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Original Article

Efficacy and safety of herbal medicine Gongjin-Dan and Ssanghwa-Tang in patients with chronic fatigue: A randomized, double-blind, placebo-controlled, clinical trial

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ABSTRACT

Background: Gongjin-dan (GJD, also known as Gongchen-dan) and Ssanghwa-tang (SHT, also known as Shuanghe-tang or Souwa-to) are herbal medicines that are widely used in Korea for treating fatigue. However, few studies have evaluated the efficacy and safety of GJD and SHT in the treatment of chronic fatigue.
Methods: In this randomized, double-blind, placebo-controlled clinical trial, 90 individuals with persistent (≥6 months) chronic fatigue of unknown cause and a Fatigue Severity Scale (FSS) score of ≥4 were randomly assigned to GJD group, SHT group, and control group in a 1:1:1 ratio. Outcomes were the changes in the self-reported fatigue questionnaire scores, levels of fatigue-related biomarkers and safety assessment.
Results: Out of 103 patients recruited, 90 were included in the analysis. A significant improvement in the Social Functioning (SF) score of Short-Form 36 Health Survey (SF-36) at week 4 was observed in the GJD group; similarly, a significant improvement compared with that in the Control group was observed in the Role Emotional (RE) score of SF-36 at weeks 4 and 6 and the Physical Functioning (PF) score of SF-36 at week 6 in the SHT group. Laboratory tests revealed no abnormalities, and serious intervention-related adverse events were not reported.
Conclusions: It is suggested that SHT can effectively treat chronic mental and physical fatigue, whereas GJD can effectively treat chronic mental and social fatigue. Furthermore, this study presents evidence supporting the safety of the long-term use of GJD and SHT (up to 4 weeks).
Trial registration: This study was registered at Clinical Research Information Service (CRIS) of Korea with the registration number KCT0007515.

1. Introduction

Fatigue is defined as decreased physical and mental capacity resulting from an imbalance between the availability, utilization, and restoration of resources needed for activity.[1] Fatigue impairs decision-making, problem-solving, and psychomotor skills, as well as processing speed and memory, thereby decreasing occupational performance.[2] Chronic fatigue is defined as fatigue that persists for a period of six months or more. Chronic fatigue of unknown cause can be categorized as chronic fatigue syndrome (CFS) or idiopathic chronic fatigue (ICF).[3] The prevalence of chronic fatigue varies across countries, with a prevalence of about 8.4 % in the Republic of Korea.[4]

The cause of chronic fatigue remains elusive, which hinders the development of appropriate treatment strategies. Thus, only a limited number of treatment options are currently available despite continued and extensive research being conducted on fatigue.[5]

Gongjin-dan (GJD, also known as Gongchen-dan) is a widely prescribed herbal prescription in Korea and China that is used for the management of fatigue-related symptoms.[6] Ssanghwa-tang (SHT, also known as Shuanghe-tang or Souwa-to) has been used for several thou-

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sand years in Korea, China, and Japan to improve a weak constitution, relieve fatigue, and facilitate recovery from illness.[7] GJD and SHT are popular traditional herbal medicines used for health promotion in Korea, with GJD and SHT ranking third (12.12 %) and fifth (5.16 %), respectively, in terms of production (totaling 126 million USD) among 134 herbal agents according to the 2021 Korean pharmaceutical production data.[8]

Laboratory and animal studies have demonstrated various pharmacological effects of GJD, including improved memory,[6,9] alleviation of fatigue,[10] antioxidant properties,[11] and neuroprotective effects.[12] A previous study reported that GJD was effective in alleviating fatigue induced by two days of sleep deprivation in healthy men[13]; however, no randomized controlled trial (RCT) has been conducted on chronic fatigue. SHT has an array of pharmacological effects, including analgesic, hepatoprotective, anti-inflammatory, and anti-osteoporotic effects.[14,15] In previous animal experiments, the efficacy of Ssanghwa-tang in improving fatigue was confirmed.[16,17] However, no RCTs have investigated the effects of SHT on chronic fatigue. Therefore, this study aimed to investigate the efficacy and safety of GJD and SHT in patients with chronic fatigue.

2. Methods

2.1. Study protocol

The study protocol[18] was registered with the Clinical Research Information Service (CRIS) managed by the Korea Disease Control and Prevention Agency (CRIS registration number: KCT0007515).

2.2. Study design

This randomized, double-blind, placebo-controlled clinical trial was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Pusan National University Korean Medicine Hospital (PNUKHIRB 2021–10–005). Written informed consent was obtained from all participants.

2.3. Participants

2.3.1. Inclusion criteria

1) Men and women aged 19–65 years
2) Fatigue of unknown cause persisting for ≥6 months, with an average Korean Fatigue Severity Scale (FSS) score of ≥4
3) No abnormalities in blood pressure, complete blood count (hemoglobin [Hb] level, hematocrit [Hct]), white blood cell [WBC] count), biochemistry (aspartate aminotransferase [AST], alanine aminotransferase [ALT], creatinine, and glucose levels), thyroid function test (thyroid stimulating hormone [TSH] and free thyroxine [FT4] levels), and electrocardiography (ECG) that may induce fatigue
4) Voluntary signing of the consent form after receiving a clear explanation about the purpose and objectives of the trial
5) Capable of communicating with the investigator and completing the questionnaire
6) Available to continue follow-up visits during the study period

2.3.2. Exclusion criteria

1) Sum of scores for items 4 and 9 of FSS is ≥7
2) Pregnant or breastfeeding women or men and women of childbearing capacity who did not consent to use medically permitted contraceptives during the study period
3) Uncontrolled hypertension (diastolic blood pressure [DBP] of >100 mmHg or systolic blood pressure [SBP] of >160 mmHg)
4) AST, ALT, or alkaline phosphatase (ALP) levels exceeding 2.5 times the normal upper limit defined by the trial facility
5) Creatinine levels exceeding 1.5 times the normal upper limit defined by the trial facility
6) Participation in another clinical trial within one month of beginning this trial or planning to participate in another clinical trial during the trial period
7) History of hypersensitivity or allergies to the ingredients of the investigational product (IP)
8) History of autoimmune diseases (e.g., multiple sclerosis, lupus erythematosus, and rheumatoid joints)
9) History of addiction, mental disorders (sleep disorders, depression, and anxiety), or drug dependence.
10) History of cognitive impairment or psychiatric problem
11) History of surgery within 2 weeks before the screening visit
12) Use of medical or Korean traditional medicines for relieving chronic fatigue or health supplements that help relieve fatigue in the preceding two weeks
13) Individuals with fatigue that can be improved via lifestyle changes, such as those on continuous night shift and rotating shifts
14) Active use of antidepressants, anxiolytics, and antihistamines at the time of the screening visit
15) Presence of a medical condition that is presumed to affect the trial outcomes or deemed inappropriate to participate in the trial by the investigator

2.4. Randomization and blinding

Eligible participants were randomly allocated at a 1:1:1 ratio to the GJD (GJD + SHT placebo), SHT (SHT + GJD placebo), or control (GJD placebo + SHT placebo) group. A block randomization method was used, and the block size was 9. The randomization table was assigned by a medical statistician independent of the interventions and evaluations used in clinical trials using the statistical program SAS® Version 9.4 (SAS institute. Inc, Cary, NC), with each subject having the same probability of being selected. A three-digit identification code (Randomized Number) is assigned to the recruited subjects according to the randomization table, and the investigational products are distributed according to the code. Random numbers once assigned are not reused.

Each participant received GJD or GJD placebo once daily (one pill a day) or SHT or SHT placebo thrice daily (three packs per day) for 28 days using a double dummy method. A randomization table was created by a statistician using SAS® Version 9.4 (SAS Institute. Inc, Cary, NC) software. Medical or Korean traditional medicine treatments for chronic fatigue and the use of health supplements that help improve fatigue was prohibited during the study period.

2.5. Interventions

2.5.1. Preparation of GJD and SHT

GJD and SHT have received approval from the Korea Ministry of Food and Drug Safety. The IP was manufactured by and purchased from Iksu Pharmaceuticals (Seoul, Republic of Korea). GJD used in this study was a 3.75-g gilt-coated black-brown pill containing *Angelica gigas* Nakai, *Cervus nippon* Temminck, *Cornus officinalis* Seibold & Zucc., *Panax ginseng* C.A. Meyer, *Rehmannia glutinosa* (Gaertn.) DC., and *Moschus moschifrus* L. SHT is a brown solution containing *Angelica gigas* Nakai, *Astragalus membranaceus* Bunge, *Cnidium officinale* Mak., *Rehmannia glutinosa* (Gaertn.) DC., *Cinnamomum cassia* J. Presl, *Zingiber officinale* Rosc, *Zizyphus jujuba* Miller var. *hoonensis* T. B. Lee, *Glycyrrhizia uralensis* Fisch, and *Paenoia lactiflora* Pall. (Table 1).

The GJD and SHT placebos were manufactured by the same pharmaceutical company. The GJD placebo mainly comprises lactose hydrate and cornstarch, with small amounts of honey, squid ink pigment, *Angelica gigas* Nakai, and *Panax ginseng* C.A. Meyer flavoring. The SHT placebo mainly comprises high-fructose syrup, which contains caramel coloring. Both placebos had the same size, shape, color, flavor, and packaging as the IP.

Table 1
Composition of GJD one-pill and SHT.

Latin name	Scientific name	Composition of raw material (g)	
		GJD	SHT
Angelicae Gigantis Radix	*Angelica gigas* Nakai	0.444	3.750
Corni Fructus	*Cornus officinalis* Seibold & Zucc.	0.444	
Ginseng Radix	*Panax ginseng* C.A. Meyer	0.444	
Rehmanniae Radix Preparata	*Rehmannia glutinosa* (Gaertn.) DC.	0.444	3.750
Moschus	*Moschus moschifrus* L.	0.074	
Cervi Parvum Cornu	*Cervus nippon* Temminck	0.444	
Additives	Honey, glycerin, gilt, corn starch, sodium benzonate	1.456	
Paeoniae Radix	*Paenoia lactiflora* Pall.		9.375
Astragali Radix	*Astragalus membranaceus* Bunge		3.750
Cnidii Rhizoma	*Cnidium officinale* Mak.		3.750
Cinnamomi Cortex	*Cinnamomum cassia* J. Presl		2.813
Glycyrrhizae Radix et Rhizoma	*Glycyrrhizia uralensis* Fisch.		2.812
Zingiberis Rhizoma Recens	*Zingiber officinale* Rosc.		3.750
Zizyphi Fructus	*Zizyphus jujuba* Miller var. *hoonensis* T. B. Lee		3.750
Total amount (g)		3.750	37.500

GJD, Gongjin-dan; SHT, Ssanghwa-tang.

2.5.2. Chemical profiling of GJD and SHT

High-purity natural products were purchased from the following manufacturer companies as reference standard compounds for standardization of the IPs: Merck KGaA (Darmstadt, Germany), Biopurify Phytochemicals (Chengdu, China), ChemFaces Biochemical (Wuhan, China), Shanghai Sunny Biotech (Shanghai, China), and Fujifilm Wako Pure Chemical Co. (Osaka, Japan) (**Supplement 1**). The purity of the samples was at least 98.0 %. Solvents, such as water, acetonitrile, and methanol, of high-performance liquid chromatography (HPLC) grade were purchased from J.T. Baker (Phillipsburg, NJ, USA). Formic acid (ACS reagent) was purchased from Merck KGaA (Darmstadt, Germany). Chemical profiling of GJD and SHT was performed using a previously reported analytical method of HPLC.[19] Briefly, the target components were separated using a Capcell Pak UG80 C_{18} column (250 × 4.6 mm, 5 μm; Shiseido, Tokyo, Japan) in a Shimadzu Prominence LC−20A series system (Kyoko, Japan) maintained 40 °C and a mobile phase of water−acetonitrile (both containing 0.1 % formic acid). The concentration of all samples for HPLC analysis was 100 mg/10 mL with 70 % methanol.

2.6. Outcome measures

2.6.1. Primary outcome

2.6.1.1. Fatigue severity scales. The Korean version of FSS was administered at four time points: before oral IP administration (V2, baseline), 2 weeks after IP administration (V3), 4 weeks after IP administration (V4), and 2 weeks after the completion of IP administration (V5). Fatigue in the preceding week was assessed using a seven-point scale, with scores ranging from 1 to 7. The scores were summed and divided by 9 to obtain the average fatigue score, with higher average scores indicating greater fatigue.[20] The changes in the FSS score from the baseline value at V4 and V5, respectively, were the primary and secondary endpoints.

2.6.2. Secondary outcomes

2.6.2.1. Multidimensional fatigue inventory-20. The Multidimensional Fatigue Inventory-20 (MFI-20) was administered at three time points: V2, V4, and V5. This 20-item inventory was rated on a five-point scale ranging from 1 (agree) to 5 (disagree), with higher average scores indicating greater fatigue.[21] The changes in the MFI-20 scores from the baseline value at V4 and V5 were secondary endpoints.

2.6.2.2. Chalder fatigue scale. The Chalder Fatigue Scale (CFQ) was administered at three time points: V2, V4, and V5. Each of the 11 items was rated on a scale ranging from 0 (not true) to 3 (true),[22] with higher total scores indicating greater fatigue.[23] The changes in the CFQ scores from the baseline values at V4 and V5 were secondary endpoints. The cut-off value for differentiating between mild and severe fatigue was set as 15.[24]

2.6.2.3. Short-Form 36 health survey. The Short-Form 36 Health Survey (SF-36) was administered at three time points: V2, V4, and V5. The SF-36 measures the health-related quality of life using two subscales with eight domains containing 36 items. Each item is rated on a Likert scale, and the scores for each item are summed. The total score is converted to a score of 0–100 points. A lower score indicates a poorer quality of life, whereas a higher score indicates a higher quality of life.[25] The changes in the SF-36 scores from the baseline values at V4 and V5 were secondary endpoints.

2.6.2.4. Korean version of schedule of fatigue and anergy/general physician. The Korean Version of Schedule of Fatigue and Anergy/General Physician (SOFA/GP), which assesses fatigue and lethargy using 10 items, was administered at three time points: V2, V4, and V5. The answers "frequently" and "almost always" were assigned a score of 1, whereas the answers "sometimes" and "rarely" were assigned a score of 0. The cut-off score was set as 3, and the percentage of individuals with the cut-off score was compared.[26] The changes in the SOFA/GP scores from the baseline values at V4 and V5 were secondary endpoints.

2.6.2.5. Fatigue-related biomarker levels. The levels of glucose, lactate, ammonia, free fatty acid (FFA), derivatives of reactive oxygen metabolites (d-ROMs), biological antioxidant potential (BAP), selenium, and cortisol were assessed at three time points: V2, V4, and V5. The energy required for physical activity is derived from the circulating glucose released from the liver. Thus, the glucose level is an important indicator of the ability of the body to continue physical activity.[27] Accumulation of lactate in the body causes oxygenation, thereby inducing fatigue.[28] Blood ammonia can cross the blood-brain barrier and increase central fatigue.[29] FFAs are used as an energy source during exercise; thus, increased FFA levels indicate reduced fatigue.[30] D-ROMs and BAP measure the level of reactive oxygen species in the body and antioxidant capacity, respectively.[31] Selenium is a crucial cofactor for maintaining the activity of glutathione peroxidase, which catalyzes the breakdown of organic peroxides and contributes to the enhancement of liver function and alleviation of fatigue.[32] Cortisol is an indicator of the physiological changes induced by physical and mental stress.[33] The changes in the glucose, lactate, ammonia, FFA, D-ROMs, BAP, selenium, and cortisol from the baseline values at V4 and V5 were secondary endpoints.

2.7. Sample size calculation

The primary outcome is the FSS score and the change in FSS score at 4 weeks after administration compared to the baseline in test group 1 (GJD + SHT placebo), test group 2 (SHT + GJD placebo), and control group (GJD placebo + SHT placebo) was compared. The hypothesis of this clinical trial is as follows.

[Hypothesis] H0 (null hypothesis): = vs. H1 (alternative hypothesis):

: average change in FSS score at 4 weeks compared to baseline in test group 1 (GJD + SHT placebo)
: average change in FSS score at 4 weeks compared to baseline in test group 2 (SHT + GJD placebo)
: average change in FSS score at 4 weeks compared to baseline in control group (GJD placebo +SHT placebo)

The significance level was 5 % two-sided, the power was 80 %, and the average (standard deviation) of the change in FSS of the test group and control group in the previous study[34] was −2.05 (1.43) and −1.04 (1.30), respectively. The mean difference between the test group and the control group is 1.01, and the pooled standard deviation is 1.36. In this clinical trial, the significance level was set at 5 % for both sides, the power was set at 80 %, the effect difference was set at 1.0, and the standard deviation was set at 1.3. The results of calculating test subjects to confirm the effect of the test group (1 or 2) compared to the control group are as follows.

$$\left\{ \frac{2\left(z1-\frac{a}{2}+z1-B\right)^{2*\sigma^2}}{\mu_T-\mu_c} \right\} = \left\{ \frac{2(1.96+0.842)^{2*}1.3^2}{1^2} \right\} = 26.529 \approx 27$$

Under the allocation ratio of 1:1 between the test group (1 or 2) and the control group (GJD placebo + SHT placebo) in this clinical trial, the number of test subjects in each group that satisfies a two-sided significance level of 5 % and a power of 80 % is 27. Considering a 10 % drop-out rate in this clinical trial, it was calculated that a total of 90 clinical trial subjects were needed, 30 in each group.

The changes in the FSS score from the baseline value after four weeks of receiving the IP was evaluated in the GJD, SHT, and Control groups. The significance level was set as 5 % for the two-tailed test. The power, effect size, and standard deviation were set as 80 %, 1.0, and 1.3, respectively. The sample size for each group was set as 27 to achieve a 1:1 ratio for the GJD or SHT groups to the Control group. Ninety participants were recruited in this study considering a dropout rate of 90 %, with 30 participants in each group.

2.8. Adverse events

The incidence of adverse events (AEs) was recorded using case report forms. Severe AEs were reported to the IRB and sponsors in accordance with the Good Clinical Practices and Ministry of Food and Drug Safety regulations.

2.9. Statistical analysis

All statistical analyses were performed by an independent statistician using SAS® (version 9.4, SAS Institute, Cary, NC, USA) with the two-sided significance level set as 5 % (primary outcome analysis has a significance level of 2.5 %). Full analysis set (FAS) was used to analyze the effectiveness and safety of the intervention. The analysis was performed using a mixed-effect model repeated measure (MMRM) method, wherein each treatment group and visit were fixed factors, and each participant was a random factor. The differences before and after treatment within each group were evaluated using the Student's paired *t*-test. The secondary outcomes were tested in the same manner as the primary outcomes; however, the significance level was set as 5 % as they were secondary outcomes.

The primary effectiveness evaluation method of this study uses the MMRM method. The MMRM method considers missing values using maximum likelihood and does not require a separate missing value replacement step. Additionally, missing values are not replaced for demographic/social information and safety variables.

3. Results

3.1. Chemical profiling of the two clinical samples using HPLC

Chemical profiling was conducted using the following marker components to standardize GJD and SHT: gallic acid, 5-hydroxymethyl-2-furaldehyde (5-HMF), morroniside, loganin, nodakenin, decursin, and decursinol angelate for GJD; and gallic acid, 5-HMF, albiflorin, paeoniflorin, liquiritin apioside, liquiritin, ferulic acid, nodakenin, benzoic acid, coumarin, cinnamic acid, cinnamaldehyde, glycyrrhizin, decursin, and decursinol angelate for SHT. All marker analytes were well separated within 50.0 min without interference from neighboring peaks (**Supplement 2**).[19] Quantification was performed using a photodiode array detector at the following wavelengths: albiflorine, paeoniflorin, and benzoic acid at 230 nm; loganin at 235 nm; morroniside at 240 nm; glycyrrhizin at 250 nm; gallic acid at 270 nm; liquiritin apioside, liquiritin, coumarin, and cinnamic acid at 275 nm; 5-HMF at 280 nm; cinnamaldehyde at 290 nm; ferulic acid at 320 nm; decursin and decursinol angelate at 330 nm; and nodakenin at 335 nm. HPLC assay revealed the presence of gallic acid, 5-HMF, morroniside, loganin, nodakenin, decursin, and decursinol angelate at concentrations of 0.19, 0.77, 0.39, 0.58, 0.28, 2.78, and 4.03 mg/g, respectively, in GJD. Fifteen marker components, including gallic acid, 5-HMF, albiflorin, paeoniflorin, liquiritin apioside, liquiritin, ferulic acid, nodakenin, benzoic acid, coumarin, cinnamic acid, cinnamaldehyde, glycyrrhizin, decursin, and decursinol angelate, were detected at concentrations of 0.71, 0.29, 2.25, 4.07, 0.60, 0.06, 0.03, 0.20, 3.51, 0.13, 0.03, 0.24, 1.50, 0.04, and 0.05 mg/g, respectively, in SHT. Decursinol angelate, a major component of *A. gigas*, was detected most abundantly in GJD (concentration of 4.03 mg/g), whereas paeoniflorin, a major component of *P. lactiflora*, was detected most abundantly in SHT (concentration of 4.07 mg/g).

3.2. Participants

Among the 103 participants screened, 90 were enrolled in this trial. The participants were randomly allocated to one of the three groups, with 30 participants in each group (Fig. 1). Four participants in the Control group withdrew consent. One, one, and two participants withdrew consent due to lack of relief in chronic fatigue with the use of IP, unpleasant taste of the IP, and personal reasons, respectively. One participant from the GJD group withdrew consent due to fear of blood sampling. However, all participants who withdrew their consent had undergone at least one round of outcome evaluation after receiving the IP at least once. Therefore, all 90 participants were included in the statistical analysis. An FAS was performed based on the intent-to-treat (ITT) population, with 30 participants each in the control, GJD, and SHT groups. The baseline characteristics (sex, age, body weight, BMI, smoking history, drinking history, blood pressure, pulse, and body temperature) did not differ significantly among the three groups (Table 2).

3.3. Primary outcome

3.3.1. Changes in the FSS score at V4 (week 4) compared with that at V2 (baseline)

The changes in the GJD and SHT groups at V4 compared with that at V2 did not differ significantly from that in the Control group ($p > 0.05$) (Fig. 2A and **Supplement 3**). The mean difference in score at V4 compared with that at V2 between the GJD and Control groups was −0.19 (97.5 % Confidence Interval [CI]: −0.64 to 0.26, $p = 0.4080$). The mean difference in the FSS score at V4 compared with that at V2

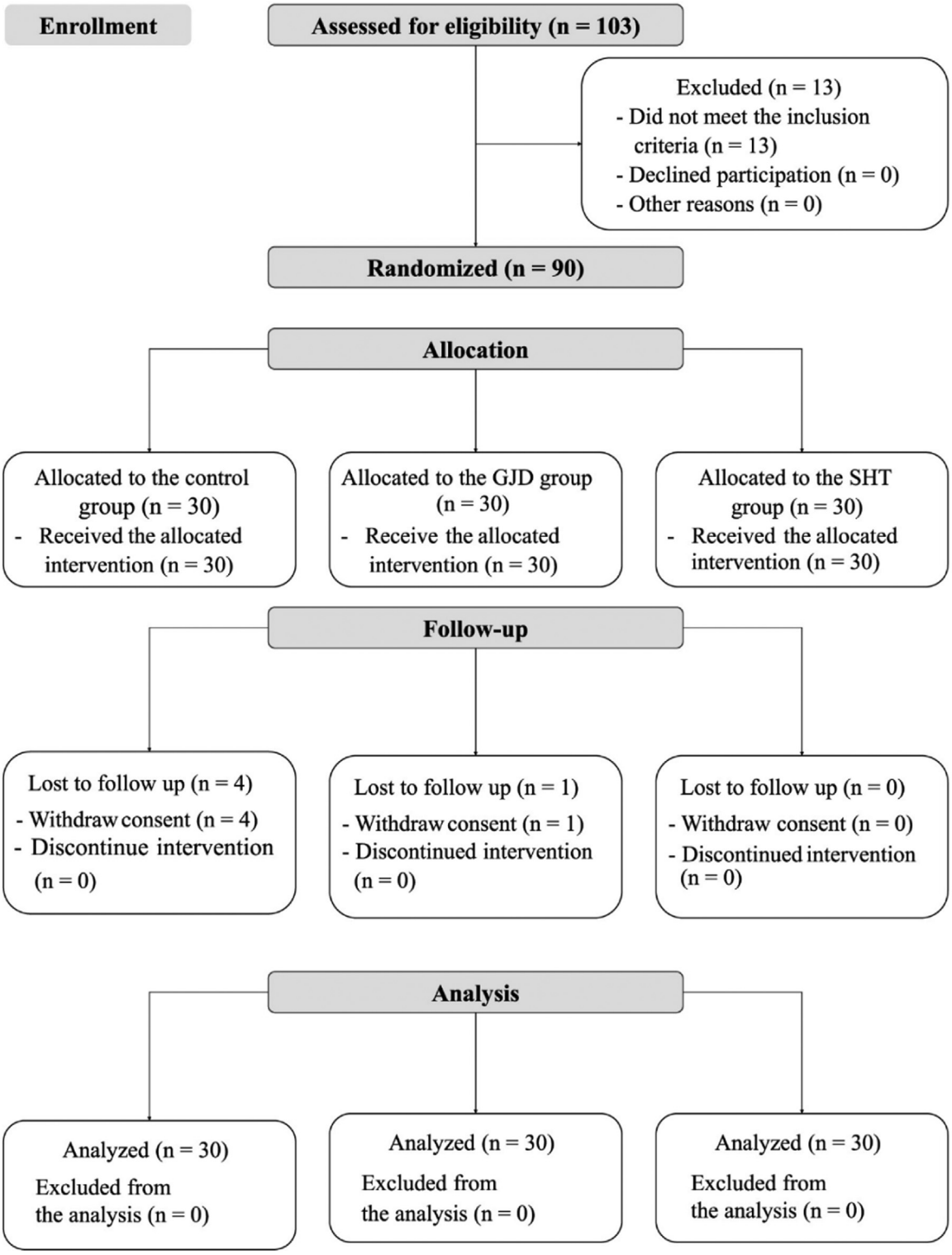

Fig. 1. Flow diagram of the participants
GJD, Gongjin-dan; SHT, Ssanghwa-tang.

Table 2
Demographic characteristics of the study participants.

Characteristics	Control group (n = 30)	GJD group (n = 30)	SHT group (n = 30)	p-value
Sex - Male/Female (n, %)†	10 (33.3) / 20 (66.7)	6 (20.0) / 24 (80.0)	13 (43.3) / 17 (56.7)	0.1522
Age (year)‡	40.57 (37.73, 43.40)	39.97 (37.30, 42.63)	40.60 (36.40, 44.80)	0.9526
Height (cm)‡	166.4 (163.1, 169.7)	164.3 (161.8, 166.9)	166.6 (163.6, 169.7)	0.4775
Weight (kg)‡	64.55 (60.33, 68.77)	63.89 (60.26, 67.52)	65.85 (61.15, 70.55)	0.7909
BMI (kg/m^2)‡	23.20 (22.15, 24.26)	23.61 (22.53, 24.69)	23.68 (22.17, 25.19)	0.8349
Smoking - Yes/No (n, %)†	4 (13.3) / 26 (86.7)	5 (16.7) / 25 (83.3)	7 (23.3) / 23 (76.7)	0.5874
Drinking - Yes/No (n, %)†	16 (53.3) / 14 (46.7)	19 (63.3) / 11 (36.7)	21 (70.0) / 9 (30.0)	0.4073
SBP‡	121.3 (115.9, 126.6)	119.2 (114.5, 123.8)	121.0 (115.9, 126.1)	0.8060
DBP‡	71.93 (68.02, 75.84)	72.30 (68.54, 76.06)	72.17 (68.45, 75.89)	0.9901
Pulse‡	79.60 (75.08, 84.12)	81.50 (76.51, 86.49)	80.20 (75.58, 84.82)	0.8378
Temp‡	36.53 (36.39, 36.67)	36.50 (36.35, 36.65)	36.56 (3644, 36.69)	0.8000

† Fisher exact test.
‡ ANOVA test; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Temp, temperature; GJD, Gongjin-dan; SHT, Ssanghwa-tang.

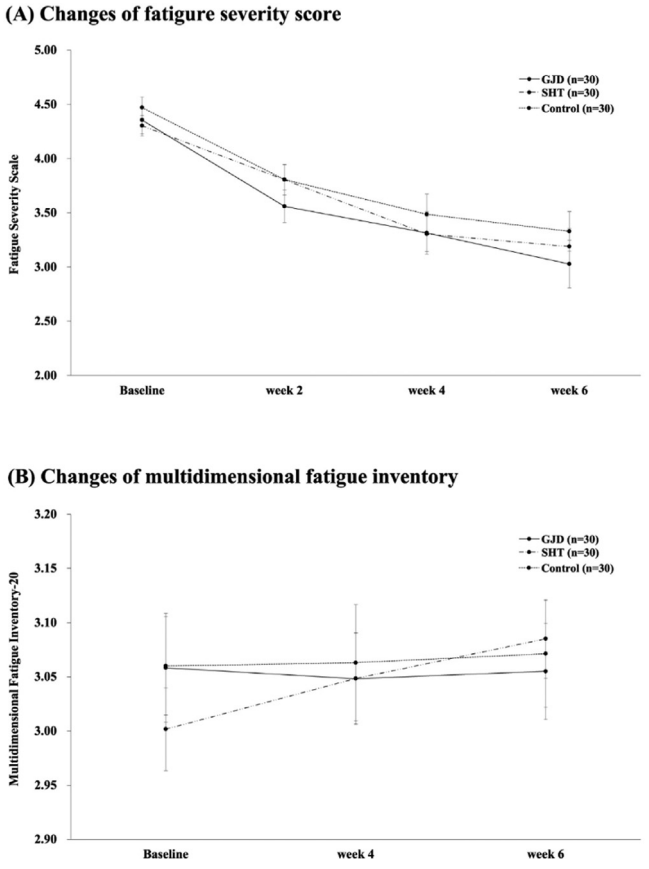

Fig. 2. Changes in the (A) FSS score and (B) MFI-20 score
FSS, Fatigue Severity Scale; MFI, Multidimensional Fatigue Inventory; GJD, Gongjin-dan; SHT, Ssanghwa-tang.

between the SHT and Control groups was −0.18 (97.5 % CI: −0.58 to 0.23, p = 0.3877).

3.4. Secondary outcomes

3.4.1. Changes in the FSS scores at V5 (week 6) compared with that at V2

The change in the FSS at V5 compared with that at V2 in the GJD and SHT groups did not differ significantly from that in the Control group (p > 0.05) (Fig. 2A and **Supplement 3**). The mean difference in score at V5 compared with that at V2 between the GJD and Control groups was −0.34 (95 % CI: −0.81 to 0.14, p = 0.1605). The mean difference in the FSS score at V4 compared with that at V2 between the SHT and Control groups was −0.19 (95 % CI: −0.54 to 0.15, p = 0.2642).

3.4.2. Changes in the MFI-20 scores at V4 (week 4) and V5 (week 6) compared with that at V2

The change in the MFI-20 score at weeks 4 and 6 compared with that at V2 in the GJD and SHT groups did not differ significantly from that in the Control group (Fig. 2B and **Supplement 4**). The mean difference in score at V4 and V5 compared with that at V2 between GJD and Control groups were −0.01 [95 % CI: −0.15 to 0.13, p = 0.8800] and −0.02 [95 % CI: −0.16 to 0.11, p = 0.7183], respectively. The mean differences in the score at V4 and V5 compared with that at V2 between the SHT and Control groups were −0.02 [95 % CI: −0.14 to 0.11, p = 0.8139] and 0.01 [95 % CI: −0.11 to 0.13, p = 0.9177], respectively.

3.4.3. Changes in the CFQ scores at V4 and V5 compared with that at V2

The changes in the CFQ score at weeks 4 and 6 compared with that at V2 in the GJD and SHT groups did not differ significantly from that in the Control group (**Supplement 5**). The mean differences in the score at V4 and V5 compared with that at V2 between the GJD and Control groups were −1.21 [95 % CI: −3.74 to 1.33, p = 0.3445] and 0.57 [95 % CI: −2.14 to 3.28, p = 0.6749], respectively. The mean differences in the score at V4 and V5 compared with that at V2 between the SHT and Control groups were 0.53 [95 % CI: −2.20 to 3.26, p = 0.7004] and 2.49 [95 % CI: −0.08 to 5.06, p = 0.0573], respectively. The change in the number of participants with a total CFQ score of ≥15 did not differ significantly (**Supplement 6**).

3.4.4. Changes in the SF-36 score at V4 and V5 compared with that at V2

The SHT group had significantly better PF scores at week 6, and the RE scores at weeks 4 and 6 were significantly improved compared with those in the Control group (p <0.05). The difference in the SF-36 PF score at week 6 between the SHT and Control groups was 2.37 [95 % CI: 0.08 to 4.67, p = 0.0427]. The differences in the RE scores at weeks 4 and 6 between the SHT and Control groups were −24.05 [95 % CI: −40.50 to −7.59, p = 0.0049] and −26.16 [95 % CI: −43.88 to −8.45, p = 0.0045], respectively (Fig. 3 and **Supplement 7**).

A significantly greater improvement in SF was observed in the GJD group at week 4 compared with that in the Control group (Fig. 3 and **Supplement 7**) (p <0.05). The difference in the SF score at week 4 between the GJD and Control groups was 10.43 [95 % CI:2.41 to 18.44, p = 0.0118].

3.4.5. SOFA/GP

The SOFA/GP score patterns displayed a discrete characteristic; therefore, it was determined that they had no analytical value and were excluded from the analysis. Based on a SOFA/GP cut-off score of 3, the number of participants with a total score of ≥3 was significantly lower

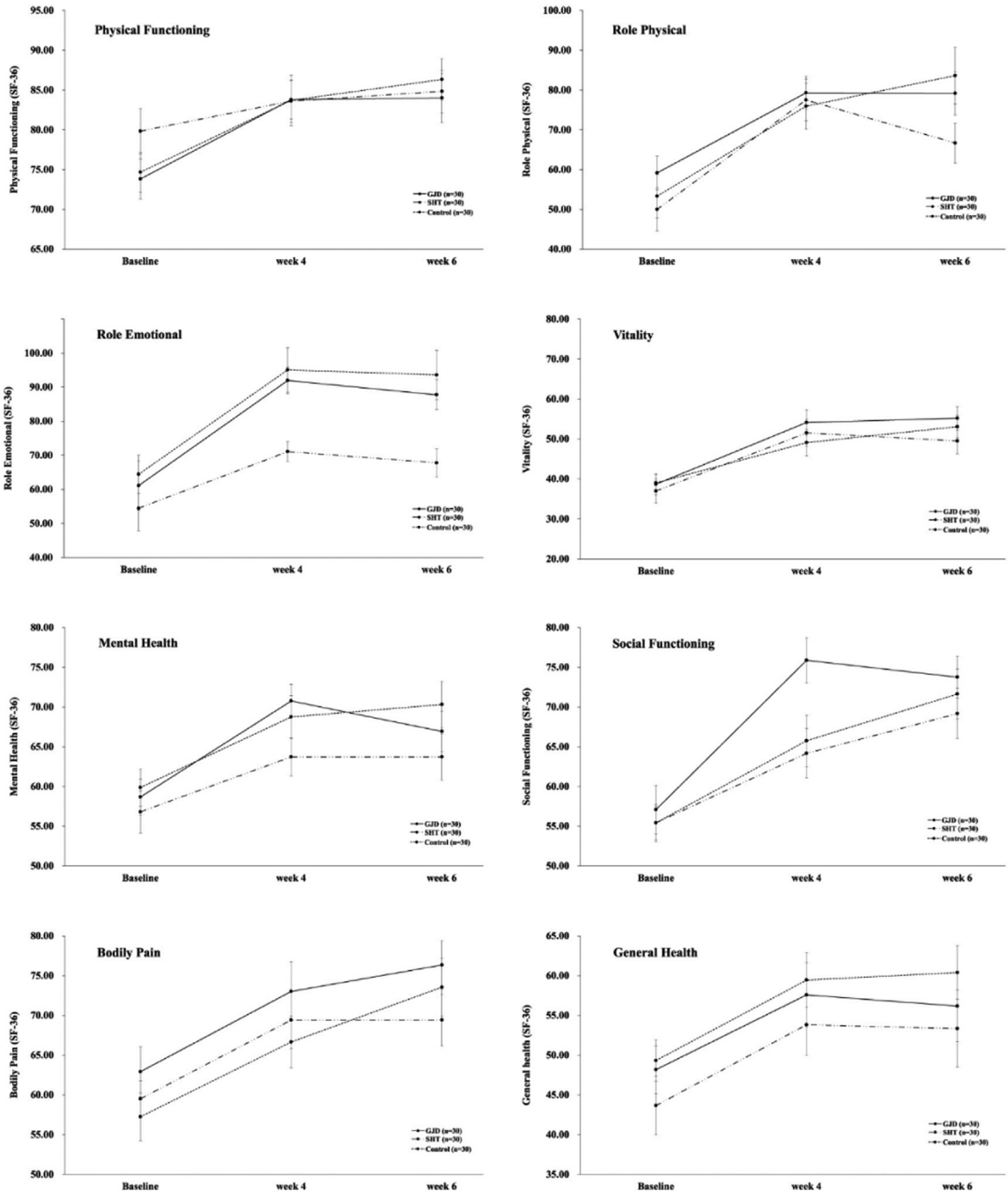

Fig. 3. Changes in the SF-36 score
SF-36, short-form 36 health survey; GJD, Gongjin-dan; SHT, Ssanghwa-tang.

in the SHT group than that in the Control group at week 4 (**Supplement 8**) (p <0.05).

3.4.6. Changes in the fatigue-related biomarkers

No significant changes in the glucose, D-ROMS, lactate, BAP, ammonia, selenium, FFA, and cortisol levels compared with those in the Control group were observed in the GJD and SHT groups at weeks 4 and 6 (Table 3) (p > 0.05).

3.4.7. Safety evaluation variables

The GJD and SHT groups showed no significant changes in the red blood cell (RBC) count, Hb levels, Hct, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), or WBC differential count (seg. neutrophils, lymphocytes, monocytes, eosinophils, and basophils) compared with those in the Control group. Similarly, the two groups showed no significant changes in the blood urea (BUN), creatinine, uric acid, AST, ALT, ALP, total protein, albumin, sodium (Na), potassium (K), chlorine (Cl), and high-sensitivity C-reactive protein (hsCRP) levels compared with those in the Control group. MCH and the total bilirubin levels differed significantly between the groups; however, all values were within the normal ranges and were not clinically significant (p >0.05).

3.5. Adverse events

Eight of the 90 participants included in this study reported intervention-related side effects. Two participants reported dizziness after receiving the GJD placebo. Four participants reported stomach dis-

Table 3
Changes in the fatigue-related biomarkers.

Lab	Control group (n = 30)	GJD group (n = 30)	MD (CONT-GJD)	p-value	SHT group (n = 30)	MD (CONT-SHT)	p-value
Glucose							
Baseline	98.73 (92.26, 105.20)	97.97 (90.59, 105.34)			96.97 (90.84, 103.09)		
Week 4	96.19 (89.04, 103.33)	98.21 (89.68, 106.73)	1.41 (−8.81, 11.63)	0.783	98.77 (90.48, 107.06)	2.50 (−7.34, 12.34)	0.613
MD (4w-0w)	−2.37 (−8.60, 3.85)	−0.41 (−5.22, 4.39)			1.80 (−6.43, 10.03)		
p-value	0.441	0.861			0.6581		
Week 6	97.31 (88.84, 105.78)	99.37 (91.06, 107.67)	1.54 (−9.19, 12.27)	0.774	98.00 (91.23, 104.77)	0.10 (−9.58, 9.79)	0.983
MD (6w-0w)	−0.31 (−6.80, 6.18)	1.40 (−7.68, 10.48)			1.03 (−6.06, 8.13)		
p-value	0.923	0.755			0.7680		
d-ROMs							
Baseline	372.6 (338.7, 406.4)	388.4 (358.9, 418.0)			360.7 (323.9, 397.5)		
Week 4	382.5 (346.7, 418.3)	380.7 (351.5, 409.8)	−2.2 (−46.7, 42.4)	0.923	364.2 (330.5, 397.9)	−18.9 (−67.5, 29.6)	0.438
MD (4w-0w)	10.9 (−21.7, 43.5)	−7.3 (−35.6, 20.9)			3.5 (−27.03, 34.0)		
p-value	0.498	0.599			0.8178		
Week 6	367.3 (327.4, 407.3)	386.4 (355.4, 417.4)	18.4 (−28.6, 65.4)	0.435	359.5 (328.1, 390.9)	−8.4 (−58.2, 41.4)	0.736
MD (6w-0w)	−3.2 (−52.5, 46.2)	−2.1 (−35.7, 31.6)			−1.2 (−39.3, 36.9)		
p-value	0.895	0.901			0.9505		
Lactate							
Baseline	1.68 (1.46, 1.90)	1.80 (1.54, 2.06)			1.73 (1.41, 2.04)		
Week 4	1.80 (1.31, 2.28)	1.75 (1.50, 2.01)	−0.05 (−0.49, 0.39)	0.828	2.08 (1.69, 2.47)	0.29 (−0.22, 0.79)	0.257
MD (4w-0w)	0.11 (−0.41, 0.63)	−0.06 (−0.26, 0.14)			0.36 (−0.09, 0.81)		
p-value	0.665	0.535			0.1168		
Week 6	1.72 (1.46, 1.98)	1.72 (1.41, 2.04)	0.00 (−0.38, 0.38)	0.991	1.83 (1.56, 2.09)	0.11 (−0.27, 0.48)	0.579
MD (6w-0w)	0.05 (−0.27, 0.36)	−0.07 (−0.42, 0.27)			0.10 (−0.24, 0.44)		
p-value	0.764	0.665			0.5538		
BAP							
Baseline	2189 (2064, 2315)	2202 (2110, 2294)			2201 (2105, 2296)		
Week 4	2161 (2034, 2288)	224 (2130, 2359)	79.09 (−82.51, 240.68)	0.331	2263 (2161, 2365)	92.48 (−65.20, 250.16)	0.245
MD (4w-0w)	−5.37 (−129.00, 118.26)	52.17 (−95.25, 199.60)			62.30 (−63.17, 187.77)		
p-value	0.930	0.475			0.3183		
Week 6	2091 (1968, 2215)	2128 (2014, 2242)	32.28 (−128.71, 193.28)	0.689	2201 (2096, 2305)	109.23 (−49.66, 268.11)	0.174
MD (6w-0w)	−59.04 (−239.33, 121.25)	−73.67 (−204.24, 56.90)			0.00 (−148.11, 148.11)		
p-value	0.506	0.258			0.9999		
Ammonia							
Baseline	26.52 (20.33, 32.70)	26.88 (20.67, 33.09)			28.38 (21.76, 34.99)		
Week 4	34.93 (28.51, 41.34)	32.47 (25.58, 39.37)	−3.60 (−12.61, 5.40)	0.426	38.57 (30.96, 46.17)	3.20 (−6.26, 12.66)	0.501
MD (4w-0w)	10.06 (3.01, 17.10)	5.01 (−0.87, 10.89)			10.19 (1.12, 19.26)		
p-value	0.007*	0.092			0.0290*		
Week 6	30.52 (23.82, 37.21)	26.82 (21.38, 32.26)	−3.70 (−12.39, 5.00)	0.397	33.49 (24.57, 42.42)	2.97 (−7.33, 13.27)	0.566
MD (6w-0w)	4.17 (−6.58, 14.93)	−0.06 (−7.05, 6.93)			5.11 (−4.69, 14.92)		
p-value	0.431	0.986			0.2945		
Selenium							
Baseline	113.2 (108.7, 117.6)	114.1 (108.3, 120.0)			114.0 (108.1, 119.9)		
Week 4	112.7 (108.4, 117.0)	114.6 (109.2, 119.9)	2.29 (−4.67, 9.26)	0.512	113.2 (108.0, 118.5)	1.31 (−5.26, 7.87)	0.695
MD (4w-0w)	−1.30 (−5.00, 2.41)	0.17 (−3.27, 3.61)			−0.77 (−3.56, 2.03)		
p-value	0.4783	0.919			0.5792		
Week 6	113.0 (108.5, 117.4)	116.0 (110.1, 122.0)	2.64 (−4.69, 9.98)	0.473	112.9 (106.9, 118.8)	−0.58 (−7.88, 6.72)	0.874
MD (6w-0w)	0.35 (−2.24, 2.93)	1.90 (−2.30, 6.10)			−1.13 (−3.77, 1.51)		
p-value	0.785	0.362			0.3871		
Free Fatty Acid (FAA)							
Baseline	351.1 (271.7, 430.4)	431.6 (338.1, 525.0)			327.2 (253.8, 400.5)		
Week 4	327.8 (246.7, 408.9)	380.1 (293.8, 466.4)	62.97 (−57.69, 183.63)	0.300	294.1 (201.5, 386.6)	−32.53 (−147.64, 82.58)	0.574
MD (4w-0w)	−33.15 (−133.63, 67.33)	−23.34 (124.80, 78.11)			−33.10 (−151.52, 85.32)		
p-value	0.5037	0.641			0.5720		
Week 6	287.9 (198.0, 377.9)	369.2 (286.5, 451.9)	82.80 (−38.98, 204.59)	0.179	361.2 (259.9, 462.5)	74.82 (−47.08, 196.73)	0.224
MD (6w-0w)	−69.38 (−171.83, 33.06)	−62.33 (−176.50, 51.83)			34.03 (−79.34, 147.40)		
p-value	0.175	0.273			0.5440		
Cortisol							
Baseline	6.51 (5.45, 7.56)	6.26 (5.39, 7.14)			6.41 (5.14, 7.68)		
Week 4	6.81 (5.69, 7.93)	7.69 (6.25, 9.13)	0.92 (−0.68, 2.52)	0.256	7.12 (5.96, 8.28)	0.38 (−1.24, 2.00)	0.639
MD (4w-0w)	0.14 (−1.23, 1.52)	1.41 (−0.08, 2.90)			0.71 (−0.47, 1.88)		
p-value	0.830	0.063			0.2273		
Week 6	6.27 (5.35, 7.19)	7.48 (6.48, 8.48)	1.03 (−0.35, 2.41)	0.140	6.99 (6.02, 7.97)	0.50 (−1.03, 2.03)	0.513
MD (6w-0w)	0.11 (−0.67, 0.89)	1.22 (0.16, 2.27)			0.58 (−0.44, 1.60)		
p-value	0.774	0.025*			0.2562		

BAP, biological antioxidant potential; CONT, Control; d-ROM, derivatives of reactive oxygen metabolites; FFA, free fatty acids; GJD, Gongjin-dan; MD: mean difference; SHT, Ssanghwa-tang.

* , $p<0.05$.

comfort (heartburn and nausea) after receiving the IPs: one, one, and two participants after receiving the GJD placebo, SHT or GJD placebo, and GJD, respectively. One participant reported abdominal bloating after receiving SHT. One participant reported loose stools and an increased number of bowel movements after receiving the GJD placebo or SHT placebo. Thus, four out of eight participants had GJD- or SHT-related side effects, and four participants had placebo-related side effects.

The side effects were transient and occurred immediately after IP administration. The symptoms did not require treatment or resolved completely after adjusting the timing of administration to immediately after meals. No serious intervention-related AEs were reported.

4. Discussion

Chronic fatigue of unknown cause that persists for ≥6 months is categorized as CFS or ICF.[3] CFS and ICF impact the physical, psychological, social, emotional, and financial aspects, thereby causing considerable disability to the patient and straining the public health system.[35] However, a definitive treatment is lacking owing to the unclear etiology, diagnostic uncertainty, and heterogeneity of populations with CFS and ICF.[36]

Patients with chronic fatigue seek various complementary and alternative medicine (CAM) treatment modalities because of the limited conventional treatment options for chronic fatigue, inadequate evidence regarding their efficacy and safety, and a high incidence of side effects.[36,37] GJD and SHT have been traditionally used to treat fatigue in South Korea.[6,7]

All three groups showed a clear reduction in fatigue, as measured using the FSS, CFQ, and SF-36 scores, in the present study. The MFI-20 did not improve significantly in any of the three groups. The primary endpoint (changes in the FSS scores) and secondary endpoints (changes in the fatigue-related biomarker levels and the MFI-20 and CFQ scores) did not differ significantly between the two study groups and the Control group.

A blinded assessment was performed using a questionnaire at V4, and 86 participants (after excluding four participants who dropped out) responded. Among the 27 patients in the Control group, 19 (70 %) reported they thought they had received GJD or SHT. The majority of the participants in the Control group believed that they received GJD or SHT, indicating a strong placebo effect. This seemed to have led to an overall reduction in fatigue across the groups, with no significant differences in the effects observed among the groups.

The placebo effect is an important psychological phenomenon wherein an individual demonstrates an actual improvement in symptoms based solely on treatment cues.[38] The strong placebo effect in the present study may be attributed to the following:

The placebo effect is a learned response. The verbal, situational, and social cues encountered by the trial participants during the intervention process prompted them to recall sensations experienced in similar settings. This, in turn, elevated expectations regarding the current situation, and these expectations influenced the central nervous system, leading to the manifestation of the placebo effect.[39] Participant visits were scheduled at a hospital facility. Thus, the participants were exposed to the intake of the IP and various factors that constitute the treatment environment, including waiting in the clinic and the physician's white coat. Furthermore, they were also exposed to verbal suggestions while obtaining informed consent, such as the explanation that "taking the IP may lead to improvements in fatigue." It is possible that the interaction of these factors increased the participants' expectations, producing a strong placebo effect.[40,41] Furthermore, although GJD and SHT are therapeutic agents, they are also consumed by healthy individuals as herbal restoratives for relieving fatigue in South Korea. The expectations learned from such sociocultural backgrounds are likely to have led to a strong placebo effect in the Control group.

Future studies on the effects of GJD and SHT on chronic fatigue should pre-investigate the recognition and satisfaction with GJD and SHT, as well as Korean traditional medicine, to eliminate any other verbal and situational components in the research environment and control for possible triggers of the placebo effect.

Various fatigue scales were used in the study. Unlike previous studies,[42] which suggested a correlation between the SOFA/GP and FSS scores, different fatigue scale scores were not significantly correlated in the present study. This discrepancy could be attributed to the participants' lack of understanding of the questionnaire items and the development of fatigue from completing several questionnaires. Some participants required elaboration of certain questionnaire items for better comprehension. The most common issue was related to question 2 of the FSS, where participants were unsure whether "exercise" referred to simple physical activity (the level of activity in their daily life) or structured sports activities (habitual and systematic physical exercise for fitness or health purposes). The same issue was observed during the translation of the FSS into the Norwegian language by Lerdal et al.[43] Accurate fatigue measurement could have been hindered by variations in the participants' comprehension of the questions.

Five fatigue scales were used in the present study. The FSS was assessed at each visit, whereas the remaining four scales were assessed at V2, V4, and V5. Many participants in the study reported feeling fatigued owing to the large number of questionnaire items and the time-consuming process. Some participants required more than 40 min to complete all five questionnaires. Thus, it is possible that the fatigue associated with responding to the fatigue questionnaires may have impacted the appropriate measurement of fatigue. It is important to consider the social and psychological variables and the appropriate number of questionnaire items for fatigue measurement in future studies on fatigue.

SF-36 is the most widely used health-related quality of life (HRQOL) instrument,[44] and it comprises eight subdomains: RF, BP, GH, VT, SF, RP, RE, and MH.[45] The scores are calculated on a scale with scores ranging from 0 (worst possible health) to 100 (best possible health).[46]

The scores of some SF-36 domains were markedly higher in the GJD and SHT groups than those in the Control group in the present study. Specifically, the SF score at week 4 in the GJD group, the RE score at weeks 4 and 6, and PF score at week 6 in the SHT group were significantly improved compared with those in the Control group. The eight subdomains of SF-36 have been defined into physical and mental health clusters in factor analysis studies.[47] PF, RF, and BP are strongly correlated with the physical components, whereas MH, RE, and SF are strongly correlated with the mental components.[48] Fatigue is generally classified into physical fatigue (muscular exhaustion and impaired physical performance) and mental fatigue (mental fatigue, attention, concentration, or motivation loss).[49] SHT is effective against both mental and physical fatigue, whereas GJD is effective against mental and social fatigue. Thus, both GJD and SHT could be helpful in treating chronic fatigue in Koreans, which is strongly related to psychosocial factors.[4] Furthermore, GJD and SHT should be administered continually for at least four weeks at the dose used in the present study to produce anti-fatigue effects. In terms of SOFA/GP, the number of participants with a score of ≥3 (cut-off score of ≥ 3) significantly decreased in the SHT group on week 4 compared with that in the Control group, suggesting that SHT should be administered for at least four weeks to achieve anti-fatigue effects.

Intervention-related severe AEs were not observed in the present study, and the laboratory findings were within the normal ranges. These results suggest that the long-term use (maximum of 4 weeks) of GJD and SHT is safe. Eight of the 90 participants reported side effects, four of whom received a placebo. The side effects were mostly gastrointestinal symptoms such as stomach discomfort (heartburn, nausea), abdominal bloating, and loose stool. However, these symptoms were transient and only observed briefly after IP administration. Moreover, the symptoms resolved without treatment or after adjusting the timing of administration.

This study has some strengths. First, this was an RCT with a large sample size that investigated the anti-fatigue effects of GJD and SHT in

the Korean population. Previous studies used small sample sizes (GJD)[13] or were not RCTs (SHT). Second, previous animal and clinical studies artificially induced acute fatigue, whereas the present study included patients with chronic fatigue that persisted for at least 6 months. Acute fatigue was induced by restricting the duration of sleep to a short period in healthy men (GJD)[13] or by indirectly examining the anti-fatigue effects of increased exercise (swimming) time in mice (SHT) in previous studies.[50] Third, the present study demonstrated that GJD may be effective against chronic mental and social fatigue, whereas SHT may be effective against chronic mental and physical fatigue. GJD and SHT led to significant reductions in chronic fatigue in certain dimensions of the SF-36 (GJD [SF] and SHT [pH, RE]) compared with those in the Control group in the present study. Fourth, the safety of long-term use (up to 4 weeks) of GJD and SHT was confirmed in the present study. Furthermore, no abnormal laboratory findings or serious AEs related to interventions were observed.

Nevertheless, this study has several limitations. First, it is possible that an optimal dose of GJD or SHT was not used to achieve maximum anti-fatigue effects. The Korean Ministry of Food and Drug Safety recommends taking three pills of GJD thrice daily. However, a dose of one pill of GJD once daily was used in the present study, which is the actual prescription in clinical practice. Future studies should investigate the appropriate dose and duration of GJD and SHT that will yield anti-fatigue effects.

Second, the findings of this study may have been influenced by COVID-19-related fatigue, as this study was conducted during the COVID-19 pandemic. The global pandemic of COVID-19 occurred during the study period (December 2021 to January 2023). The prevalence of fatigue increased to 46–52 % in several countries during the pandemic.[51,52] The COVID-19 pandemic has induced intense and pervasive stress that is difficult to control.[53,54] Factors such as fear of infection, repeated media mentions, and an endless cycle of social distancing contributed to high levels of mental fatigue among individuals.[55] Furthermore, psychological fatigue among Korean workers has increased since the beginning of the COVID-19 pandemic.[56] Although fatigue due to depression was excluded using the FSS scores (scores of ≥7 for items 4 and 9) at the screening visit, the impact of self-quarantine and social distancing policies prioritized during the COVID-19 pandemic on the participants' mental health was beyond our control. Some participants had undergone self-quarantine or isolation due to close contact or COVID-19 infection. Self-quarantine due to the COVID-19 pandemic has had a significant impact on mental health, leading to high levels of anxiety and depression.[57] Individuals reported higher levels of mental fatigue than physical or social fatigue during the COVID-19 pandemic.[58] Thus, assessing and tracking the changes in the mental health of the participants using anxiety and depression scales, such as the Beck Depression Inventory, along with FSS, would have been more appropriate. The pandemic is anticipated to have lingering effects on individuals even after its end, causing mental fatigue and resulting in serious sequelae.[59] Therefore, future studies on fatigue should differentiate between chronic fatigue and COVID-19-related fatigue.

Third, ICF and CFS were not differentiated. ICF and CFS are distinct conditions with different etiologies and clinical courses. CFS is a multisystem neuroimmune disorder that is often associated with inflammation of the brain.[60,61] ICF typically has a favorable clinical course with recovery rates ranging from 54 to 94 %; however, CFS has a recovery rate of <10 %.[62] All three groups in this study showed improvements in the FSS, CFQ, and SF-36 scores. Therefore, ICF and CFS were not differentiated in this study, and it is unlikely that any of the participants had CFS.

Fourth, lifestyle factors closely related to the alleviation and exacerbation of chronic fatigue, such as sleep, diet, and exercise, could not be controlled as the participants visited the trial facility on designated schedules. Although not conclusively established, fatigue is a multifactorial condition influenced by various factors, including inflammation, psychological and mental health, metabolic changes, micronutrient deficiencies, and sleep disturbances.[63-65] This study did not gather information on sociodemographic variables affecting the participants' lifestyles and behavioral norms, such as diet, exercise, sleep habits, education, occupation, and marital status. The absence of investigation and control over lifestyle factors may have influenced the results of the self-reported questionnaires and fatigue-related biomarker levels.

In conclusion, improvements in chronic fatigue, as measured using the FSS, CFQ, and SF-36 scores, were observed in the GJD, SHT, and Control groups; however, the differences in the FSS and CFQ scores were not statistically significant. This was attributed to a strong placebo effect. Furthermore, no significant changes were observed in the MFI-20 score or fatigue-related biomarker levels. Nevertheless, the GJD group showed statistically significant improvements in the SF score in SF-36 at week 4, whereas the SHT group showed significant improvements in the RE score at weeks 4 and 6 and the PF score at week 6 compared with those in the Control group. Thus, SHT may be effective for treating chronic mental and physical fatigue, whereas GJD may be effective for treating chronic mental and social fatigue. This study provides evidence supporting the safety of long-term use (up to 4 weeks) of GJD and SHT. Future studies should consider controlling variables that induce placebo effects, determine appropriate dosages and durations of GJD and SHT that yield adequate anti-fatigue effects, distinguish between chronic and COVID-19 pandemic-related fatigue, and investigate and control lifestyle factors related to fatigue.

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CRediT authorship contribution statement

Jun-Yong Choi: Methodology, Project administration, Writing – review & editing, Supervision, Writing – original draft. **Bom Choi:** Project administration, Writing – review & editing, Writing – original draft, Investigation. **Ojin Kwon:** Formal analysis, Data curation. **Chang-Seob Seo:** Writing – original draft, Formal analysis. **Hyeun-kyoo Shin:** Conceptualization, Funding acquisition. **Kibong Kim:** Project administration, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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Ethical statement

The clinical trial was approved by the Institutional Review Board of the Pusan National University Korean Medicine Hospital (PNUKHIRB 2021-10-005). Informed consent was obtained from all participants.

Data availability

The data that support the finding of this study are available within the article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2024.101025.

Supplement 1. Chemical structures of the analyzed components in (A) Gongjin-dang (GJD) and (B) Ssanghwa-tang (SHT).

Supplement 2. HPLC chromatogram of (A) the standard solution and (B) clinical sample of SHT.

Supplement 3. Changes in the Fatigue Severity Scale scores.

Supplement 4. Changes in the Multidimentional Fatigue Inventory-20 scores.

Supplement 5. Changes in Chalder Fatigue Scale scores.

Supplement 6. Chalder Fatigue Scale (cut-off 15).

Supplement 7. Changes in the Short-Form 36 health survey scores.

Supplement 8. Schedule of Fatigue and Anergy/General Physician (cut-off score of 3).

Supplement 9. CONSORT 2010 checklist.

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