

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

## Integrative Medicine Research

journal homepage: [www.imr-journal.com](http://www.imr-journal.com)

## Study Protocol

# Effects of Bu-Zhong-Yi-Qi-Tang for the treatment of functional dyspepsia: a feasibility study protocol

Jihye Kim<sup>a</sup>, Hyunho Kim<sup>b</sup>, Keun Ho Kim<sup>a,\*</sup>

<sup>a</sup> KM Fundamental Research Division, Korea Institute of Oriental Medicine, Daejeon, Korea

<sup>b</sup> Department of Biofunctional Medicine & Diagnostics, College of Korean Medicine, Kyung Hee University, Seoul, Korea

## ARTICLE INFO

## Article history:

Received 26 December 2016

Received in revised form 2 July 2017

Accepted 5 July 2017

Available online 13 July 2017

## Keywords:

Bu-Zhong-Yi-Qi-Tang

functional dyspepsia

herbal medicine

traditional Korean medicine

## ABSTRACT

**Background:** Bu-Zhong-Yi-Qi-Tang (BZYQT) has long been used for the treatment of severe weakness caused by general fatigue, loss of appetite, or indigestion. The aim of this feasibility study is to assess the effectiveness and safety of BZYQT for the treatment of functional dyspepsia (FD) with spleen qi deficiency.

**Methods:** This study will be conducted at a single center as a prospective, nonrandomized, nonblinded, single-arm feasibility study. A total of 30 participants diagnosed with FD in accordance with the Rome III criteria will be enrolled. All patients will receive BZYQT for 4 weeks. The primary outcome is the change in the Nepean Dyspepsia Index-Korean version (NDI-K) scores between the baseline and 4-week images. The secondary outcomes include the tongue coating thickness, blood parameters, and BZYQT Questionnaire score. The NDI-K score will be acquired four times, at Weeks 0 (baseline), 2 (during treatment), 4 (after treatment), and 8 (after follow-up). Written informed consent will be obtained from all study participants prior to enrollment. This study has been approved by the Institutional Review Board of Kyung Hee University Korean Medicine Hospital. This study protocol is registered with the national clinical trial registry of the World Health Organization International Clinical Trials Registry Platform. Results will be published in a journal and will be disseminated both electronically and in print.

**Discussion:** The results of this study may serve as a guide for researchers seeking to effectively evaluate the effects of BZYQT.

**Trial Registration No.:** KCT0002114 (date of registration: October 21, 2016).

© 2017 Korea Institute of Oriental Medicine. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

\* Corresponding author at: KM Fundamental Research Division, Korea Institute of Oriental Medicine, 1672 Yuseongdae-Ro, Yuseong-Gu, Daejeon 34054, Korea.

E-mail address: [rkim70@kiom.re.kr](mailto:rkim70@kiom.re.kr) (K.H. Kim).

<http://dx.doi.org/10.1016/j.imr.2017.07.003>

2213-4220/© 2017 Korea Institute of Oriental Medicine. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Functional dyspepsia (FD) is a common gastrointestinal disorder that is defined as discomfort centered in the upper digestive tract. The cause of FD is unknown; however, several hypotheses could explain this condition, even though none can be consistently associated with FD.<sup>1,2</sup> According to the Rome III and IV consensus, the diagnostic criteria for FD include symptoms such as bothersome postprandial fullness, early satiation, epigastric pain, or epigastric burning.<sup>2–4</sup> Patients must have had one or more of these symptoms for the previous 3 months, with symptom onset at least 6 months prior to diagnosis. In addition, patients should have no evidence of organic, systemic, or metabolic disease that explains these symptoms, including any condition detected by upper endoscopy.<sup>3–5</sup>

In recent years, herbal treatments for FD have received increasing attention.<sup>6</sup> Bu-Zhong-Yi-Qi-Tang (BZYQT) is an herbal formula described in an important text of the Chinese tradition, the *Pi Wei Lun* (Treatise on Spleen and Stomach, 1249 ad), which focuses on a deficiency of the spleen and stomach as the origin of numerous diseases.<sup>7</sup> The name BZYQT is often translated as “the decoction to tonify the center and boost the qi.” BZYQT can nourish the spleen and promote the qi due to a qi deficiency. The central qi provides the vital energy of the body, including the internal organs and physical activities. When the qi is weak, organs such as the stomach, uterus, and rectum fail to support themselves and thus wither; the body loses physical strength and exhibits fatigue, tiredness, and weakness.<sup>8–10</sup>

BZYQT can be obtained as an over-the-counter herbal formula in Korea. Therefore, reliable clinical evidence regarding BZYQT as treatment for FD is needed. BZYQT has been studied to meet the growing need for FD treatments. Recently, several animal studies have examined the dyspeptic symptoms and related mechanisms of BZYQT.<sup>9–12</sup> However, no relevant randomized controlled trials have been conducted.

To encourage evidence-based practices for BZYQT, well-designed studies must be conducted to evaluate the effects and mechanisms of action of BZYQT. The aim of this study is to evaluate the effects and safety of BZYQT.

## 2. Methods

### 2.1. Hypothesis

We hypothesized that 4 weeks of BZYQT treatment will improve FD symptoms and the Nepean Dyspepsia Index-Korean version (NDI-K) score will differ before, during, and after treatment.

### 2.2. Design and setting

This study will be conducted at Kyung Hee University Korean Medicine Hospital, Seoul, Republic of Korea. The study period is expected to last from September 2016 to April 2017.

This study will be performed according to the protocol approved by the Institutional Review Board (IRB) of Kyung

Hee University Korean Medicine Hospital (KOMCIRB-160719-HR-037-03), the standards of the International Committee on Harmonization on Good Clinical Practice, and the revised version of the Declaration of Helsinki. Any protocol modifications will be approved by the IRB of Kyung Hee University Korean Medicine Hospital. This study protocol is registered with the National Clinical Trial Registry of the World Health Organization International Clinical Trials Registry Platform (identifier number KCT0002114).

Written informed consent will be obtained from all study participants prior to enrollment in the study, and participants will be given the option to decline to participate or withdraw at any time without disadvantage.

## 3. Recruitment period and methods

Participant recruitment began in October 2016 at Kyung Hee University Korean Medicine Hospital and completed in March 22, 2017. The IRB approved the advertisements for the study.

Thirty participants will be recruited for this study using two strategies. First, participants will be recruited through classified advertisements and hospital websites. Second, printed recruitment posters will be posted throughout Kyung Hee University Korean Medicine Hospital and Kyung Hee University campus. The relevance of the study information will be conveyed to potential participants prior to their first visit to the hospital.

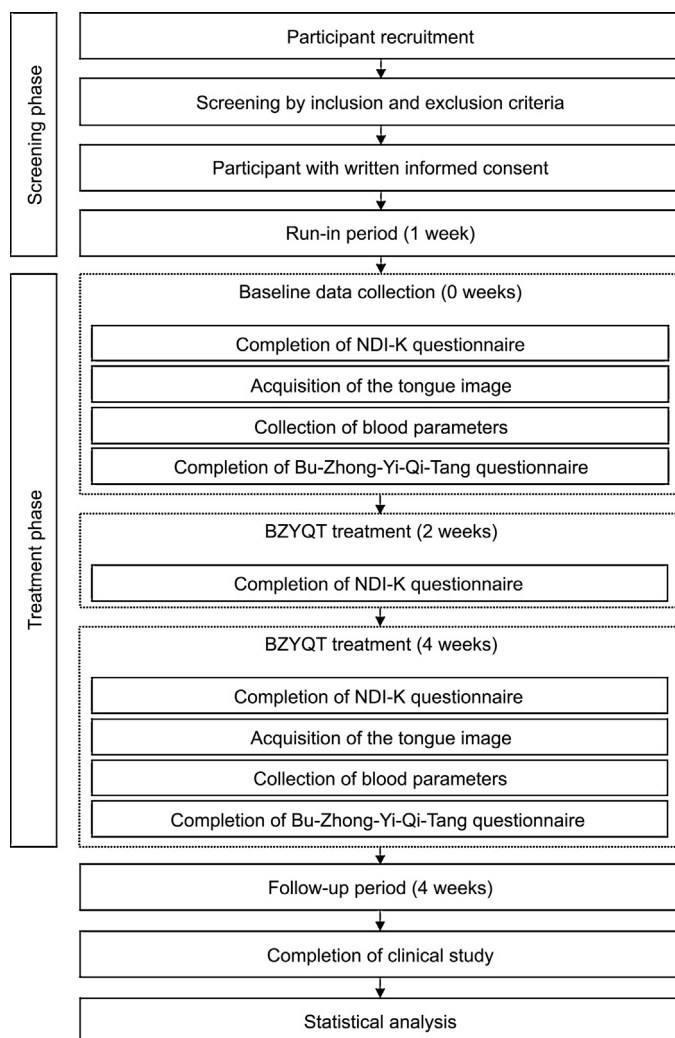
### 3.1. Study plan

The entire observation process will be carried out at Kyung Hee University Korean Medicine Hospital. Fig. 1 shows the experimental procedures.

All participants between the ages of 20 and 70 diagnosed with FD with spleen qi deficiency in accordance with the Rome III criteria and Spleen Qi Deficiency Questionnaire (SQDQ) will be enrolled in this study. The SQDQ was developed by Oh et al.<sup>13</sup> and is a reliable and validated questionnaire<sup>14</sup> that consists of 11 questions. These items are measured using 5-point Likert scales, where 0 indicates not at all or not applicable; 1 indicates a little applicable; 2 indicates moderately applicable; 3 indicates quite applicable; and 4 indicates extremely applicable. The cut-off value is 43.18 (spleen qi deficiency >43.18 and nonspleen qi deficiency ≤43.18).

Participants will then be briefly introduced to the clinical study and will be asked to complete a baseline questionnaire during the initial visit to the study institution. Family history; daily activity; quality of sleep; tobacco, alcohol, and caffeine intake will be noted for all participants.

An independent assessor will initially assess each potential participant according to the inclusion and exclusion criteria. We will perform the following tests on all participants at screening: white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, erythrocyte sedimentation rate, blood urea nitrogen (BUN), creatinine, total protein, albumin, aspartate aminotransferase/alanine aminotransferase (AST/ALT), gamma-glutamyl transpeptidase, total/direct bilirubin, uric acid, C-reactive protein, sodium, potassium, chloride, and thyroid-stimulating



**Fig. 1 – Flowchart of this study. BZYQT, Bu-Zhong-Yi-Qi-Tang; NDI-K, Nepean Dyspepsia Index-Korean version.**

hormone (TSH) levels. These tests will help us exclude participants who have serious diseases and abnormal liver, heart, kidney, or other organ function.

After completing a screening test, participants will enter a run-in period of 1 week.

After the run-in period, primary and secondary outcomes will be acquired four times (before, during, after treatment, and after follow-up). The participants will refrain from eating and drinking for 2 hours prior to the experiment.

#### 4. Participant selection criteria

The inclusion and exclusion criteria are based on previous studies.<sup>15,16</sup>

#### 5. Inclusion criteria

FD patients meeting the following criteria will be included: (1) age between 20 and 70 years; (2) meeting the definition of FD according to the Rome III criteria; (3) FD symptoms over

the past 6 months; (4) over the cutoff value (43.18) for the SQDQ score; (5) patient has no communication problems; and (6) patient provides consent to participate in this study and signs an informed consent statement after listening to a clear explanation of the purpose and characteristics of the clinical study.

#### 6. Exclusion criteria

Participants meeting one or more of the following criteria will be excluded: (1) individuals who have serious diseases, including digestive, kidney, heart, lung, and metabolic diseases or cancer; (2) individuals who have undergone surgery related to the gastrointestinal tract with the exception of an operation for appendicitis; (3) patients with a body mass index greater than the range between 18.5 kg/m<sup>2</sup> and 30 kg/m<sup>2</sup>; (4) patients who have taken another medicine or a Korean herbal medicine within 4 weeks of the study period; (5) pregnant and lactating women; (6) patients with severe psychological and mental illness, dementia, and drug addiction; (7) patients with a history of another clinical study within the preceding 2 months; (8) patients who have abnormal blood test results (more than three times over the normal range); (9) patients who have difficulty imposing strict restrictions on any oral activities (such as eating or brushing teeth) for at least 4 hours; (10) patients exhibiting hypersensitivity to the test drug; (11) patients who were disqualified as a suitable patient by a Korean medicine doctor; and (12) anyone considered inappropriate for trial participation as determined by the clinical study directors.

#### 7. Dropout criteria

Participants meeting one or more of the following dropout criteria will be excluded: (1) those who prefer not to be subjected to the assigned measurement for various reasons at any stage of the study; (2) the occurrence of adverse events (AEs) or severe AEs necessitating withdrawal from the study; (3) an inability to fully participate in at least 75% of follow-up appointments; and (4) any measurements are made in a manner inconsistent with the device's standard operating procedures (SOPs).

#### 8. Intervention

Study medications will be prepared by HANPOONG Pharm & Foods Co., Ltd. (Jeonju, Republic of Korea). HANPOONG Pharm & Foods Co., Ltd. is certified in Good Manufacturing Practices for the manufacture of herbal medicine extract pills and granules by the Ministry of Food and Drug Safety.

BZYQT has long been used to treat severe weakness caused by general fatigue, loss of appetite, or indigestion.<sup>17</sup> BZYQT was originally composed of 10 species of medicinal plants. However, the BZYQT used in this study is an over-the-counter drug, which contains eight species of plants: *Astragali Radix*, *Ginseng Radix*, *Atractylodis Rhizoma Alba*, *Glycyrrhizae Radix et Rhizoma*, *Angelicae Gigantis Radix*, *Citri Unshius Pericarpium*, *Cimicifugae Rhizoma*, and *Bupleuri Radix*. The amounts and sources of each component in the standard herb formula are shown

**Table 1 – Herbal formula for Bu-Zhong-Yi-Qi-Tang.**

Chinese name	Crude drug name	Pharmaceutical name	Quantity (g)	
Huangqi	黄芪	Astragali radix	Astragalus root	0.41
Renshen	人参	Ginseng radix	Ginseng	0.30
Baizhu	白朮	Atractylodis rhizoma Alba	Atractylodes rhizome white	0.46
Gancao	甘草	Glycyrrhizae radix et rhizoma	Licorice	0.34
Danggui	当归	Angelicae gigantis radix	Angelica gigas root	0.23
Chenpi	陈皮	Citri unshius pericarpium	Citrus unshiu peel	0.20
Shengma	升麻	Cimicifugae rhizoma	Cimicifuga rhizome	0.06
Chaihu	柴胡	Bupleuri Radix	Bupleurum root	0.06

in Table 1. The decoction was filtered, concentrated, and sterilized according to herbal medicine preparation methods, and was stored between 1 °C and 30 °C.

The participants will take 2.06 g of BZYQT orally each time, three times per day at 30 minutes after breakfast, lunch, and dinner. For the duration of this study, the participants will not be allowed to take any concomitant medications associated with FD treatment. The participants will also be required to stop taking such drugs at least 1 week before their treatment; moreover, they will be asked to stop smoking and drinking alcohol or caffeine throughout the study.

According to a previous study, the effects of herbal medicines appear to last up to 4 weeks after the completion of treatment<sup>6</sup>; therefore, this study comprises both a 4-week treatment period and a 4-week follow-up period. The quantity of dyspeptic symptom-relieving medication taken during the treatment period will be recorded at each visit.

### 8.1. Outcome measures

A practitioner who is also a licensed doctor will evaluate the outcome variables as an assessor.

#### 8.1.1. Primary outcome

The primary outcome of this study is the NDI-K score. The effects of BZYQT will be assessed by observing differences in the NDI-K score before treatment (Visit 1), after 2 weeks of treatment (Visit 2), after 4 weeks of treatment (Visit 3), and after 4 weeks of follow-up (8 weeks after the initiation of treatment).

The NDI was developed by Talley et al.<sup>18</sup> The Korean version of the NDI was standardized and validated by Lee et al.<sup>19</sup> The NDI-K Questionnaire measures health-related quality of life consists of 15 questions. These items are measured using 5-point or 6-point Likert scales, where 0 indicates not at all or not applicable, 1 indicates a little, 2 indicates moderately, 3 indicates quite a lot, and 4 indicates extremely. Higher scores indicate a worse quality of life.<sup>20</sup> In this study, we will ask symptom-based questions regarding the period, severity, and degree of distress of 15 symptoms at baseline, after 2 weeks, and again after 4 weeks.

#### 8.1.2. Secondary outcomes

The secondary outcome measures include the tongue coating thickness (TCT) as determined by the computerized tongue analysis system (CTIS), blood parameters, and the SQDQ score. The secondary outcomes will be collected at baseline (before BZYQT treatment) and after 4 weeks or 8 weeks (after BZYQT treatment).

8.1.2.1. *Tongue coating thickness.* The TCT will be determined using a CTIS (TAS-4000, Korea Institute of Oriental Medicine, Republic of Korea). The TAS-4000 comprises both hardware, including an image-acquisition component, lighting, a tongue positioner, and a color chart, and software for color correction and tongue region segmentation. The TAS-4000 components and image analysis have previously been described in detail elsewhere.<sup>21</sup> Fig. 2 shows a scene of tongue image acquisition.

Once the practitioner successfully captures a tongue image, the CTIS performs color correction on the original image. To precisely segment the tongue region, the combined polar edge method and the gradient vector flow snake technique are applied (Fig. 3A). Pixel values in the red–green–blue color space from the acquired images are converted to the Commission Internationale de L'Éclairage (CIE) 1987 color space, which includes all human-perceivable colors and consists of L\*, a\*, and b\* coordinates. The CIE b\* value was used as threshold, and can be divided into two areas: the tongue body and the tongue coating. CTIS then calculated the area of the tongue body without tongue coating (Fig. 3B) and the tongue coating area (Fig. 3C), respectively. CTIS will measure the percentage of tongue coating.

8.1.2.2. *Blood parameters.* A metabolomics study will be performed to analyze differences between before and after BZYQT treatment. Blood parameters (white blood cell, red blood cell, hemoglobin, hematocrit, platelet, erythrocyte sedimentation rate, BUN, creatinine, total protein, albumin, AST/ALT, gamma-glutamyl transpeptidase, total/direct bilirubin, uric acid, C-reactive protein, sodium, potassium, chloride, and TSH) will be collected at baseline and after 4 weeks.

8.1.2.3. *Bu-Zhong-Yi-Qi-Tang Questionnaire score.* The effects of BZYQT questionnaire will be assessed by observing differences in the BZYQT score before treatment and 4 weeks after the initiation of treatment. The BZYQT questionnaire was developed by Yoon et al.<sup>22</sup> and is a reliable and validated questionnaire<sup>23</sup> that consists of 19 questions. These items are measured using 7-point Likert scales, where 0 indicates not at all or not applicable; 4 indicates moderately; and 7 indicates extremely. The cutoff value is 6 (BZYQT >6 and non-BZYQT ≤ 6).

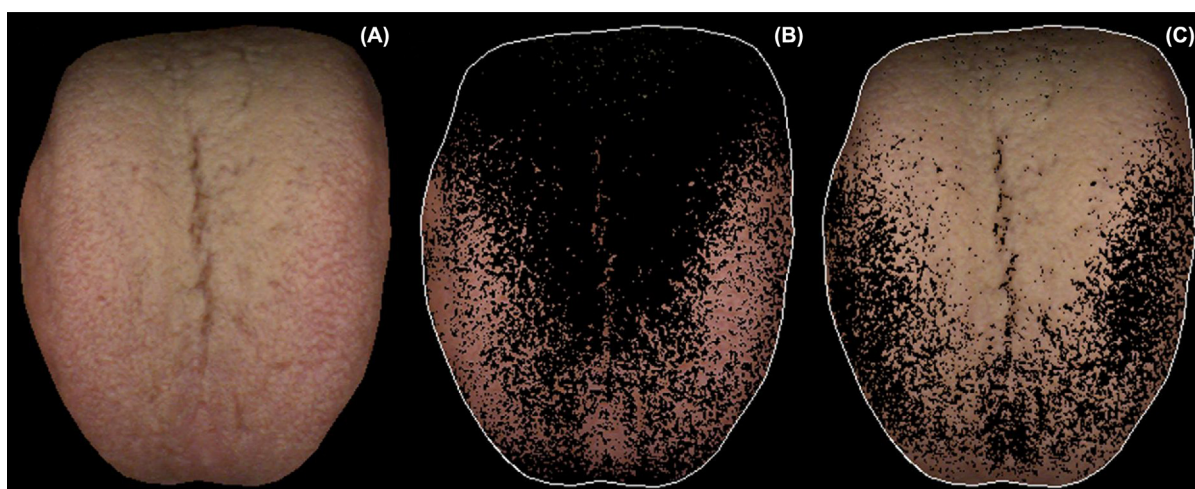
### 8.2. Randomization, allocation concealment, and blinding

Because the study is a feasibility observational study, this protocol is not randomized or blinded.





**Fig. 2 – Scene of the tongue image acquisition.**



**Fig. 3 – Tongue areas. (A) Segmented tongue area; (B) tongue body area; and (C) tongue coating area.**

### 8.2.1. Sample size

No references exist to guide sample size calculation. This study is designed as a feasibility study to determine initial data for the primary outcome measure and to perform a sample size calculation for a large-scale, randomized controlled trial.

The estimated sample size is 27 participants. Based on a dropout rate of 10%, 30 participants should be recruited. Consequently, the total sample size is 30 participants.

### 8.3. Statistical analysis

The analysis of primary and secondary outcomes will focus on changes between baseline and the end of the study in terms of the measurements for each individual participant. Statistical analysis will be carried out by an independent statistician using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). All continuous variables will be presented as the means and standard deviations, and categorical variables will be shown as numbers and percentages (%). Missing values for all measured param-

eters will be imputed using the last observation carried forward method.

All analyses will be based on the full analysis set. The full analysis set is considered the primary analysis set, and per protocol, which is an alternative to intention-to-treat analysis, will be used as the secondary analysis set. Per protocol is defined as a subset of the intention-to-treat population that completes the study without any major protocol violations.<sup>24</sup>

Repeated-measures analysis of variance will be used to test for statistically significant changes in the TCT based on repeated measures before, during, and after treatment. Pre-specified covariates measured at baseline, such as age, sex, smoking duration, caffeine and alcohol intake duration, the use of concomitant medicine, physical activity, and sleep quality, will be included in all analyses. The least squared mean and 95% confidence interval for each stage within the thermal stage group will be derived based on models. We will perform Dunnett test to assess the mean changes during stress in contrast to the baseline within each thermal stress group in the final model.

## 9. Safety assessment

To assess the safety of the 4-week treatment, routine blood and urine tests, as well as blood biochemical tests and a listening and smelling examination, will be conducted prior to treatment and immediately after treatment completion. The blood biochemical tests will include AST, ALT, BUN, and creatinine.

All unexpected and unintended responses due to BZYQT will be reported as AEs by the researcher at each visit, even if they may not be related to CTIS measurement. AEs will be carefully recorded in the case report form by the research staff. Participants will report any AEs experienced during CTIS measurement, and laboratory test results will be evaluated at each visit. All AEs will be described in the case report form. If an AE is severe and is associated with the study, the participant will be withdrawn from the study, and appropriate treatment will be provided. Clinicians will conduct a safety assessment using a checklist during each visit.

## 10. Quality control

Sponsor monitoring will be performed by highly trained monitoring staff throughout the trial. All sponsors, assistants, principal researchers, assessors, and coordinators must attend a training session to ensure that all practices are consistent with SOPs. In addition, all researchers must understand the study purpose and process. The sponsors will visit sites once per month to verify SOP compliance. Audit reports will be presented to the chief monitor. Monitoring will begin after the first participant completes the entire study. The clinical trial institution will be monitored while the trial is in process to ensure that SOPs are followed.

## 11. Discussion

FD is a common heterogeneous disorder<sup>1</sup> that is difficult to cure due to the lack of satisfactory treatments.<sup>2</sup> Therefore, several alternative therapies have been considered for the treatment of FD. Among alternative therapies, herbal medicines are widely used to treat FD in Korea, China, Japan, and many other areas of the world.<sup>6</sup>

BZYQT is one of most useful and important herbal medicines. BZYQT replenishes the qi of the middle burner and raises spleen yang to treat prolonged diarrhea as well as rectal and uterine prolapse. The multiple targets of various active ingredients in BZYQT may be of benefit for the treatment of a variety of different symptoms.<sup>10</sup> Various studies have been conducted to evaluate the effects of BZYQT.<sup>25–32</sup>

Kiyohara et al<sup>25</sup> reported that BZYQT was able to strengthen the antibody response in the upper respiratory mucosal immune system by enhancing influenza virus-specific immunoglobulin A (IgA) and IgG antibody titers in the nasal cavity and sera. Guo and Liu<sup>26</sup> studied the anti-inflammatory effects of BZYQT in patients with perennial allergic rhinitis and demonstrated that BZYQT could suppress nasal inflammation by an anti-inflammatory effect. Ma<sup>27</sup> reported that BZYQT alleviated clinical signs better than

cisapride therapy on 40 patients with irritable bowel syndrome. In a clinical study of 60 elderly patients with FD, BZYQT alleviated upper abdominal pain, bloating, loss of appetite, and nausea and promoted gastric emptying.<sup>28</sup> Luo<sup>29</sup> observed that BZYQT protected from the side effects (e.g., tissue mucosal injury, dyspepsia, vomiting, nausea, stomach pain, diarrhea, and constipation) of radiotherapy and had no significant adverse side effects. Protection from gastrointestinal mucosa disorders and promotion of bowel movements by BZYQT have been shown in animal studies.<sup>30–32</sup>

However, the available evidence to support the effectiveness and safety of BZYQT on FD patients with specific pattern identification, such as spleen qi deficiency, is inadequate. Therefore, to encourage evidence-based practices for BZYQT, we are conducting a feasibility study to evaluate the effects and safety of BZYQT.

We aim to assess the effectiveness and safety of BZYQT in the treatment of FD with spleen qi deficiency. This study is a prospective, nonrandomized, nonblinded, single-arm, single-center feasibility study. A total of 30 participants diagnosed with FD will be enrolled, and the entire observation process will occur at Kyung Hee University Korean Medicine Hospital.

The primary outcome is the change in the NDI-K score between the baseline and 4 weeks. The NDI-K score will be determined four times, at Weeks 0 (baseline), 2 (during treatment), 4 (after treatment), and 8 (after follow-up). The NDI-K is a reliable and validated questionnaire to measure the severity of dyspeptic symptoms and quality of life. Therefore, a quantitative and objective evaluation of the effects of BZYQT is expected to be possible.

The secondary outcomes are TCT, blood parameters, and BZYQT Questionnaire scores.

The tongue has many relationships and connections within the body, both to the meridians and to the internal organs. The tongue coating is particularly useful and important during inspection for confirming clinical diagnoses. The tongue coating refers to the layer over the tongue surface that is produced by the stomach qi. Therefore, it is related to the functional state of the qi and the internal organs.<sup>33,34</sup> The severity of dyspeptic symptoms can be observed as changes in the TCT acquired by CTIS.<sup>35,36</sup> Kim et al.<sup>35</sup> suggested that TCT could be classified as either no coating, a thin, or thick coatings. Kim et al.<sup>36</sup> investigated the usefulness of TCT as diagnostic tools on FD patients.<sup>36</sup>

To ensure participant's safety, the following blood parameters will be collected at baseline and after treatment: routine blood tests, renal function (BUN and creatinine), liver function (AST and ALT), and thyroid function (TSH). Therefore, we will attempt to assess the safety of BZYQT and to explore the relationship between blood parameter values and the severity of dyspeptic symptoms.

Using the BZYQT Questionnaire developed by Oh et al,<sup>13</sup> it is thought that the treatment effect of BZYQT can be directly evaluated. The BZYQT score will be collected before treatment and 4 weeks after the initiation of treatment. The effects of BZYQT will be assessed by observing differences in the BZYQT score before and after treatment.

There are several limitations to this proposed study. First, this is a feasibility study with a small sample size; thus, it is not powered to determine treatment effectiveness. Second, this

is a nonrandomized, nonblinded, single-arm, single-center feasibility study; therefore, there is neither a placebo nor a comparison group. Further studies with large sample sizes involving comparison groups will be required.

Nevertheless, this is the first study to assess the efficacy and safety of BZYQT on patients with FD in the Republic of Korea. This study may provide basic information for a large-scale, randomized controlled trial and serve as a guide for researchers seeking to effectively evaluate the effects of BZYQT on FD. Further studies will be needed to determine the treatment effectiveness of BZYQT and its precise mechanisms of action.

## 12. Study status

Participant recruitment opened in October 2016, and the study will close in October 2017. At the time of manuscript submission, the study was in the recruitment phase.

## Conflicts of interest

The authors declare that they have no competing interests.

## Acknowledgments

We thank all of our colleagues who participated in this study. This study was supported by the Korea Institute of Oriental Medicine funded by the Korean government (grant no. K17011), Republic of Korea.

## REFERENCES

- Talley NJ, Stanghellini V, Heading RC, Koch KL, Malagelada JR, Tytgat GN. Functional gastroduodenal disorders. *Gut* 1999;45:II37–42.
- Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, Stanghellini V. Functional gastroduodenal disorders. *Gastroenterology* 2006;130:1466–79.
- Karamanolis G, Caenepeel P, Arts J, Tack J. Association of the predominant symptom with clinical characteristics and pathophysiological mechanisms in functional dyspepsia. *Gastroenterology* 2006;130:296–303.
- Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features, and Rome IV. *Gastroenterology* 2016;150:1262–79.
- Lee H, Jung HK, Huh KC. Functional Dyspepsia Study Group in the Korean Society of Neurogastroenterology and Motility. Current status of functional dyspepsia in Korea. *Korean J Intern Med* 2014;29:156–65.
- Lu CL, Lang HC, Chang FY, Chen CY, Luo JC, Wang SS, et al. Prevalence and health/social impacts of functional dyspepsia in Taiwan: a study based on the Rome criteria questionnaire survey assisted by endoscopic exclusion among a physical check-up population. *Scand J Gastroenterol* 2005;40:402–11.
- Mönkemüller K, Malfertheiner P. Drug treatment of functional dyspepsia. *World J Gastroenterol* 2006;12:2694–700.
- Shouzhong Y, Jianyong L, translators. *Li Dongyuan's treatise on the spleen and stomach*. Boulder, CO: Blue Poppy Press; 1993.
- Xu Q, Wang J, Wang R, Liu X, Chen Z, Wu Y. Effect of Buzhong Yiqi decoction on gastrin receptor combination and its protective mechanism for gastric mucosa damage in spleen-deficiency rats. *J Guangzhou Univ Trad Chin Med* 2002;20:51–6.
- Zheng XW, Wang Y, Song H. Experimental study on effect of Buzhong Yiqi decoction on serum gastrin in spleen-qi deficiency rats. *Zhonghua Zhongyiyao Zazhi* 2006;21:393–5.
- Zheng XF, Tian JS, Liu P, Xing J, Qin XM. Analysis of the restorative effect of Bu-zhong-yi-qi-tang in the spleen-qi deficiency rat model using <sup>1</sup>H NMR-based metabonomics. *J Ethnopharmacol* 2014;151:912–20.
- Yan X, Kita M, Minami M, Yamamoto T, Kuriyama H, Ohno T, et al. Antibacterial effect of Kampo herbal formulation Hochu-ekki-to (Bu-Zhong-Yi-Qi-Tang) on *Helicobacter pylori* infection in mice. *Microbiol Immunol* 2002;46:475–82.
- Oh HW, Lee JW, Kim JS, Song EY, Shin SW, Han GJ, et al. Study on the development of a standard instrument of diagnosis and assessment for spleen Qi deficiency pattern. *J Korean Med* 2014;35:157–70.
- Kim J, Kim J, Kim J, Kim KH. Reliability and validity analysis of a standard instrument of diagnosis and assessment for spleen Qi deficiency pattern in chronic dyspepsia patients. *J Korean Med* 2015;36:23–34.
- Ko SJ, Park K, Kim J, Kim M, Kim JH, Lee J, et al. Effect of acupuncture and its influence on cerebral activity in functional dyspepsia patients: study protocol for a randomized controlled trial. *Trials* 2016;17:183.
- Han G, Ko SJ, Park JW, Kim J, Yeo I, Lee H, et al. Acupuncture for functional dyspepsia: study protocol for a two-center, randomized controlled trial. *Trials* 2014;15:89.
- Kuroiwa A, Liou S, Yan H, Eshita A, Naitoh S, Nagayama A. Effect of a traditional Japanese herbal medicine, hochu-ekki-to (Bu-Zhong-Yi-Qi Tang), on immunity in elderly persons. *Int Immunopharmacol* 2004;4:317–24.
- Talley NJ, Verlinden M, Jones M. Validity of a new quality of life scale for functional dyspepsia: a United States multicenter trial of the Nepean Dyspepsia Index. *Am J Gastroenterol* 1999;94:2390–7.
- Lee SY, Choi SC, Cho YK, Choi MG. Validation of the Nepean Dyspepsia Index–Korean version. *Korean J Neurogastroenterol Motil* 2003;9:48S.
- Hong SJ, Sung IK, Kim JG, Lee SW, Choi SC, Yang CH, et al. Failure of a randomized, double-blind, placebo-controlled study to evaluate the efficacy of *H. pylori* eradication in *H. pylori*-infected patients with functional dyspepsia. *Gut Liver* 2011;5:468–71.
- Jung CJ, Nam JH, Jeon YJ, Kim KH. Color distribution differences in the tongue in sleep disorder. *Evid Based Complement Alternat Med* 2014;2014:323645.
- Yoon TD, Park YJ, Park YB, Lee SC, Oh HS. Development of questionnaires for pathogenesis analysis of Bojungkigutang symptom. *J Korea Inst Orient Med Diagn* 2007;11:61–71.
- Yoon KJ, Park YB, Park YJ, Kim MY. Development and validation of a Lao Juan Questionnaire. *Chin J Integr Med* 2015;21:500–6.
- Matilde Sanchez M, Chen X. Choosing the analysis population in non-inferiority studies: per protocol or intent-to-treat. *Stat Med* 2006;25:1169–81.
- Kiyohara H, Nagai T, Munakata K, Nonaka K, Hanawa T, Kim SJ, et al. Stimulating effect of Japanese herbal (kampo) medicine, hochuekkito on upper respiratory mucosal immune system. *Evid Based Complement Alternat Med* 2006;3:459–67.
- Guo H, Liu MP. Mechanism of traditional Chinese medicine in the treatment of allergic rhinitis. *Chin Med J* 2013;126:756–60.
- Ma C. 40 Cases of Bu Zhong Yi Qi Tang for irritable bowel syndrome. *Chin J Gerontol* 2012;32:5269–70.

28. Guo GL, He JJ, Wu MF. Clinical efficacy of 60 cases of Bu Zhong Yi Qi Tang for dyspepsia of old people. *China Health Ind* 2012;13:167.
29. Luo GH. Conclusion of 30 cases of modified Bu Zhong Yi Qi Tang on radiation proctitis. *Hunan J Trad Chin Med* 2012;28:25–7.
30. Wang RJ, Fu DZ, Shao TY. Effect of Buzhong Yiqi decoction on castric mucosal vulnerability in rats with deficiency of spleen. *Ghuangzhou Zhongyiyao Daxue Xuebao* 1995;12:31–2.
31. Wu L, Liu XQ, Guo XJ. Effect of Bu Zhong Yi Qi Tang on gastric mucosal injury in diabetic rats. *J New Chin Med* 2011;43:138–9.
32. Li Y, Wu CM, Li X, Sun N. Research of dual directional regulation on gastrointestinal peristalsis and anti-inflammatory effects of Bu Zhong Yi Qi Tang in mice. *J Med Forum* 2011;32:18–22.
33. Anastasi JK, Currie LM, Kim GH. Understanding diagnostic reasoning in TCM practice: tongue diagnosis. *Altern Ther Health Med* 2009;15:18–28.
34. Fei ZF, Gu YD. *Mirror of health: tongue diagnosis in Chinese medicine*. Beijing, China: People's Medical Publishing House; 2007.
35. Kim J, Son J, Jang S, Nam DH, Han G, Yeo I, et al. Availability of tongue diagnosis system for assessing tongue coating thickness in patients with functional dyspepsia. *Evid Based Complement Alternat Med* 2013;2013, 348272.
36. Kim J, Han G, Ko SJ, Nam DH, Park JW, Ryu B, et al. Tongue diagnosis system for quantitative assessment of tongue coating in patients with functional dyspepsia: a clinical trial. *J Ethnopharmacol* 2014;155:709–13.