Bojungikki-Tang for Cancer-Related Fatigue: A Pilot Randomized Clinical Trial

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Abstract

Background: Bojungikki-tang (Bu-Zhong-Yi-Qi-Tang in Chinese or Hochu-ekki-to in Japanese) is a widely used herbal prescription in traditional medicine in China, Japan, and Korea. The aim of this study was to investigate the effectiveness of Bojungikki-tang for cancer-related fatigue. Methods: A total of 40 patients with cancer-related fatigue were randomized into an experimental or a waiting list control group. Patients in the experimental group were treated with Bojungikki-tang (TJ-41) and patients in the waiting list group remained without any intervention for 2 weeks. Results: The experimental group showed statistically significant improvements in fatigue level assessed by the Visual Analogue Scale of Global Fatigue (VAS-F) measuring the severity of fatigue (experimental vs control: -1.1 ± 2.1 vs 0.1 ± 0.9, \( P < .05 \)) and results of Functional Assessment of Cancer Therapy–General (FACT-G), Functional Assessment of Cancer Therapy–Fatigue (FACT-F), and Trial Outcome Index–Fatigue (TOI-F) also showed significant improvements (FACT-G, 3.7 ± 9.9 vs -2.4 ± 9.5, \( P < .05 \); FACT-F, 8.0 ± 13.6 vs -2.2 ± 14.1, \( P < .05 \); TOI-F, 6.5 ± 9.2 vs -0.5 ± 10.9, \( P < .05 \)). Conclusions: The results of this study indicate that Bojungikki-tang may have beneficial effects on cancer-related fatigue and quality of lives in cancer patients. More rigorous trials are needed to confirm the efficacy of Bojungikki-tang.

Keywords

cancer, fatigue, Bojungikki-tang, alternative medicine, complementary therapy, TJ-41, Hochu-ekki-to, herbal medicine, Bu-Zhong-Yi-Qi-Tang, traditional Korean medicine

Introduction

Fatigue is regarded as a common and unavoidable side effect experienced during the course of cancer and its treatment. Cancer-related fatigue interferes with daily activities of cancer patients and affects various aspects of life, including physiological, social, and psychological level.¹ Many studies have found that the prevalence rates of fatigue in cancer patients exceed 60%². In a study by Blesch et al.,³ 99% of the studied breast and lung cancer patients experienced some level of fatigue. A study of almost 3000 cancer patients revealed that fatigue was the most common problem (48.5%), followed by pain (26.4%), managing emotions/stress (24.8%), depression (24.0%), and anxiety (24.0%).⁴ Despite the frequency of cancer-related fatigue in cancer patients and various pharmacologic and nonpharmacologic approaches that have been studied, it still remains underrecognized and undertreated, partly because of limited understanding of its pathophysiology and lack of effective treatments.⁵,⁶

Bojungikki-tang (Bu-Zhong-Yi-Qi-Tang in Chinese or Hochu-ekki-to in Japanese), originally meaning “Tonify the Middle and Augment the Qi Decoction,” has been widely used in traditional medicine in China, Japan, and Korea. This herbal prescription has been identified as an effective medication to improve the function of digestive systems; treat conditions such as general fatigue, poor appetite, spontaneous sweating, and intermittent fever; and as an adjunct to treating debilitating condition resulting from chronic diseases.⁷,⁸ Some clinical studies have been performed regarding the effect of Bojungikki-tang on fatigue, such as a double-blind, placebo-controlled study by Kuratsune,⁹ which suggested that the use of Bojungikki-tang may be helpful for chronic fatigue syndrome. Animal studies also showed positive results in a murine model of chronic fatigue syndrome.¹⁰

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Based on these research results, Bojungikki-tang has been suggested as an alternative therapy to control the cancer-related fatigue and as far as we know, Bojungikki-tang has not been clinically studied for its effect on cancer-related fatigue. The objective of the present study was to evaluate whether Bojungikki-tang has beneficial effects on fatigue and overall quality of life in patients with cancer.

Method

Design

The study was performed as a randomized controlled trial comparing an experimental group (intervention group) with a waiting list control group. A random list was generated with a computer and was used in allocating the subjects into 2 groups. Patients in the experimental group were administered with Bojungikki-tang for 2 weeks. The waiting list control group received no intervention for 2 weeks. After assessing the outcome variables at the end of 2 weeks of waiting list period, the control group was also offered the same intervention as the experimental group but was not further assessed in this study to avoid lead time bias. All patients gave informed consent for the study. This investigation was reviewed and approved by the Institutional Review Board of East-West Neo Medical Center, Kyung Hee University, Seoul, Republic of Korea.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (a) 18 years of age or older diagnosed with a malignancy; (b) had fatigue after cancer diagnosis due to cancer therapy or cancer itself with baseline global fatigue level 40 mm or above as measured by 100-mm Visual Analogue Scale (VAS); (c) Eastern Cooperative Oncology Group (ECOG) scale 2 or below; (d) at least 2 months must have elapsed since the last chemotherapy or radiotherapy. The exclusion criteria applied to patients who (a) had anemia, defined as hemoglobin level <9 g/dL or patients with platelets <50 000/μL or an absolute neutrophil count <1000/μL; (b) had thyroid disorder with abnormal thyroid stimulating hormone and free T4 level; (c) showed levels of abnormal range in serum alanine transaminase (ALT), aspartic acid transaminase (AST), blood urea nitrogen (BUN), or creatinine level. Patients with elevation of ALT or AST not exceeding 2-fold of the maximum of the reference range were allowed in enrolling the trial; (d) had any significant comorbidity, poor oral intake with serum protein level below normal range or with severe insomnia or depression.

Outcome Measurement

At the baseline, all patients were assessed for outcome variables. Visual Analogue Scale of Global Fatigue (VAS-F) was used as the primary outcome variable. Patients were asked to rate their overall fatigue on a 100-mm line anchored at each end by the following statements: “not at all tired” or “extremely tired.”

The Functional Assessment of Cancer Therapy–General (FACT-G) and Functional Assessment of Cancer Therapy–Fatigue (FACT-F) scales were also used as secondary outcome measures of the quality of life of the participants. The FACT-G questionnaire includes 27 items with 4 distinct subscales: physical well-being (PWB; 7 items), social well-being (SWB; 7 items), emotional well-being (EWB; 6 items), and functional well-being (FWB; 7 items). FACT-F consists of 27 items of FACT-G to assess overall quality of life and additional 13 items to assess fatigue level. Each
item is rated on a 5-point Likert-type scale ranging from 0 (not at all) to 4 (very much). These questionnaires are scored such that higher scores indicating more favorable health or less fatigue.

Additionally, we also used Trial Outcome Index–Fatigue (TOI-F) to exclude the influence of change of social or emotional status, as TOI-F is a fatigue-specific score that includes only the physical, functional, and fatigue subscales of the FACT-F questionnaire. These 3 scores (FACT-F, FACT-G, and TOI-F) are a composite of subscale scores: FACT-F = PWB + SWB + EWB + FWB + FS (score 0-160); FACT-G = PWB + SWB + EWB + FWB (score 0-108); TOI-F = PWB + FWB + FS (score 0-108). The Korean version of FACT-G was validated by Lee et al. A Korean version of the additional 13 items for FACT-F was developed by translation of 2 separate translators followed by internal validation based on patient group feedback.

Safety and Toxicity

Tests for safety and toxicity included serum ALT, AST, BUN, and creatinine levels at baseline and end of the administration period (week 2). A questionnaire about abnormal symptoms or any possible adverse effect was also used and each adverse effect was assessed using the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0) scale.

Statistics

An “intention-to-treat” analysis was performed using the “last observation carried forward” method. The primary analysis was based on general linear models, with the outcome measures applied as dependent variables. Each analysis of an individual patient’s baseline level was used as a covariate in the corresponding one-way analysis of covariance (ANCOVA). Independent t-test was also used to compare the changes of the scores between the 2 groups after performing Kolmogorov–Smirnov test and analysis for normality of the distribution. Values are expressed as the mean ± standard deviation (mean ± SD) unless otherwise stated and analyzed by independent t-test.

Results

Demographic Characteristics

The study was carried out from May to October 2009. The study population had a mean age (SD) of 52.6 (11.4) years with 15 male participants (37.5%). The participants who enrolled in the trial consisted of 11 breast cancer patients (27.5%), 5 stomach cancer patients (12.5%), 5 colon cancer patients (12.5%), 5 lung cancer patients (12.5%), and the remaining patients with other cancers (35%). The baseline characteristics were not significantly different between the intervention group and the waiting list control group (Table 1). A total of 18 patients for each group completed the protocol. During the period of the trial, 4 patients (2 patients from each group) were withdrawn from the study protocol because of delayed follow-up visitation for 3 patients and newly started chemotherapy for 1 patient (Figure 1).

Table 1. Demographics of Patients in Each Group

|                         | Experimental Group (n = 20) | Waiting List Group (n = 20) | P-Value |
|-------------------------|-----------------------------|----------------------------|---------|
| Age (years)             | 49.4 (10.8)                 | 53.4 (8.0)                 | .230    |
| Male gender, n (%)      | 8 (40)                      | 7 (35)                     |         |
| Weight (kg)             | 62.7 (13.0)                 | 59.5 (9.7)                 | .424    |
| BMI                     | 23.3 (3.7)                  | 23.1 (2.9)                 | .833    |
| Initial VAS-F           | 6.5 (1.4)                   | 6.1 (1.4)                  | .355    |
| Duration of illness (years) | 2.6 (2.4)                  | 2.3 (2.2)                  | .650    |
| History of CTx or RTx (CTx/RTx) | 16 (80%) (12/5)     | 15 (75%) (14/4)            | .787    |
| Duration since last CTx or RTx (months) | 26.0 (28.9)     | 23.3 (26.6)                |         |
| Type of cancer, n (%)   |                            |                            |         |
| Breast                  | 4 (20)                      | 7 (35)                     |         |
| Stomach                 | 4 (20)                      | 1 (5)                      |         |
| Colorectal              | 3 (15)                     | 2 (10)                     |         |
| Lung                    | 2 (10)                     | 3 (15)                     |         |
| Other                   | 7 (35)                     | 7 (35)                     |         |

Abbreviations: BMI, body mass index; VAS-F = visual analogue scale–fatigue; FACT-G, functional assessment of cancer therapy–general; CTx, chemotherapy; RTx, radiotherapy.

*Values are shown as mean (standard deviation) unless otherwise stated and analyzed by independent t-test.
Outcome Measures

The experimental group had statistically significant improvements in the VAS-F measuring the severity of fatigue (experimental vs control in mean change ± SD: −1.1 ± 2.1 vs 0.1 ± 0.9, \( P = .04 \) in ANCOVA). The assessment of FACT-G also showed significant improvements (experimental vs control in mean change ± SD: 3.7 ± 9.9 vs −2.4 ± 9.5, \( P = .047 \) in ANCOVA), though independent t-test comparing the changes of the scores between the 2 groups was not statistically significant \( (P = .055) \). FACT-F (experimental vs control in mean change ± SD: 8.0 ± 13.6 vs −2.2 ± 14.1, \( P = .025 \) in ANCOVA) and TOI-F (experimental vs control in mean change ± SD: 6.5 ± 9.2 vs −0.5 ± 10.9, \( P = .049 \) in ANCOVA), 2 fatigue-focused measurements, also showed significant changes in the experimental group (Table 2, Figures 2 and 3).

Safety and Toxicity

No serious adverse effects occurred during the study. However, one patient who had taken antihypertensive medication for 3 years with baseline serum creatinine at cut-off level showed slightly increased BUN and creatinine level above the reference range. Further analysis using Wilcoxon signed-rank test on liver and renal toxicity revealed no significant change between baseline and week-2 test results. Two patients reported minor adverse effects including increased flatulence and dyspepsia and these were assessed as grade 1 on the NCI-CTC scale.

Discussion

This pilot study suggests that Bojungikki-tang may have beneficial effects on cancer-related fatigue and quality of life in cancer patients without any significant adverse effect. With statistical significance, decreased fatigue levels were observed in patients who were administered with Bojungikki-tang for 2 weeks. Furthermore, scales for assessing overall general quality of life were also improved with the Bojungikki-tang administration in comparison to the waiting list group. These results are compatible with the research of Barton et al., which showed that a high dose of American ginseng was effective in relieving cancer-related fatigue. Although a different species was used, ginseng is one of the main herbs in Bojungikki-tang for relieving fatigue.

Cancer-related fatigue is thought to be a multifactorial condition attributed to cancer itself, side effects of therapy, diminished activity, poor nutrition, depression, and intercurrent illness. Nonpharmacological interventions for improving fatigue in cancer patients include exercise, dietary management, sleep therapy, and active management. Of these interventions, exercise has the strongest evidence base for treating fatigue but others need large randomized trials to properly define their roles in the clinical
Pharmacological interventions for cancer-related fatigue are methylphenidate, corticosteroids, anabolic steroids, antidepressants, donepezil, l-carnitine, modafinil, and amantadine. However, few of these agents have been studied in large placebo-controlled trials and, so far, of those that have been studied, none have been proven to be helpful and ready for general clinical practice.\textsuperscript{18}

We focused on whether Bojungikki-tang affects cancer-related fatigue in terms of physical and functional aspects rather than social and emotional aspects. Patients with depression were excluded at patient recruitment for this reason. In this study, VAS-F was used as the primary outcome measurement for assessing global fatigue level and FACT-F was used as the secondary outcome measurement for assessing quality of life. In a validation by Van Belle et al,\textsuperscript{19} both FACT-F scale and VAS reflected the intensity of fatigue, and were evaluated as suitable tools for follow-up of cancer-related fatigue. FACT-G and TOI-F, which are part of the FACT-F questionnaire, were also used and analyzed. TOI-F was a fatigue-specific subscale from the FACT-F questionnaire mainly reflecting physical and functional outcomes. As social and emotional well-being are less likely to change as quickly or dramatically over time or in response to physical health interventions, the TOI endpoint is considered as an efficient measurement in clinical trials because it mainly focuses on physical and functional outcomes.\textsuperscript{14,15} The results of FACT-F and TOI in this study showed significant improvements and this corresponds with the report by Satoh et al\textsuperscript{20} showing that Bojungikki-tang improved fatigue and weakness functionally in elderly patients. As Astragali radix is also one of the main

| Table 2. Outcome Measures for Experimental Group and Waiting List Group |
|------------------|------------------|------------------|------------------|
|                   | Mean ± SD        |                   |                   |
|                   | Experimental Group (n = 20) | Waiting List Group (n = 20) | P-Value          |
| VAS               |                   |                   |                   |
| Week 0            | 6.5 ± 1.4         | 6.1 ± 1.4         | .040\textsuperscript{b,d} |
| Week 2            | 5.3 ± 1.9         | 6.1 ± 1.3         |                   |
| Δ\textsuperscript{a} | −1.1 ± 2.1       | 0.1 ± 0.9         | .025\textsuperscript{c,d} |
| FACT-G            |                   |                   |                   |
| Week 0            | 66.3 ± 14.7       | 65.7 ± 15.3       | .047\textsuperscript{b,d} |
| Week 2            | 70.0 ± 14.8       | 63.4 ± 16.2       |                   |
| Δ\textsuperscript{a} | 3.7 ± 9.9         | −2.4 ± 9.5        | .055\textsuperscript{c} |
| FACT-F            |                   |                   |                   |
| Week 0            | 92.8 ± 23.5       | 94.9 ± 23.2       | .026\textsuperscript{b,d} |
| Week 2            | 100.8 ± 23.9      | 92.8 ± 22.2       |                   |
| Δ\textsuperscript{a} | 8.0 ± 13.6        | −2.2 ± 14.1       | .025\textsuperscript{c,d} |
| TOI-F             |                   |                   |                   |
| Week 0            | 60.2 ± 19.3       | 63.9 ± 17.3       | .049\textsuperscript{b,d} |
| Week 2            | 66.6 ± 18.3       | 63.4 ± 15.4       |                   |
| Δ\textsuperscript{a} | 6.5 ± 9.2         | −0.5 ± 10.9       | .037\textsuperscript{c,d} |

Abbreviations: FACT-G, functional assessment of cancer therapy–general = PWB + SWB + EWB + FWB (score 0-108); FACT-F = functional assessment of cancer therapy–fatigue = PWB + SWB + EWB + FWB + FS (score 0-160); TOI-F, trial outcome index–fatigue = PWB + FWB + FS (score 0-108), where PWB = physical well-being subscale (score 0-28), SWB = social well-being subscale (score 0-28), EWB = emotional well-being subscale (score 0-24), FWB = functional well-being subscale (score 0-28), and FS = fatigue subscale (score 0-39).

\textsuperscript{a} Δ is the score at 2 weeks minus the baseline (week 0).

\textsuperscript{b} P-values from analysis of covariance for the 2-week score with baseline score as a covariate.

\textsuperscript{c} P-values from independent t-test.

\textsuperscript{d} P < .05.
ingredients in Bojungikki-tang, a previous report about Myelophil, an extract mix of Astragali radix and Salviae radix, ameliorating chronic fatigue is compatible with this result.21

The effect of Bojungikki-tang administration was attributed to the mechanism of activating the immune system through significantly increasing lymphocyte cell-surface antigens, CD3-positive cells, and CD3/CD4 double-positive cells in the treatment group.20 Shin et al22 reported that Bojungikki-tang treats chronic fatigue by inhibiting TNF-α, IL-6, IL-10, TGF-β1, and INF-γ production in chronic fatigue syndrome patients. Bojungikki-tang also improves systemic inflammation and nutritional status associated with chronic diseases.23,24 These results suggest that Bojungikki-tang may affect the pathogenesis of the chronic fatigue syndrome or other chronic diseases.

Bojungikki-tang is a herbal prescription with 10 different herbs, and Astragali radix and Ginseng radix are 2 major herbs that account for highest portion of the prescription. Astragali radix showed immunomodulatory effects in patients with systemic lupus erythematosus (SLE),25 enhanced immune function in HIV/AIDS patients,26 and improved cancer-related anorexia in cancer patients.27 Ginseng is known to have the ability to enhance immune system and liver function, and also to have antifatigue and antistress effects as well as anti-oxidative and anti-aging effects.28 Individual herbs may play a limited role in the overall effects of Bojungikki-tang, but these study results may also help at least partly explain the effect of Bojungikki-tang.

This study has some limitations. First of all, the waiting list control was used as the control group instead of placebo control. We initially considered using placebo control group but as Bojungikki-tang is a herbal extract with distinct flavor and taste, and was provided in extract granule form, not in a capsule or tablet form, it was difficult to acquire placebo material with similar color and flavor. Furthermore, poor patient recruitment was expected when we use the placebo setting as many cancer patients in the local community did not want to get placebo treatment in preliminary survey. However, as some studies showed considerable response to placebo, using appropriate placebo treatment should be considered in the future studies.29,30 Another limitation is the two week treatment period without follow-up. While many studies use 1- or 2-week treatment period in the clinical trial setting,30,31 it would be appropriate in the future studies to administer for longer periods of time with long-term follow-up research as fatigue is a rather chronic symptom and in most cases, affecting the patients longer than several weeks. A recent study by Kobayashi et al32 also adopted a longer administration protocol with Bojungikki-tang, which is considered to work in a slower manner.

Considering that Bojungikki-tang originated and developed mainly from traditional medical system in East Asia (China, Japan, or Korea), which considered the constitution or specific characteristics of health status in prescribing medication, the concurrent use of outcome measurements reflecting the perspective of traditional medicine will be of interest in future studies. In traditional medicine in East Asia, Bojungikki-tang is prescribed not for everyone but for those who are in Qi-deficiency syndrome, which is defined as a hypersensitive, easily fatigable constitution that typically is associated with poor gastrointestinal functions or night sweats.33 Though fatigue is one of the typical symptoms of this Qi-deficiency syndrome, other factors that constitute the syndrome may also be considered in studying Bojungikki-tang.

Acupuncture is also a well-known nonpharmacological treatment modality of traditional medical systems in East Asia, but we did not provide acupuncture treatment to avoid bias as previous studies also report positive results in post-chemotherapy fatigue or other cancer-related fatigue.31,34
It would be interesting, however, to combine both pharmacologic and nonpharmacological approaches together in actual clinical practice or in future studies.

Despite its limitations, we believe that our study reports interesting data on the potentials of Bojungikki-tang to be used for cancer-related fatigue and to improve quality of life in cancer patients. Based on the results of the study, future studies should employ more subjects, have an appropriate control group, and include long-term administration and follow-up.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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References

1. Sood A, Barton DL, Bauer BA, Loprinzi CL. A critical review of complementary therapies for cancer-related fatigue. Integr Cancer Ther. 2007;6:8-13.
2. Morrow GR, Shelke AR, Roscoe JA, Hickok JT, Mustian K. Management of cancer-related fatigue. Cancer Invest. 2005;23:229-239.
3. Blesch KS, Paice JA, Wickham R, et al. Correlates of fatigue in people with breast or lung cancer. Oncol Nurs Forum. 1991;18:81-87.
4. Carlson LE, Angen M, Cullum J, et al. High levels of untreated distress and fatigue in cancer patients. Br J Cancer. 2004;90:2297-2304.
5. Sood A, Moynihan TJ. Cancer-related fatigue: an update. Curr Oncol Rep. 2005;7:277-282.
6. Dimeo FC. Effects of exercise on cancer-related fatigue. Cancer. 2001;92(6 Suppl):1689-1693.
7. Bensky D, Barolet R. Chinese Herbal Medicine: Formulas & Strategies. Seattle, WA: Eastland Press; 1990.
8. Kobayashi H, Mizuno N, Teramae H, et al. The effects of Hochu-ekki-to in patients with atopic dermatitis resistant to conventional treatment. Int J Tissue React. 2004;26:113-117.
9. Kuratsune H. Effect of Kampo medicine, “Hochu-ekki-to,” on chronic fatigue syndrome. Clin and Research. 1997;74:1837-1845.
10. Wang XQ, Takahashi T, Zhu SJ, et al. Effect of Hochu-ekki-to (TJ-41), a Japanese herbal medicine, on daily activity in a murine model of chronic fatigue syndrome. Evid Based Complement Alter Med. 2004;1:203-206.
11. Auret KA, Schug SA, Bremner AP, Bulsara M. A randomized, double-blind, placebo-controlled trial assessing the impact of dexamphetamine on fatigue in patients with advanced cancer. J Pain Symptom Manage. 2009;37:613-621.
12. Barton DL, Soori GS, Bauer BA, et al. Pilot study of Panax quinquefolius (American ginseng) to improve cancer-related fatigue: a randomized, double-blind, dose-finding evaluation: NCCTG trial N03CA. Support Care Cancer. 2010;18:179-187.
13. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. J Pain Symptom Manage. 2002;24:547-561.
14. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: properties, applications, and interpretation. Health Qual Life Outcomes. 2003;1:79.
15. Hwang SS, Chang VT, Kasimis BS. A comparison of three fatigue measures in veterans with cancer. Cancer Invest. 2003;21:363-373.
16. Lee EH, Chun M, Kang S, Lee HJ. Validation of the Functional Assessment of Cancer Therapy–General (FACT-G) scale for measuring the health-related quality of life in Korean women with breast cancer. Jpn J Clin Oncol. 2004;34:393-399.
17. Mitchell SA, Beck SL, Hood LE, Moore K, Tanner ER. Putting evidence into practice: evidence-based interventions for fatigue during and following cancer and its treatment. Clin J Oncol Nurs. 2007;11:99-113.
18. Mitchell SA, Berger AM. Cancer-related fatigue: the evidence base for assessment and management. Cancer J. 2006;12:374-387.
19. Van Belle S, Paridaens R, Evers G, et al. Comparison of proposed diagnostic criteria with FACT-F and VAS for cancer-related fatigue: proposal for use as a screening tool. Support Care Cancer. 2005;13:246-254.
20. Satoh N, Sakai S, Kogure T, et al. A randomized double-blind placebo-controlled clinical trial of Hochuekkito, a traditional herbal medicine, in the treatment of elderly patients with weakness, N of one and responder restricted design. Phytotherapy. 2005;12:549-554.
21. Cho JH, Cho CK, Shin JW, Son JY, Kang W, Son CG. Myeloph, an extract mix of Astragali Radix and Salviae Radix, ameliorates chronic fatigue: a randomised, double-blind, controlled pilot study. Complement Ther Med. 2009;17:141-146.
22. Shin HY, Shin CH, Shin TY, Lee EJ, Kim HM. Effect of bojungikki-tang on lipopolysaccharide-induced cytokine production from peripheral blood mononuclear cells of chronic fatigue syndrome patients. Immunopharmacol Immunotoxicol. 2003;25:491-501.
23. Shinozuka N, Tatsumi K, Nakamura A, et al. The traditional herbal medicine Hochuekkito improves systemic inflammation in patients with chronic obstructive pulmonary disease. J Am Geriatr Soc. 2007;55:313-314.
24. Tatsumi K, Shinozuka N, Nakayama K, Sekiya N, Kuriyama T, Fukuchi Y. Hochuekkito improves systemic inflammation and nutritional status in elderly patients with chronic obstructive pulmonary disease. J Am Geriatr Soc. 2009;57:169-170.
25. Cai XY, Xu YL, Lin XJ. Effects of radix Astragali injection on apoptosis of lymphocytes and immune function in patients with systemic lupus erythematosus. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2006;26:443-445.
26. Wei JA, Sun LM, Chen YX. Effects of Ailing Granule on immuno-reconstruction in HIV/AIDS patients. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2006;26:319-321.
27. Lee JJ, Lee JJ. A phase II study of an herbal decoction that includes Astragali radix for cancer-associated anorexia in patients with advanced cancer. Integr Cancer Ther. 2010; 9:24-31.
28. Choi KT. Botanical characteristics, pharmacological effects and medicinal components of Korean Panax ginseng C A Meyer. Acta Pharmacol Sin. 2008;29:1109-1118.
29. Bruera E, Valero V, Driver L, et al. Patient-controlled methylyphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol. 2006;24:2073-2078.
30. Bruera E, El Osta B, Valero V, et al. Donepezil for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol. 2007;25:3475-3481.
31. Molassiotis A, Sylt P, Diggins H. The management of cancer-related fatigue after chemotherapy with acupuncture and acupressure: a randomised controlled trial. Complement Ther Med. 2007;15:228-237.
32. Kobayashi H, Ishii M, Takeuchi S, et al. Efficacy and safety of a traditional herbal medicine, Hochu-ekki-to in the long-term management of Kikyo (Delicate Constitution) patients with atopic dermatitis: a 6-month, multicenter, double-blind, randomized, placebo-controlled study. Evid Based Complement Alternat Med. 2010;7:367-373.
33. Terasawa K. Evidence-based reconstruction of Kampo medicine: part II—the concept of Sho. Evid Based Complement Alternat Med. 2004;1:119-123.
34. Vickers AJ, Straus DJ, Fearon B, Cassileth BR. Acupuncture for postchemotherapy fatigue: a phase II study. J Clin Oncol. 2004;22:1731-1735.