1039
Reason for drop out (n)					
	Unexpected diseases	3	2	2	
	Pregnancy	1			
	Withdrawal	3		3	

Abbreviations: BIT, Bojungikgi-tang group; KOG, Kyungok-go group; CBD, Cheonwangbosim-dan group; NEWS, The national early warning score; CIS, Checklist individual strength; VAS, visual analogue scale.
Data are presented as mean ± SD or n (%).
[a] Kruskal–Wallis test.
[b] Chi-squared test.

(31 %) dropped out due to various reasons. During the 12-week intervention period, 4 participants dropped out. At the 25th week after the study began, 5 participants dropped out, and at the 37th week, another 5 participants dropped out. A significant number of these dropouts were attributed to unexpected diseases, with six individuals experiencing a reinfection of COVID-19. However, no withdrawals were linked to AEs from the administered drug. In the BIT group, seven participants dropped out due to unexpected diseases ($n = 3$), pregnancy ($n = 1$), and withdrawal of consent ($n = 3$). In the KOG group, two dropped out due to unexpected diseases. In the CBD group, five dropped out due to unexpected diseases ($n = 2$) and withdrawal ($n = 3$) (Table 4 and Fig. 1). Medication adherence among participants who completed 12 weeks of drug administration was high (92.27 %, 96.26 %, and 85.66 % in the BIT, KOG, and CBD groups, respectively, Table 5). Considering these factors as well as participant recruitment, intervention administration, and long-term follow-up, the study design can be considered feasible. Participant recruitment was conducted over a year, and a significant number of dropouts (5 out of 14) occurred at the last visit in the 37th week of the study. Additionally, many participants contracted COVID-19 again during the pandemic period, resulting in dropouts due to this unexpected disease. Considering these factors, the study design is not considered to be excessively stringent or impractical.

3.4. Assessments of fatigue and cognitive dysfunction symptoms

After 12 weeks of herbal drug administration, fatigue symptoms improved significantly in each group, with treatment success rates

Table 5
Primary outcomes and outcomes for feasibility assessment.

	BIT (n = 15)	KOG (n = 15)	CBD (n = 15)	P-value[c]
Treatment success of VAS for fatigue n (%)[a]	12 (80)	8 (53.33)	7 (46.67)	0.1431
Treatment success of VAS for cognitive dysfunction n (%)[a]	6 (40)	7 (46.67)	2 (13.33)	0.1225
Medication adherence % (SD)[b]	92.27(16.28)	96.26 (15.75)	85.66 (23.61)	
Withdrawal (n)	3	0	3	

Abbreviations: BIT, Bojungikgi-tang group; KOG, Kyungok-go group; CBD, Cheonwangbosim-dan group; VAS, visual analogue scale; SD, Standard deviation.
[a] Chi-squared test.
[b] ANCOVA test (or Kruskal-Wallis test).
[c] p-value for group comparison.

of 80 %, 53.33 %, and 46.67 % in the BIT, KOG, and CBD groups, respectively. However, treatment success rates for cognitive dysfunction symptoms were comparatively low (40 %, 46.67 %, and 13.33 % in the BIT, KOG, and CBD groups, respectively) (Table 5). In addition, CIS showed significant improvement in each group at 13 weeks (mean difference: −29.53, 95 % confidence interval [CI]: −40.96 to −18.1 in the BIT group, −31.47, 95 % CI: −43.47 to −19.46 in the KOG group, and −23.4, 95 % CI: −34.79 to −12.01 in the CBD group), 25 weeks, and 37 weeks, with no significant difference between groups after treatments. Similarly, the VAS score for fatigue showed significant improvement at 13 weeks in each group (mean difference: −32.53, 95 % CI: −46.07 to −19.00 in the BIT group, −30.13, 95 % CI: −47.11 to −13.16 in the KOG group, and −16.73, 95 % CI: −27.48 to −5.98 in the CBD group), 25 weeks, and 37 weeks in each group, with no significant difference between groups after treatments. In terms of the total, physical health, and mental health scores of ChFS significant improvement in each group was observed at 13 weeks (mean difference: −23.67, 95 % CI: −35.09 to −12.24 in the BIT group, −21.27, 95 % CI: −32.91 to −9.62 in the KOG group, and −10.93, 95 % CI: −19.93 to −1.93 in the CBD group for the total score; −17.27, 95 % CI: −25.38 to −9.15 in the BIT group, −14.2, 95 % CI: −21.41 to −6.99 in the KOG group, and −6.27, 95 % CI: −11.99 to −0.54 in the CBD group for the physical health score; −6.4, 95 % CI: −10.98 to −1.82 in the BIT group, −7.07, 95 % CI: −11.98 to −2.16 in the KOG group, and −4.67, 95 % CI: −8.3 to −1.03 in the CBD group for the mental health score), 25 weeks, and 37 weeks, with no significant difference between groups except mental health (p = −0.0469) (Table 6).

In terms of cognitive dysfunction symptoms, no significant improvements were observed in each group. The VAS score for cognitive dysfunction did not show significant improvement at 13 weeks (mean difference: −6.27, 95 % CI: −26.71 to 14.17 in the BIT group, −5.4, 95 % CI: −27.98, 17.18 in the KOG group, and 1.4, 95 % CI: −10.8 to 13.6 in the CBD group), 25 weeks, or 37 weeks, with no significant difference between groups. However, the Korean–Montreal Cognitive Assessment score showed significant improvement in the KOG group at 13 weeks (mean difference: 1.80, 95 % CI: 0.77 to 2.83), 25 weeks (mean difference: 1.87, 95 % CI: 1.03 to 2.70), and 37 weeks (mean difference: 1.47, 95 % CI: 0.53 to 2.40). In addition, the Cognitive Failure Questionnaire score showed significant improvement in the BIT, KOG, and CBD groups at 37 weeks (mean difference: −4.40, 95 % CI: −7.57 to −1.23 in the BIT group, −3.93, 95 % CI: −11.57 to 3.70 in the KOG group, and −11.67, 95 % CI: −21.07 to −2.26 in the CBD group), which might imply potential effects of CBD for cognitive dysfunction. Scores for the DF-forward test and DB-backward test did not show significant improvements at 13 weeks (mean difference: 0.27, 95 % CI: −0.27 to 0.8 in the BIT group, 0, 95 % CI: −0.47 to 0.47 in the KOG group, and −0.07, 95 % CI: −0.46 to 0.42 in the CBD group for the DF-forward score and 1.4, 95 % CI: 0.4 to 2.4 in the BIT group, 0.4, 95 % CI: −0.26 to 1.06 in the KOG group, and 0.8, 95 % CI: −0.21 to 1.81 in the CBD group for the DB-backward score), 25 weeks, or 37 weeks. Furthermore, the Korean–Boston Naming Test–15 score did not show significant improvement at 13 weeks (mean difference: 0.13, 95 % CI: −0.06 to 0.33 in the BIT group, 0.13, 95 % CI: −0.06 to 0.33 in the KOG group, and 0.33, 95 % CI: −0.21 to 0.87 in the CBD group), 25 weeks, or 37 weeks (Table 7).

Table 6
Secondary outcomes for fatigue symptoms.

			BIT (n = 15)	KOG (n = 15)	CBD (n = 15)	P-value[b]
CIS[a]	5 weeks		−18.4 (−26.89, −9.91)	−23 (−33.03, −12.97)	−8.93 (−16.27, −1.6)	0.0181[c]
	9 weeks		−27.2 (−36.15, −18.25)	−25.93 (−35.46, −16.41)	−15.53 (−24.8, −6.27)	0.0394[c]
	13 weeks		−29.53 (−40.96, −18.1)	−31.47 (−43.47, −19.46)	−23.4 (−34.79, −12.01)	0.3391
	25 weeks		−30.2 (−40.68, −19.72)	−25.33 (−35.78, −14.89)	−26.87 (−41, −12.73)	0.7643
	37 weeks		−29.6 (−39.11, −20.09)	−29.2 (−39.72, −18.68)	−26.07 (−40.95, −11.18)	0.6119
VAS for fatigue[a]	5 weeks		−28.87 (−40.27, −17.47)	−22.27 (−36.95, −7.59)	−6.47 (−13.12, 0.18)	0.0275[c]
	9 weeks		−30.07 (−42.12, −18.01)	−27.67 (−43.02, −12.32)	−14 (−25.25, −2.75)	0.2353
	13 weeks		−32.53 (−46.07, −19.00)	−30.13 (−47.11, −13.16)	−16.73 (−27.48, −5.98)	0.2509
	25 weeks		−28.6 (−40.93, −16.27)	−28.73 (−43.44, −14.03)	−15.2 (−24.56, −5.84)	0.2537
	37 weeks		−32.27 (−46.45, −18.08)	−20.07 (−36.12, −4.01)	−15.67 (−26.24, −5.1)	0.2784
ChFS[a]	5 weeks	Total	−12.73 (−21.48, −3.99)	−11.33 (−18.93, −3.73)	−5.27 (−9.66, −0.87)	0.1198
		Physical	−9.13 (−14.11, −4.15)	−7.2 (−12.11, −2.29)	−1.53 (−4.78, 1.71)	0.0461[c]
		Mental	−3.6 (−8.53, 1.33)	−4.13 (−7.42, −0.85)	−3.73 (−5.44, −2.03)	0.3220
	9 weeks	Total	−20.07 (−29, −11.13)	−15.2 (−25.83, −4.57)	−5.6 (−12.08, 0.88)	0.0199[c]
		Physical	−13.8 (−19.62, −7.98)	−9.87 (−16.27, −3.46)	−2.27 (−6.42, 1.89)	0.0139[c]
		Mental	−6.27 (−10.36, −2.17)	−5.33 (−9.86, −0.8)	−3.33 (−6.34, −0.32)	0.0174[c]
	13 weeks	Total	−23.67 (−35.09, −12.24)	−21.27 (−32.91, −9.62)	−10.93 (−19.93, −1.93)	0.0991
		Physical	−17.27 (−25.38, −9.15)	−14.2 (−21.41, −6.99)	−6.27 (−11.99, −0.54)	0.0808
		Mental	−6.4 (−10.98, −1.82)	−7.07 (−11.98, −2.16)	−4.67 (−8.3, −1.03)	0.0469[c]
	25 weeks	Total	−22.4 (−30.36, −14.44)	−17 (−28.89, −5.11)	−14.6 (−25, −4.2)	0.4634
		Physical	−16.53 (−22.48, −10.59)	−11.93 (−19.19, −4.67)	−8.73 (−15.56, −1.91)	0.2541
		Mental	−5.87 (−9.23, −2.5)	−5.07 (−9.97, −0.16)	−5.87 (−10.13, −1.6)	0.5669
	37 weeks	Total	−25.53 (−33.1, −17.97)	−18.27 (−30.04, −6.49)	−14.93 (−25.55, −4.32)	0.2411
		Physical	−19 (−24.43, −13.57)	−12.6 (−19.66, −5.54)	−8.27 (−15.26, −1.28)	0.0717
		Mental	−6.53 (−10.45, −2.62)	−5.67 (−10.59, −0.74)	−6.67 (−10.75, −2.58)	0.5402

Abbreviations: BIT, Bojungikgi-tang group; KOG, Kyungok-go group; CBD, Cheonwangbosim-dan group; VAS, visual analogue scale, ChFS, Chalder Fatigue Scale.

Data are presented as mean difference from baseline (95 % confidence intervals).

[a] ANCOVA test (or Kruskal-Wallis test).

[b] p-value for group comparison.

[c] $p < 0.05$.

Table 7
Secondary outcomes for cognitive dysfunction symptoms.

		BIT (n = 15)	KOG (n = 15)	CBD (n = 15)	P-value[b]
VAS for cognitive dysfunction[a]	5 weeks	−11.13 (−32.3, 10.04)	−4.4 (−22.91, 14.11)	−0.4 (−9.84, 9.04)	0.0477[c]
	9 weeks	−7.73 (−27.2, 11.73)	−9.33 (−29.15, 10.48)	−3.87 (−17.04, 9.3)	0.0358[c]
	13 weeks	−6.27 (−26.71, 14.17)	−5.4 (−27.98, 17.18)	1.4 (−10.8, 13.6)	0.0472[c]
	25 weeks	−6.73 (−26.23, 12.77)	−7.27 (−25.25, 10.71)	−5.87 (−14.48, 2.75)	0.2454
	37 weeks	−12.73 (−32.8, 7.33)	−7.13 (−24.32, 10.06)	−7.13(-15.81, 1.54)	0.2193
K-MoCA[a]	5 weeks	−0.53 (−2.34, 1.28)	0.20 (−0.79, 1.19)	0.87 (−0.77, 2.50)	0.5767
	9 weeks	0.60 (−1.10, 2.30)	1.33 (0.43, 2.24)	1.27 (−1.40, 3.93)	0.5382
	13 weeks	1.00 (−0.51, 2.51)	1.80 (0.77, 2.83)	1.13 (−1.96, 4.22)	0.3176
	25 weeks	1.00 (−0.29, 2.29)	1.87 (1.03, 2.70)	0.80 (−2.09, 3.69)	0.1525
	37 weeks	1.07 (−0.30, 2.43)	1.47 (0.53, 2.40)	1.00 (−1.89, 3.89)	0.4059
CFQ[a]	37 weeks	−4.40 (−7.57, −1.23)	−3.93 (−11.57, 3.70)	−11.67 (−21.07, −2.26)	0.9368
DF-forward[a]	13 weeks	0.27 (−0.27, 0.8)	0 (−0.47, 0.47)	−0.07 (−0.46, 0.32)	0.4532
	25 weeks	0.07 (−0.42, 0.56)	0.47 (0.11, 0.82)	−0.07 (−0.86, 0.73)	0.3573
	37 weeks	0.33 (−0.01, 0.68)	0.47 (0.11, 0.82)	−0.2 (−0.96, 0.56)	0.1230
DB-backward[a]	13 weeks	1.4 (0.4, 2.4)	0.4 (−0.26, 1.06)	0.8 (−0.21, 1.81)	0.2095
	25 weeks	0.87 (−0.04, 1.78)	0.47 (−0.31, 1.25)	0.8 (−0.23, 1.83)	0.8091
	37 weeks	1.13 (0.13, 2.13)	1.07 (0.36, 1.78)	0.8 (−0.21, 1.81)	0.4459
K-BNT-15[a]	13 weeks	0.13 (−0.06, 0.33)	0.13 (−0.06, 0.33)	0.33 (−0.21, 0.87)	0.5933
	25 weeks	0.13 (−0.06, 0.33)	0.2 (−0.11, 0.51)	0.07 (−1.14, 1.28)	0.6532
	37 weeks	0.2 (−0.11, 0.51)	0.27 (−0.06, 0.6)	0.13 (−1.07, 1.33)	0.6417

Abbreviations: BIT, Bojungikgi-tang group; KOG, Kyungok-go group; CBD, Cheonwangbosim-dan group; VAS, visual analogue scale; K-MoCA, Korean–Montreal Cognitive Assessment scale for cognitive function; CFQ, Cognitive Failure Questionnaire; DF, Digit Span Forward; DB, Digit Span Backward; K-BNT-15, Korean-Boston Naming Test-15.
Data are presented as mean difference from baseline (95 % confidence intervals).
[a] ANCOVA test (or Kruskal-Wallis test).
[b] p-value for group comparison.
[c] $p < 0.05$.

3.5. Other outcome and safety assessments

The EQ-5D did not show a significant difference between groups at 13 weeks, 25 weeks and 37 weeks. At 13 weeks, slight improvement in EQ-5D was observed in BIT group (mean difference: 0.06, 95 % CI: 0.02 to 0.11 in the BIT group, 0.02, 95 % CI: −0.04 to 0.07 in the KOG group, and −0.01, 95 % CI: −0.11 to 0.88 in the CBD group). In addition, the Pittsburgh Sleep Quality Index-K score showed significant improvement in the KOG group at 13 weeks (mean difference: −2.71, 95 % CI: −3.76 to −1.67), 25 weeks (−2.08, 95 % CI: −3.28 to −0.89), and 37 weeks (−2.82, 95 % CI: −3.94 to −1.70), with no significant improvements in the BIT and KOG groups. Furthermore, the Beck's Depression Inventory score showed significant improvement in the BIT and KOG groups at 13 weeks (mean difference: −3.80, 95 % CI: −6.86 to −0.74 in the BIT group, −4.73, 95 % CI: −6.87 to −2.59 in the KOG group, and −5.53, 95 % CI: −11.21 to 0.14 in the CBD group), 25 weeks, and 37 weeks (Table 8).

Table 8
Secondary outcomes for EQ-5D-5L, PSQI-K, and BDI.

		BIT (n = 15)	KOG (n = 15)	CBD (n = 15)	P-value[b]
EQ-5D-5L[a]	5 weeks	0.01 (−0.03, 0.04)	−0.03 (−0.07, 0.02)	−0.04 (−0.09, 0.01)	0.1040
	9 weeks	0.03 (0, 0.06)	0.01 (−0.05, 0.07)	−0.01 (−0.05, 0.04)	0.2034
	13 weeks	0.06 (0.02, 0.11)	0.02 (−0.04, 0.07)	−0.01 (−0.11, 0.08)	0.1417
	25 weeks	0.06 (0.02, 0.11)	−0.01 (−0.05, 0.03)	0.03 (−0.06, 0.11)	0.3256
	37 weeks	0.07 (0.03, 0.11)	0 (−0.04, 0.05)	0.03 (−0.06, 0.12)	0.4582
PSQI-K[a]	5 weeks	0.14 (−1.16, 1.44)	−2.14 (−3.10, −1.19)	0.07 (−1.14, 1.28)	0.0364[c]
	9 weeks	−0.85 (−1.92, 0.22)	−3.07 (−4.10, −2.05)	−0.64 (−2.19, 0.90)	0.0557
	13 weeks	−1.15 (−2.96, 0.66)	−2.71 (−3.76, −1.67)	−1.50 (−3.35, 0.35)	0.6978
	25 weeks	−1.25 (−3.40, 0.90)	−2.08 (−3.28, −0.89)	−1.55 (−4.72, 1.63)	0.9725
	37 weeks	−1.64 (−3.72, 0.45)	−2.82 (−3.94, −1.70)	−2.33 (−4.51, −0.16)	0.9540
BDI[a]	5 weeks	−3.40 (−5.50, −1.30)	−2.20 (−3.77, −0.63)	−1.27 (−4.87, 2.34)	0.1882
	9 weeks	−3.27 (−5.76, −0.77)	−3.40 (−5.14, −1.66)	−4.13 (−8.05, −0.21)	0.8568
	13 weeks	−3.80 (−6.86, −0.74)	−4.73 (−6.87, −2.59)	−5.53 (−11.21, 0.14)	0.8669
	25 weeks	−4.60 (−7.82, −1.38)	−3.80 (−6.20, −1.40)	−6.53 (−13.15, 0.08)	0.9885
	37 weeks	−4.47 (−7.38, −1.55)	−4.00 (−6.62, −1.38)	−6.33 (−11.20, −1.47)	0.9212

Abbreviations: BIT, Bojungikgi-tang group; KOG, Kyungok-go group; CBD, Cheonwangbosim-dan group; EQ-5D-5L, Standardized 5-level EuroQol 5-Dimensional Questionnaire; PSQI-K, the Korean version of Pittsburgh Sleep Quality Index; BDI, Beck's Depression Inventory.
Data are presented as mean difference from baseline (95 % confidence intervals).
[a] ANCOVA test (or Kruskal-Wallis test).
[b] p-value for group comparison.
[c] $p < 0.05$.

Among the 45 participants, 10 (22.22 %) reported AEs, with no significant differences in the incidence rates of AEs among groups ($p = 0.2805$). All AEs were mild, and none were found to be causally related to the medication. Furthermore, there were no significant differences among groups in terms of the proportion of normal laboratory test results after treatment termination (Table 9).

4. Discussion

Through this pilot study, we found that the research design and intervention for this study were feasible. Although a considerable number of participants dropped out during the follow-up period due to the COVID-19 pandemic, there were no AEs directly related to the intervention, and adherence to the medication was high. Fatigue symptoms improved significantly in all groups, regardless of the type of prescription administered. For patients with long COVID experiencing fatigue, a 12-week administration of BIT or KOG may be considered, with effects persisting not only during the intervention period but also up to six months post-intervention. Significant decrease in CFQ score of the CBD group suggests that CBD might have potential effect for the recovery of cognitive dysfunction in the long COVID patients. However, since there were no significant changes observed in other cognitive function assessments after treatment, this result should be interpreted carefully. Nonetheless, some improvement was observed six months after the intervention ended, which may be attributed to the natural course of the disease. Further research is warranted to explore the potential effects of herbal medicine in long COVID patients.

In this study, three interventions were selected as treatments for fatigue and cognitive dysfunction symptoms that may occur after COVID-19. BIT had been widely used as a prescription to treat various symptoms of impaired gastric function caused by dietary irregularities or overexertion. It has been approved by the Korean regulatory agency (MFDS) for weakness, fatigue, lethargy, post-disease debility, poor appetite, night sweating, and vulnerability to fatigue due to a lack of vitality and sluggish gastrointestinal movement. It is composed of *Panax ginseng*, *Atractylodes japonica*, *Astragalus membranaceus*, *Angelica gigas*, *Zizyphus jujuba*, *Bupleurum falcatum*, *Citrus unshiu*, *Glycyrrhiza uralensis*, *Cimicifuga heracleifolia*, and *Zingiber officinale*. It has been to have many clinical effects, and the therapeutic mechanism may be related to immunological, neuropsychiatric, anti-inflammatory, and musculoskeletal regulation [30]. It has been suggested to be effective in alleviating chronic fatigue-related general symptoms [31]. In addition, it can improve the quality of life, fatigue, and immunological status of elderly patients with weakness [32]. A previous case report reported the use of BIT for fatigue symptoms after COVID-19. In a case report of a 55-year-old woman experiencing chronic fatigue syndrome for over six months, 21 weeks of treatment with BIT resulted in improvements in subjective fatigue levels and Brief Fatigue Inventory scores [33]. KOG has been widely used to treat chronic diseases and is approved for conditions such as illness-related weakness,

Table 9
Safety outcomes.

		BIT (n = 15)	KOG (n = 15)	CBD (n = 15)	P-value[b]
Number participants with adverse events (%)[a]		5 (33.33)	1 (6.67)	4 (26.67)	0.2805
Type of AEs (n)[a]					
	Back pain	1	0	0	
	Hypothyroidism	1	0	0	
	Common cold	0	1	0	
	High blood glucocorticoids level	0	0	1	
	Hypertension	0	0	1	
	Arthritis	0	0	1	
	Animal hair allergy	1	0	0	
	Insomnia	1	0	0	
	Rhinitis	1	0	0	
	Mucous cyst	0	0	1	
Severity of AEs (n)[a]					
	Mild	5	1	4	
	Moderate	0	0	0	
	Severe	0	0	0	
Causality (n)[a]					
	Drug-related AEs	0	0	0	
	Non-related AEs	5	1	4	
Number of participants with normal laboratory test results at 13 weeks (n, %)[a]		BIT (n = 13)[c]	KOG (n = 14)[c]	CBD (n = 14)[c]	
	BUN	10 (76.92)	9 (64.29)	12 (85.71)	0.4423
	Creatinine	11 (84.62)	14 (100)	14 (100)	0.0951
	AST	12 (92.31)	14 (100)	14 (100)	0.3171
	ALT	12 (92.31)	13 (92.86)	13 (92.86)	1.0000
	ECG	12 (92.31)	14 (100)	14 (100)	0.3171

Abbreviations: BIT, Bojungikgi-tang group; KOG, Kyungok-go group; CBD, Cheonwangbosim-dan group; AEs, adverse events.
Data are presented as n (%) or n.
[a] Chi-squared test.
[b] p-value for group comparison.
[c] Those who completed laboratory tests after treatment termination (13 weeks).

post-disease debility, weak constitution, physical fatigue, lethargy, and menopausal disorders, serving as a tonic and strengthener in Korea. It is composed of *Rehmannia glutinosa*, *Panax ginseng*, *Poria cocos*, and Mel Honey. Its therapeutic mechanism may be related to immune system activation [34], fatigue reduction [35,36], and cognitive function enhancement [37] as well as its anti-inflammatory effects [38–40]. CBD has been used for the treatment of anxiety, palpitation, and cognitive dysfunction. It has been approved in Korea for a variety of conditions, including insomnia, anxiety, restlessness, thirst, palpitations, shortness of breath, nervous debility, cognitive dysfunction and feverishness. It is composed of *Rehmannia glutinosa*, *Panax ginseng*, *Scrophularia buergeriana*, *Salvia miltiorrhiza*, *Polygala tenuifolia*, *Platycodon grandiflorum*, *Poria cocos*, *Schisandra chinensis*, *Angelica gigas*, *Asparagus cochinchinensis*, *Liriope platyphylla*, *Thuja orientalis*, *Zizyphus jujuba*, and *Coptis japonica*. In animal models, it has been found to inhibit learning and memory impairment, suggesting a potential effect on cognitive function [41]. CBD has also been shown to reduce inflammatory responses [42] and improve sleep quality in patients with primary insomnia [43]. Furthermore, it exhibits neuroprotective [44], vasorelaxant, hypotensive [45], and anti-Alzheimer's disease [46,47] effects. It is commonly prescribed for alleviating the psychological and behavioral symptoms of dementia related to Alzheimer's disease [48].

This study has some limitations. First, it was a pilot study with no control group. Therefore, concrete evidence regarding the efficacy and safety of these three herbal medications for long COVID could not be established. However, the feasibility of the study design was confirmed, and future large-scale clinical trials are required. Second, the outcomes assessed may be inappropriate for assessing fatigue and cognitive dysfunction in patients with long COVID. The definition of long COVID is currently ambiguous, and there is no clear description of the underlying pathologic mechanism of its symptoms. While the diagnosis and treatment of long COVID-related fatigue may be approached by considering post-viral syndrome, approaching cognitive dysfunction is more challenging due to its distinct presentation from cognitive impairments observed in dementia. One possible reason for the lack of significant improvement in cognitive function before and after drug treatment in patients with cognitive dysfunction in this study is that the condition they are experiencing differs from cognitive decline in Alzheimer's dementia. As a result, existing assessment tools designed for patients with dementia may not be able to adequately evaluate their cognitive function, which is a significant consideration in this context. Third, approximately 30 % of study participants dropped out, demonstrating a high dropout rate. This may be attributed to the study's long-term participation requirements, which included a 12-week intervention period followed by a six-month follow-up. Furthermore, the ongoing COVID-19 pandemic has led to a significant number of patient re-infections. When conducting clinical trials for the management of patients with long COVID, it is important to consider the potential for a high dropout rate in the study design.

5. Conclusions

This clinical study aimed to evaluate the feasibility of a research design by administering three types of herbal medicine traditionally used in Korean medicine to treat two predominant symptoms of long COVID—fatigue and cognitive dysfunction—over a 12-week period, followed by a 6-month follow-up. The feasibility of this study has been demonstrated. Recruitment of participants, dropout rates, and occurrence of adverse events indicated that the administration of these interventions appeared feasible. However, the occurrence of significant dropouts at the 6-month follow-up and unexpected dropouts due to factors such as reinfection during the COVID-19 pandemic highlight considerations for future clinical trial designs. For interventions such as BIT or KOG, which demonstrated potential efficacy for fatigue in this study, establishing definitive evidence of efficacy through prospective studies with adequate sample sizes, including pre-post designs or large-scale randomized controlled trials incorporating placebos, is imperative. Screening potentially effective treatments for cognitive dysfunction should also be revisited. Furthermore, given that cognitive impairment in chronic COVID-19 presents differently from that in dementia, appropriate assessment tools tailored to evaluating these patients need development. Given the impact of long COVID and the scarcity of studies evaluating the effects of interventions on fatigue and cognitive dysfunction this study is deemed valuable. Future clinical studies with an appropriate control group and a sufficient sample size are needed to establish the evidence for herbal medicine in the management of long COVID-19.

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Data availability statement

Data are included in this article and/or supp. materials.

CRediT authorship contribution statement

Tae-Hun Kim: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Jiwon Yoon:** Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Conceptualization. **Sanghyun Kim:** Writing – review & editing, Visualization, Conceptualization. **Byoung-Kab Kang:** Visualization, Validation, Formal analysis. **Jung Won Kang:** Writing – review & editing, Validation. **Sunoh Kwon:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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