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# Efficacy and Safety of Yukgunja-Tang for Patients with Cancer-related Anorexia: A Randomized, Controlled Trial, Pilot Study

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## Abstract

**Objective:** The purpose of this study is both to estimate the efficacy and the safety of Yukgunja-tang (YGJT) and to establish evidence for the use of herbal medicines in the management of patients with cancer-related anorexia. **Methods:** We enrolled 40 patients with cancer-related anorexia. The enrolled participants were randomly allocated to 2 groups: the control group (n = 20), which received nutrition counseling, and the treatment group (n = 20), which received nutrition counseling and was administered YGJT at twice a day for 4 weeks (a total of 56 times @ 3.0 g each time). The primary outcome of this study was the score on the anorexia/cachexia subscale (ACS) of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT). The secondary outcomes were the FAACT score with the ACS score excluded, the score on the Visual Analog Scale (VAS) for appetite, and the results on laboratory tests regarding appetite, such as leptin, tumor necrosis factors (TNF-$\alpha$), interleukin-6 (IL-6), and ghrelin. All variables related to the safety assessment, such as vital signs, electrocardiography results, laboratory test results (complete blood cell count, chemistry, urine test), and adverse events, were documented on the case report form (CRF) at every visit. **Result:** The difference in the primary outcome, that is, the score on the anorexia/cachexia subscale (ACS) of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT), between the control and the treatment groups was statistically significant ($P = .023$) as was the difference in the FAACT scores with the ACS score excluded, a secondary outcome, between the 2 groups; however, no statistically significant differences were noted in the scores on the VAS or the levels of leptin, TNF-$\alpha$, IL-6, and ghrelin. In addition, no significant differences in the numbers and the types of adverse events or in the results on the laboratory tests between the control and the treatment groups were recorded. **Conclusion:** These results obtained in this research confirmed the efficacy and the safety of using YGJT as a herb-medicine treatment option for patients with cancer-related anorexia.

## Keywords

anorexia, cancer, clinical trials, Liu-Jun-Zi-Tang, malnutrition, Rikkunshito, Yukgunja-Tang

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## Introduction

Cancer-related anorexia is a complex phenomenon that can be characterized by metabolic abnormalities, pro-inflammatory cytokines produced by the host's immune system, circulating tumor-derived catabolic factors, decreased food intake, and probably more unknown factors.[1] It is a common cause of malnutrition and deteriorates the quality of life (QOL) in patients with cancer.[2,3] Recent studies have shown that 30% to 60% of cancer patients with anorexia are malnourished, which is usually associated with long-term hospitalization.[4,5] Thus, one may conclude that cancer and its treatments may cause malnutrition and side effects that affect the nutritional status of patients suffering from the

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condition.[3] Cancer-related anorexia is associated with poor prognosis, poor response rate to chemotherapy, and deteriorated performance status.[2] Therefore, managing anorexia is important for patients with cancer. Appetite stimulants, such as corticosteroids (dexamethasone, methylprednisolone, and prednisolone) and progestins (medroxyprogesterone and megestrol acetate), are recommended for patients with anorexia,[6] but appetite stimulants have limitations.

Some patients take alternative, safe and effective therapies, such as herbal medicines, for the treatment of cancer-related anorexia.[7] Yukgunja-Tang (YGJT) is a traditional Korean medicine that has been prescribed to treat upper gastrointestinal symptoms, such as anorexia, nausea, dyspepsia, and gastroesophageal reflux.[8-14] Many experimental studies have shown that YGJT may be effective in treating chemotherapy-induced anorexia.[15-17] Recently, many clinical studies have been conducted to improve the quality of life (QOL) of cancer patients and manage their symptoms,[18] but most studies of YGJT have focused on anorexia in cancer patients after chemotherapy, such as with cisplatin. Therefore, we conducted this clinical trial to evaluate YGJT as treatment options for cancer patients with anorexia.

## Materials and Methods

### Trial Design

This study was conducted as a randomized, controlled trial that aimed to estimate the efficacy and the safety of YGJT when used to manage patients with cancer-related anorexia. The enrolled participants were randomly allocated to 2 groups: The control group received nutrition counseling, and the YGJT group received nutrition counseling and was administered YGJT. In this randomized clinical trial, 40 patients with cancer-related anorexia were enrolled and allocated to either the control group (n = 20) or the treatment group (n = 20). The Institutional Review Board of Daejeon Korean Medicine Hospital of Daejeon University approved this study (reference DJDSKH-17-DR-17), and it was performed in compliance with the Helsinki Declaration and according to Good Clinical Practice as described by the Korea Food and Drug Administration.

### Participants

Participants were recruited from Daejeon Korean Medicine Hospital of Daejeon University from 10 August 2017 to 9 September 2020. The inclusion criteria were the following: (1) patients with a histologically or cytologically confirmed solid tumor, who were suffering from anorexia; (2) men and women aged 20 to 80 years who were able to read and write and to understand the protocols; (3) score on the Visual Analog Scale (VAS) for anorexia ≥40/100 mm, absolute neutrophils count ≥1500/μL, and platelets ≥100 000/μL; (4) total bilirubin at the maximum normal level or less (1.2 mg/dL); (5) alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels lower than twice the upper normal limit (35/45 U/ℓ); (6) creatinine level lower than 1.5 times the upper normal limit (1.09 mg/dL); (7) patients who had provided written informed consent for participation in the trial. The exclusion criteria consisted of the following: (1) patients who were unable to intake medicine orally; (2) patients who were undergoing chemotherapy and those who had completed such therapy less than 1 month earlier; (3) patients who had survived for at least 5 years after having been diagnosed with cancer; (4) Eastern Cooperative Oncology Group (ECOG) performance status score ≥ 3; (5) patients who had dementia, delirium or depression, and patients who had scored more than 7 points on the Numeric Pain Rating Scale within 2 weeks of screening; (6) patients who had diseases that could affect their appetite, like hypoadrenalism; (7) patients who were taking appetite stimulants, such as megestrol acetate, corticosteroids, and thalidomide, (8) patients who were judged by a doctor to be inappropriate for inclusion in this study; (9) women who were pregnant or were planning to become pregnant within the study period.

### Interventions

The control group received nutrition counseling individually, and the treatment group received nutrition counseling individually and was administered YGJT. The nutrition counseling consisted of diet recommendations according to cancer conditions and cancer-related treatments, such as diets for chemotherapy, diets for radiotherapy, post-operative diets, or cancer-preventive diets. Nutritional counseling and monitoring conducted in the control group are known to have a positive effect on improving the awareness of the importance of eating and improving eating habits when administered during cancer treatment.[19] In addition to the nutrition counseling, the treatment group was administered YGJT at a dose of 3 g twice a day before meals for 4 weeks, for a total of 56 times at a dose of 3 g each time. Kracie Pharma Korea Co, Ltd, Seoul, Korea, produced the YGJT used in this trial in accordance with Korea Good Manufacturing Practice (KGMP) standards. YGJT was manufactured by spray-drying a hot water extract that was a mixture of the following 8 crude drugs: Atractylodis lanceae rhizoma (4.0 g), Ginseng radix (4.0 g), Pinelliae tuber (4.0 g), Poria cocos (4.0 g), Zizyphi fructus (2.0 g), Aurantii nobilis pericarpium (2.0 g), Glycyrrhizae radix (1.0 g), and Zingiberis rhizoma (0.5 g). These raw materials were extracted and concentrated to 3 g per dose. The daily doses followed the recommended dosage of the Korea Ministry of Food and Drug Safety (MFDS). During the trial, participants were prohibited from receiving any other treatments for anorexia.

### Outcomes

The primary outcome was the score on the anorexia/cachexia subscale (ACS) of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) between baseline (visit 2) and the end of the period during which YGJT had been administered (visit 4). The FAACT is a clinical questionnaire for assessing the general aspects of QOL, as well as specific anorexia-related concerns, in patients with cancer.[20] Especially, the FAACT_ACS has a total of 39 items, of which 12 items focus on anorexia and cachexia. The Korean version of FAACT (Ver.4), which was translated by the Functional Assessment of Chronic Illness Therapy (FACIT) organization, was used. A trained investigator using standard operating procedures (SOPs) determined and recorded the FAACT_ACS score at each visit. Secondary outcomes were the changes between baseline (visit 2) and the end of the period during which YGJT had been administered (visit 4) (1) in the FAACT score for the results of treatment with the FAACT_ACS score excluded (FAACT_General Physical, FAACT_General Social, FAACT_General Emotional, and FAACT_General Functional), (2) in the VAS score for appetite, and (3) in the levels of leptin, tumor necrosis factor-α (TNF-α), IL-6, and ghrelin on laboratory results.

### Sample Size Determination

This study was a pilot trial conducted before a confirmatory trial to establish the validity of using YGJT to manage patients with cancer-related anorexia. The efficacy of YGJT was to be estimated in order to provide information that would lead to a better design for a future clinical trial. Considering a dropout rate of 20%, we calculated that a total of 52 subjects, 26 per group, should be enrolled in this study.

The sample size was set using an effective size of 0.9, which is the ratio of the standard deviation of each group from the mean difference of outcomes between the control group and the treatment group at a significance level of 5% and a power of 80%. The formula for estimating the sample size is as follows:

$$\mathrm{n}' \geq 2 \times \frac{\sigma^2}{\left(\mu t - \mu c\right)^2} \times \left(t_{\alpha,v} + t_{\beta(1),v}\right)^2,$$

$$\mathrm{n}' \geq 2 \times \left(\frac{1}{0.9}\right)^2 \times \left(t_{\alpha,v} + t_{\beta(1),v}\right)^2,$$

where n is the approximate sample size required for each group, $t_{\alpha,v}$ is the 97.5 percentile score of the $t$ distribution with $v$ degrees of freedom, and $t_{\beta(1),v}$ is the 80 percentile score of the t distribution with $v$ degrees of freedom. If $v=40$, $\mathrm{n}' \geq 2 \times 1.2346 \times \left(2.0211 + 0.8507\right)^2 = 20.3632\left(21\right)$. For a dropout rate of 20%, the sample size for each group is given by $\mathrm{n} = 21 \div 0.8 = 26.25\left(26\right)$ Therefore, a total of 52 subjects, 26 in each of the 2 groups, was needed for this study.

### Randomization

After informed consent had been obtained, each participant was randomly assigned into either the treatment group or the control group. Randomization was performed by using a computer-generated permuted blocks with block sizes of 4 and 8, a random-allocation sequence with an allocation ratio of 1:1, a pre-generated randomization table, and an assigned randomized number, which had been prepared in advance of the first enrollment. The computer-generated block randomization with block sizes of 4 and 8 was done by a member of the Department of Information and Statistics, Chungnam National University, Daejeon, Korea; that member had no clinical involvement in the trial. The allocation table was then concealed in an opaque envelope to ensure that it was securely concealed from the researchers who subsequently informed the patients of their allocations

### Data Analysis

As the main analysis, we used the intent-to-treat analysis (ITT), which is a method of comparing the treatments of randomly assigned groups. In other words, an ITT is an analysis according to the assigned group regardless of noncompliance with the clinical trial plan and/or the participant withdrawal. To treat any missing value, we carried the last observation forward (LOCF). As a sub-analysis, we used per-protocol (PP), which refers to an analysis of a set of subjects who have completed more than 70% of the number of treatments specified in the clinical trial plan, have all of the parameters measured, and have no violations with respect to the major clinical trial plan.

For each group, continuous data were presented as means, standard deviations, and minimum and maximum values. Categorical data were presented as frequency tables. Comparative evaluations of demographic and basic data were performed for the continuous variables by using the paired two-sample $t$-test whereas Fisher's exact test was used for categorical variables.

For the primary outcome, we used the Shapiro–Wilk method to test for normality, and we used the paired two-sample test to compare the changes in the FAACT scores between baseline (week 2) and the end of treatment (week 4). Significance was $P \leq .05$. For the secondary outcomes, the changes in FAACT scores, with the ACS excluded, between baseline and the end of treatment, we used the Shapiro–Wilk method to test for normality, and we used the independent two-sample t-test technique to compare the changes between the 2 averages. All tests were two-sided, with a significance level of 0.05. Adverse events (AEs)

**Table 1.** Baseline Characteristics of the Participants in the 2 Groups.

| | Control group (n = 20) | Treatment group (n = 20) | |
|---|---|---|---|
| Characteristic | n | n | *P*-value |
| Gender, n | | | |
| Male | 1 | 0 | 1 |
| Female | 19 | 20 | |
| Age (y), mean (SD) | 47.55 (6.05) | 51.5 (7.51) | .075 |
| Smoke history | | | |
| Yes | 1 | 0 | 1 |
| No | 19 | 20 | |
| Alcohol intake | | | |
| Yes | 1 | 0 | 1 |
| No | 19 | 20 | |
| ECOG, n | | | |
| 0 | 1 | 2 | 1 |
| 1 | 19 | 18 | |
| Comorbidity | | | |
| Yes | 20 | 20 | 1 |
| No | 0 | 0 | |
| Concomitant drug | | | |
| Yes | 20 | 18 | .487 |
| No | 0 | 2 | |

Abbreviations: ECOG, eastern cooperative oncology group.

were reported and recorded in detail during the entire study. The following were used to assess safety: vital signs, complete blood cell count, chemistry, urine tests, and electrocardiography. Safety-related variables were analyzed using the ITT data set. Comparisons between the ratio of the number of participants who experienced 1 or more AEs to the total number in that group were performed using the Fisher exact test (Excel, Microsoft Co, Washington, USA).

## Result

Figure 1 shows the trial flow for this randomized, controlled trial. Of 40 participants, 39 completed the trial (20 in the control group and 19 in the treatment group). Due to adverse events (AEs), such as heartburn, 1 participant from treatment group was dropped at visit 3.

### *Patient Characteristics*

The participants, except for one male in the control group, were female. The mean (standard deviation) ages were 47.55 (6.05) in the control group and 51.50 (7.51) in the treatment group. Only 1 participant in the control group had a history of smoking, and had a history of alcohol consumption. Most of the participants were ECOG 1; 1 in the control group and 2 in the experimental group were ECOG 0. All participants had comorbidity. All members of the control group had concomitant drug use whereas 2 members of the treatment group did not. No significant differences in the demographic data between the 2 groups at baseline were noted (Table 1).

### *Primary Outcome*

The FAACT_ACS scores in the ITT, in which a total of 40 patients including 1 patient who dropped treatment after the 3rd visit were analyzed, were significantly increased from $27.25 \pm 5.39$ to $32.90 \pm 4.94$ in the treatment group and from $29.35 \pm 6.56$ to $30.95 \pm 5.93$ in control group ($P = 0.023$) (Figure 2). In addition, in Figure 3, the scores for the effectiveness assessment variables in the PP analysis, except for 1 person who was dropped due to AEs, were significantly increased from $26.74 \pm 5.01$ to $32.68 \pm 4.98$ in treatment group and from $29.35 \pm 6.56$ to $30.95 \pm 5.93$ in control group ($P = 0.016$).

### *Secondary Outcomes*

In the ITT analyses, which analyzed a total of 40 patients, including 1 patient who dropped after the 3rd visit, the secondary outcomes of FAACT_GP and FAACT_GS were significantly increased from $16.90 \pm 4.20$, and $13.00 \pm 4.74$, respectively, to $23.15 \pm 2.66$ and $13.65 \pm 5.57$ (GP: $P = 0.020$, GS: $P = .011$) (Figure 2). In addition, Figure 3 shows the results of the PP analyses for all but 1 participant who was dropped due to an AE. The secondary outcomes of FAACT_GP, FAACT_GS, and FAACT_GF can be seen to have been significantly increased from $16.53 \pm 3.96$,

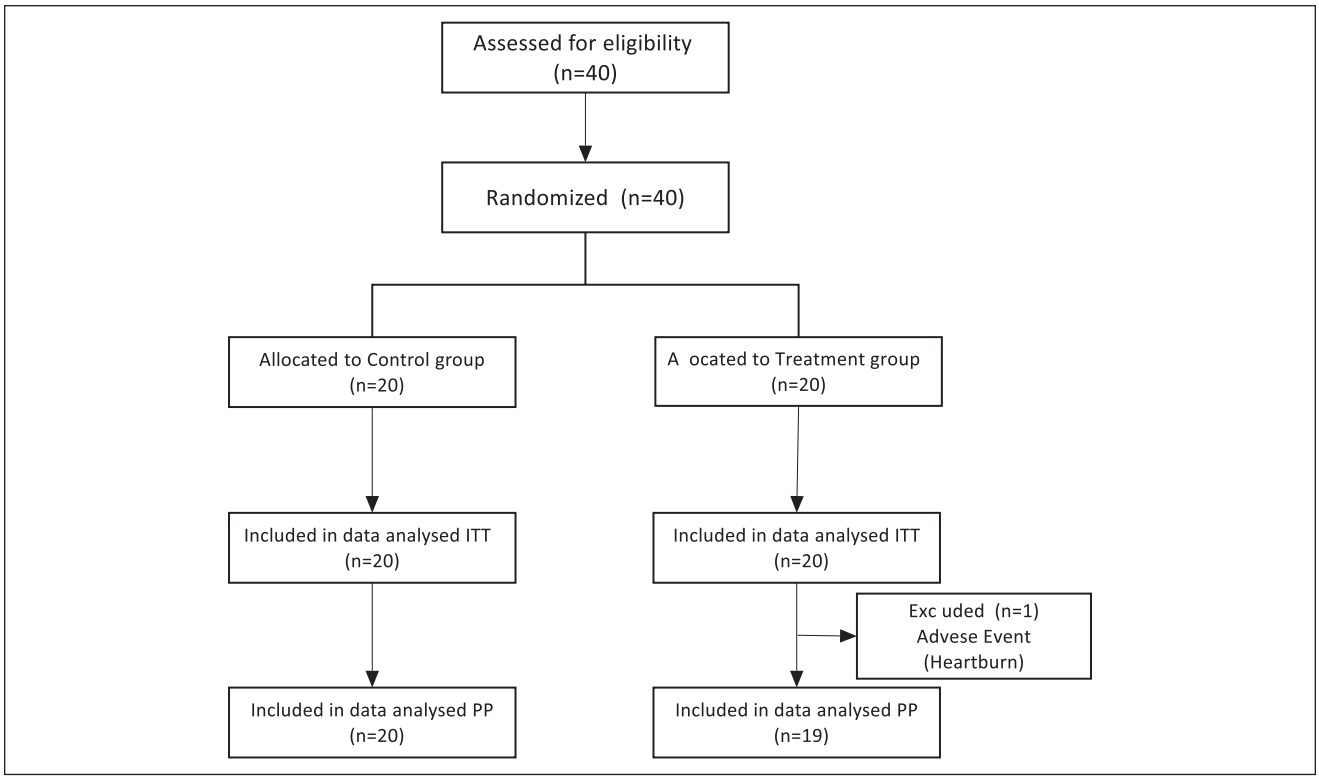


**Figure 1.** Flow diagram of the trial with 2 groups.
Abbreviations: ITT, intention-to-treat analysis; PP, per protocol analysis.

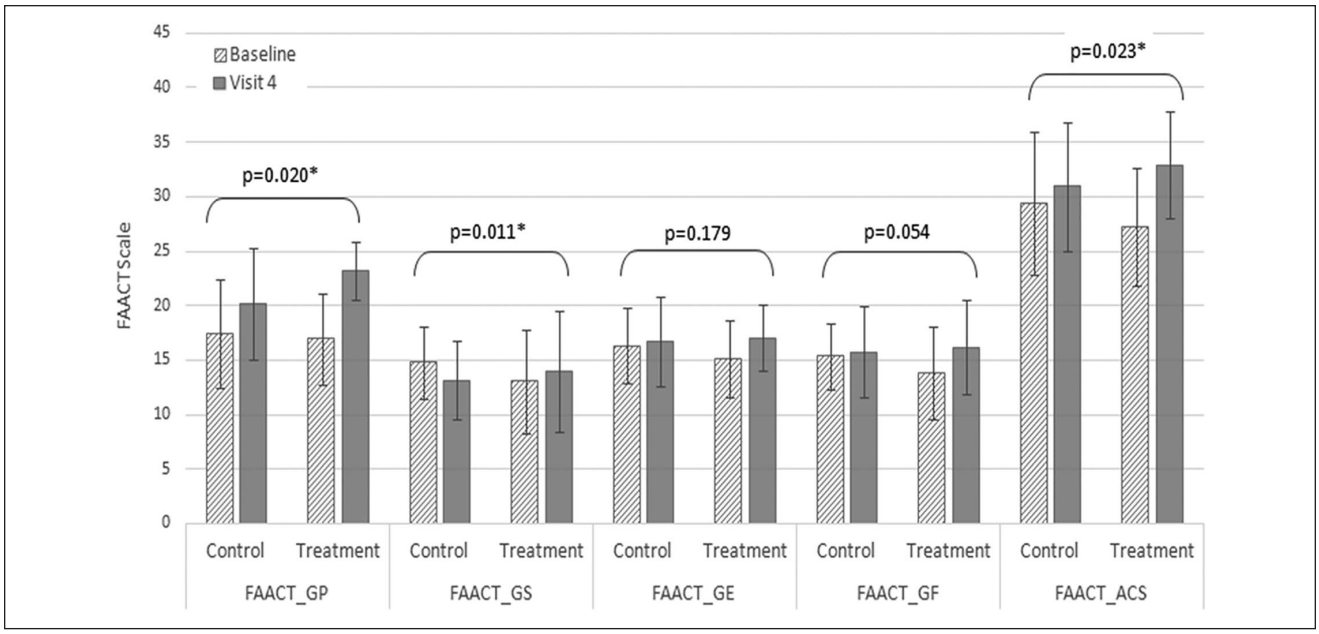


**Figure 2.** Means and SDs for the FAACT scales of the treatment and the control groups at baseline and visit 4 (ITT).
Abbreviations: SD, standard deviation; FAACT, functional assessment of anorexia/cachexia therapy; GP, general physical; GS, general social; GE, general emotional; GF, general functional; ACS, anorexia cachexia subscale; ITT, intentionto-treat analysis.
*$P$-value $<$ .05.

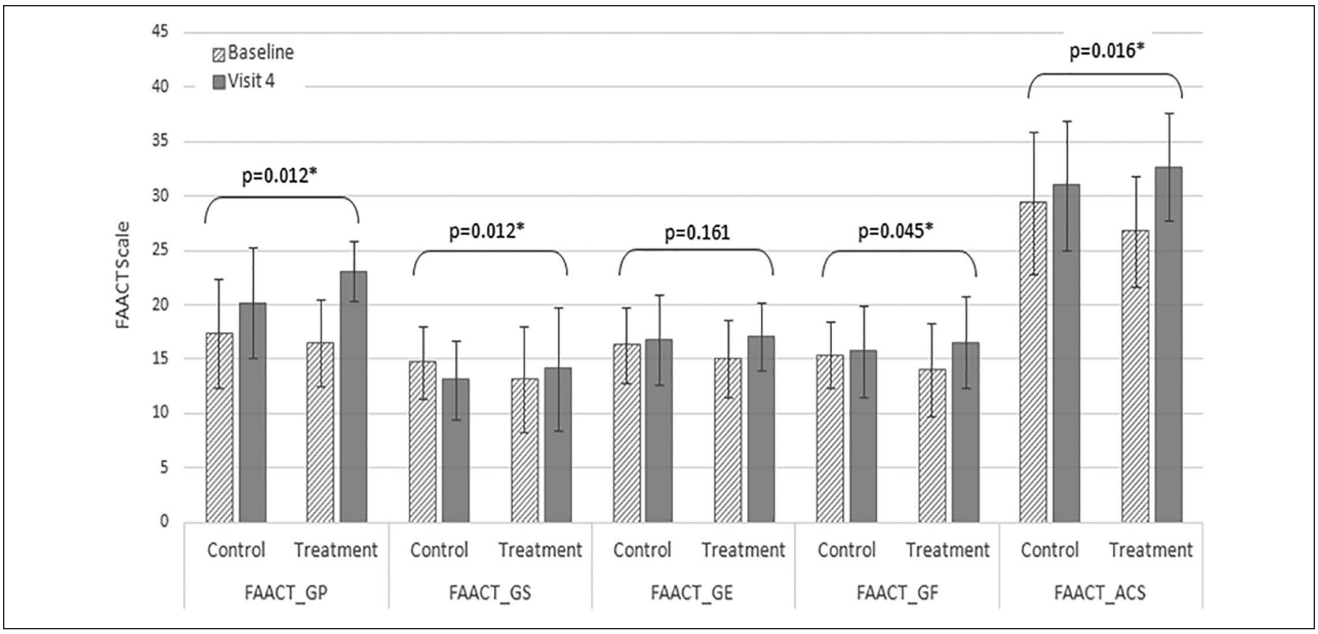


**Figure 3.** Means and SDs for the FAACT scales of the treatment and the control groups at baseline and visit 4 (PP).
Abbreviations: SD, standard deviation; FAACT, functional assessment of anorexia/cachexia therapy; GP, general physical; GS, general social; GE, general emotional; GF, general functional; ACS, anorexia cachexia subscale; PP, per protocol analysis.
*$P$-value $<.05$.

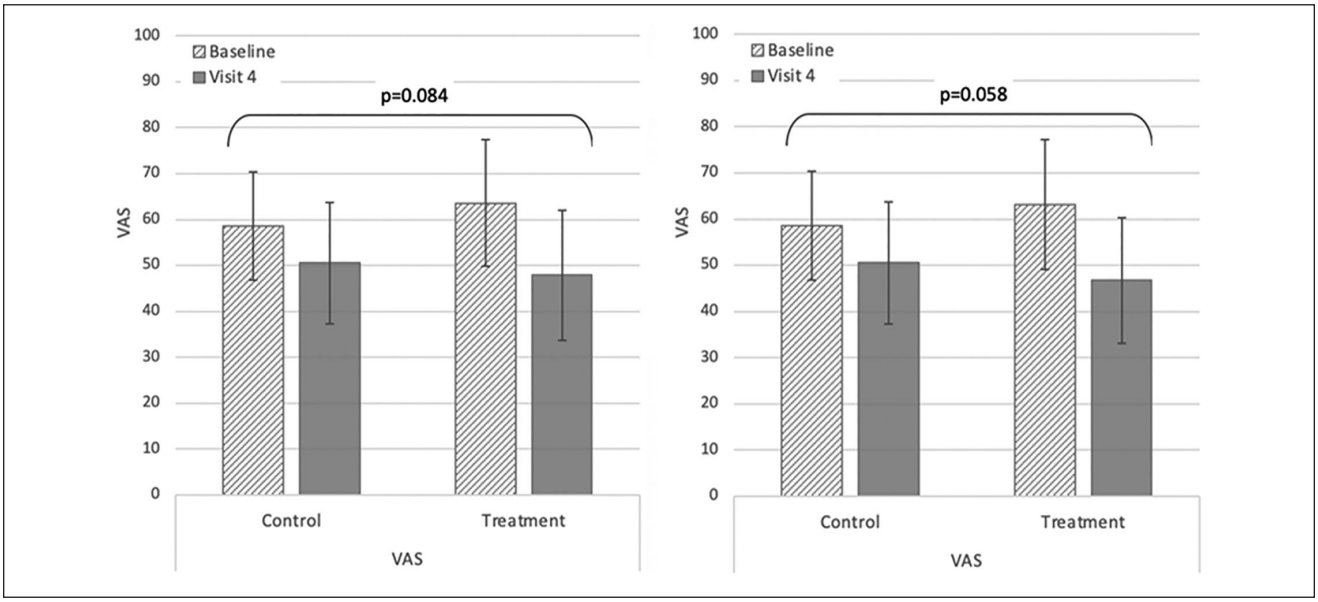


**Figure 4.** Means and SDs for the VAS of the treatment and the control groups at baseline and visit 4.
Abbreviations: SD, standard deviation; VAS, Visual Analog Scale; ITT, intention-to-treat analysis; PP, per protocol analysis.

$13.16 \pm 4.81$, and $14.05 \pm 4.22$ at baseline to $23.11 \pm 2.73$, $14.16 \pm 5.64$, and $16.53 \pm 4.20$, respectively at 4 weeks (GP: $P=0.012$, GS: $P=0.012$, GF: $P=0.045$).

No significant difference in the VAS scores was observed between the 2 groups (ITT: $P=0.084$, PP: $P=0.058$) (Figure 4). Moreover, no significant differences were observed in the leptin, TNF-α, IL-6, and ghrelin levels between the 2 groups (ITT: leptin, $P=0.242$, TNF-α, $P=0.070$, IL-6, $P=0.201$, ghrelin, $P=0.251$; PP: leptin, $P=0.228$, TNF-α, $P=0.070$, IL-6, $P=0.210$, ghrelin, $P=0.224$). Both the ITT and the PP analyses showed greater increases in the treatment group than in the control

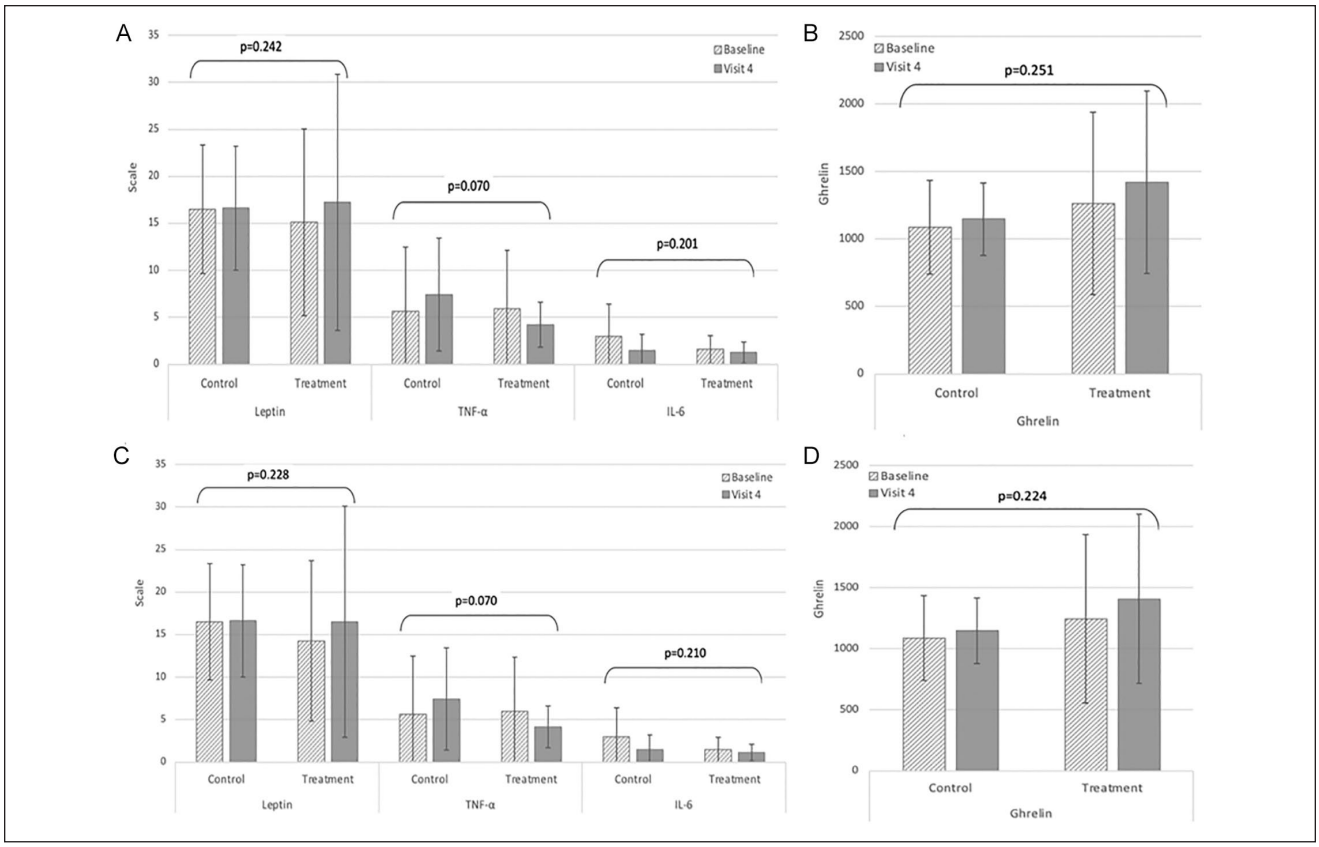


**Figure 5.** Means and SDs for the (A) leptin, TNF-α and IL-6 changes from and the (B) ghrelin changes on the laboratory tests at baseline and visit 4 (ITT analyses). Means and SDs for the (C) leptin, TNF-α and IL-6 and the (D) ghrelin changes on the laboratory tests at baseline and visit 4 (PP analyses).
Abbreviations: SD, standard deviation; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; ITT, intention-to-treat analysis; PP, per protocol analysis.

group; however, the TNF-α level rose in the control group, but decreased in treatment group (Figure 5).

### *Safety Assessment*

According to Table 2, a single participant in the control group experienced parotitis, hordeolum, and posterior neck pain and was dropped from the study. Upper respiratory inflammation and heartburn were reported in the treatment group, and the participant with heartburn was dropped. No serious YGJT-related adverse events occurred. In the treatment group, no significant adverse events and no significant changes in the safety assessment variables based on laboratory tests were reported (Table 3). Thus, based on these data, one can conclude that YGJT can be safely used to treat cancer patients with anorexia.

**Table 2.** Adverse Events of the Participants in the 2 Groups.

| | Control group (n = 20) | Treatment group (n = 20) |
|---|---|---|
| Adverse event | n | n |
| Parotitis/hordeolum | 1 | 0 |
| Upper respiratory inflammation | 0 | 1 |
| Heartburn | 0 | 1 |
| Posterior neck pain | 1 | 0 |

## Discussion

This study investigated the clinical efficacy and safety of using YGJT to manage cancer-related anorexia. Both the ITT and the PP analyses showed that the primary outcome in the treatment group was significantly improved while in the control group it was not. Also, the secondary outcomes were seen to have changed significantly in both the ITT and the PP analyses. The VAS score and the results of the laboratory test also showed an improvement in the treatment group, but without statistical significance. Moreover, the safety of using YGJT was confirmed by the observation that compared to the control group, the treatment group showed

**Table 3.** Results of Laboratory Tests.

| | | | Mean ± SD | | *P*-value | | |
|---|---|---|---|---|---|---|---|
| Hematology | Group | N | Baseline | Visit 4 | Shapiro–Wilk | *t*-test | Mann–Whitney |
| WBC | C | 20 | 4.51 ± 1.20 | 4.61 ± 1.18 | .960 | .749 | .846 |
| | T | 20 | 4.48 ± 1.21 | 4.67 ± 1.28 | .004* | | |
| RBC | C | 20 | 4.15 ± 0.35 | 4.17 ± 0.39 | .132 | .760 | .606 |
| | T | 20 | 4.17 ± 0.29 | 4.21 ± 0.37 | .927 | | |
| Hemoglobin | C | 20 | 12.89 ± 1.07 | 12.98 ± 1.11 | .534 | .928 | .931 |
| | T | 20 | 12.85 ± 0.95 | 12.96 ± 1.06 | .048* | | |
| Hematocrit | C | 20 | 38.74 ± 2.90 | 38.86 ± 2.97 | .085 | .498 | .379 |
| | T | 20 | 38.69 ± 2.59 | 39.17 ± 3.02 | .056 | | |
| ESR | C | 20 | 14.65 ± 8.03 | 16.20 ± 8.83 | .258 | .915 | .919 |
| | T | 20 | 17.00 ± 10.37 | 18.70 ± 10.73 | .495 | | |
| Platelet | C | 20 | 22.12 ± 5.32 | 21.81 ± 4.77 | .025* | .362 | .351 |
| | T | 20 | 21.63 ± 4.44 | 21.94 ± 4.71 | .606 | | |
| AST | C | 20 | 21.55 ± 6.37 | 21.90 ± 6.80 | .008* | .504 | .224 |
| | T | 20 | 21.40 ± 5.94 | 20.95 ± 5.00 | .050 | | |
| ALT | C | 20 | 17.95 ± 6.23 | 18.75 ± 8.62 | .106 | .711 | .460 |
| | T | 20 | 17.00 ± 9.58 | 17.00 ± 6.76 | <.001* | | |
| ALP | C | 20 | 57.10 ± 16.20 | 58.80 ± 17.20 | .882 | .741 | .506 |
| | T | 20 | 68.75 ± 24.42 | 69.80 ± 24.24 | .662 | | |
| Creatinine | C | 20 | 0.70 ± 0.15 | 0.70 ± 0.14 | .523 | .593 | .507 |
| | T | 20 | 0.67 ± 0.10 | 0.68 ± 0.11 | .070 | | |
| BUN | C | 20 | 12.45 ± 2.60 | 12.80 ± 3.11 | .522 | .284 | .358 |
| | T | 20 | 13.36 ± 3.25 | 12.67 ± 3.96 | .690 | | |

Abbreviations: WBC, white blood cells; RBC, red blood cells; ESR, erythrocyte sedimentation rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; C, control group; T, test group; N, number of participants.
*$P$-value < .05.

no serious AEs. Thus, one can conclude that the use of YGJT to manage patients with cancer-related anorexia effective and safe.

The improvement in the QOL, which is influenced by nutritional status,[20] of the participants in this study was confirmed by the changes in the FAACT scores between baseline and week 4. Thus, anorexia accompanied by reduced food intake is a significant issue in the management of such patients because it contributes to the development of malnutrition, increases morbidity and mortality, and has an adverse influence on QOL. Nutritional counseling is the first and most common intervention utilized for the management of malnourished cancer patients and for the treatment of problems of the gastrointestinal tract.[21] Generally, steroids, megestrol acetate, prokinetic agents (metoclopramide), ghrelin, and melatonin are administered to treat cancer patients with anorexia. Although, steroids can improve the quality of life and appetite, they can only be used for a short term due to limitations in metabolism and infectious side effects. In addition, although megestrol acetate can promote appetite, it has the potential for side effects, such as fluid retention and venous embolism.[22] Prokinetic agents, such as metoclopramide, have no apparent proven effect in improving appetite, and ghrelin has only been identified as an appetite-promoting hormone, but there are minority-procedural reports of cancer patients with anorexia.[23-27]

Recently, several herbal medicines have been used to treat patients suffering from anorexia using the metabolism that was decreased by inflammatory cytokines and induced the secretion of ghrelin,[7,12,28] and the mechanisms underlying the effects of those medicines have been reported.[29-31] YGJT administration and plasma ghrelin level correlate with each other in patients with chemotherapy-induced anorexia.[17,32] YGJT stimulates ghrelin secretion from the stomach, and the response to it in the hypothalamus regulates plasma ghrelin levels, sensitizes ghrelin receptors, and antagonizes 5-HT2b/c receptors.[15,33] Unfortunately, in this study, the increase in ghrelin was not significant. But ghrelin level of the treatment groups was higher than the control groups. Acute anorexia after chemotherapy can induce prominent change in plasma ghrelin level, and recovery of the ghrelin level indicates alleviation of the anorexia symptoms. However, chronic cancer-related anorexia, which is the object under study in this trial, does not occur in concordance with the plasma ghrelin level.[34] According to a literature review, the ghrelin level patients with chronic cancer cachexia was 50% higher than it was

in patients without cachexia and 80% higher than it was in non-cancer patients because of inflammation and the extent of fat mass.[35] Although there were no significant results on TNF-α, the results show the decresed TNF-α levels. So we could consider that the YGJT decreased the plasma TNF-α levels.

In this study, we found the use of YGJT to manage patients with cancer-related anorexia to be safe and effective. Even though this trial may provide scientific evidence for the efficacy of YGJT in relieving anorexia, it has limitations that are mostly derived from the sample sizes. We calculated the sample sizes to 52 considering dropout rate 20%, we were unable to recruit the desired number of participants during the study period, so our results may not be statistically valid. In addition, identifying clearly whether the anorexia resulted from cancer or from cancer treatment, such as operation, chemotherapy, or radiotherapy, was problematic. However, because this trial, a pilot study, did reveal some significant effects of using TGJT to manage cancer-related anorexia, its results can be used to guide the design of future large-scale, randomized controlled trail, for example, increasing the number of participants. In addition, further research to observe the effects of YGJT by cancer type is needed.

## Conclusion

This results obtained in this research confirmed the efficacy and the safety of using YGJT as an herb-medicine treatment option for patients with cancer-related anorexia.

### Authors' Note

This trial was registered with the Clinical Research Information Service (CRIS), Republic of Korea, ID: KCT0002847.

### Declaration of Conflicting Interests

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