대한한방내과학회지 제44권 3호(2023년 6월)
J. Int. Korean Med. 2023;44(3):285-293
http://dx.doi.org/10.22246/jikm.2023.44.3.285

Yukgunja-tang for Irritable Bowel Syndrome: A Protocol for a Systematic Review and Meta-Analysis

Kangwook Lee[1*], Seok-Jae Ko[2,3*], Minjeong Kim[1,3], Chaehyun Park[1], Min-Seok Cho[1], Jae-Woo Park[2,3]

[1]Dept. of Clinical Korean Medicine, Graduate school of Kyung Hee University
[2]Dept. of Gastroenterology, College of Korean Medicine, Kyung Hee University
[3]Dept. of Internal Medicine, Kyung Hee University Hospital at Gangdong

Yukgunja-tang for Irritable Bowel Syndrome: A Protocol for a Systematic Review and Meta-Analysis

Kangwook Lee[1*], Seok-Jae Ko[2,3*], Minjeong Kim[1,3], Chaehyun Park[1], Min-Seok Cho[1], Jae-Woo Park[2,3]

[1]Dept. of Clinical Korean Medicine, Graduate school of Kyung Hee University
[2]Dept. of Gastroenterology, College of Korean Medicine, Kyung Hee University
[3]Dept. of Internal Medicine, Kyung Hee University Hospital at Gangdong

ABSTRACT

Background: Irritable bowel syndrome (IBS) is a digestive disorder characterized by abdominal discomfort or pain accompanied by a change in stool condition. Owing to its complicated mechanisms, a standard treatment for IBS has not yet been established.

Yukgunja-tang (YGT) is a Korean herbal medicine known in Asia to be effective in the treatment of gastrointestinal symptoms. In this study, we will conduct a systematic review of randomized controlled trials (RCTs) to assess the efficacy and safety of YGT in IBS treatment.

Methods and analysis: English databases, such as Embase, Medline (via PubMed), Allied and Complementary Medicine Database, and Cochrane Central Register of Controlled Trials, will be searched for articles published up to April 2023. Additional databases, such as five Korean, one Chinese, and one Japanese database, will be included. RCTs and quasi-RCTs will also be included in the assessment of the efficacy of YGT. The overall efficacy rate will be the primary outcome, and data such as IBS quality-of-life measurements, global symptom scores, and adverse events will be the secondary outcomes. Review Manager Version 5.3 will be used for evaluation, and the risk of bias (RoB) will be evaluated using Cochrane Collaboration's RoB tool. The Grading of Recommendations Assessment, Development, and Evaluation approach will be used to score the quality of evidence.

Conclusion: This study will demonstrate the efficacy and safety of YGT for treating patients with IBS.

Key words: irritable bowel syndrome, *Yukgunja-tang*, systematic review, randomized controlled trial

Ⅰ. Introduction

Irritable bowel syndrome (IBS) is a digestive disorder characterized by abdominal discomfort or pain accompanied by a change in stool condition without structural abnormalities[1]. Many patients'

· 투고일: 2023.04.10, 심사일: 2023.06.19, 게재확정일: 2023.06.19
· Corresponding author: Jae-Woo Park Kyung-Hee Dae-ro 26, Dongdaemun-gu, Seoul 02447, Republic of Korea
TEL: 02-440-7141 FAX: 02-440-7143
E-mail: pjw2907@khu.ac.kr
* These authors contributed equally to this work.

quality of life is adversely affected because of recurrent symptoms[2]. The global prevalence of IBS was 9.2% in 2020 based on Rome III criteria[3].

IBS seems to involve complicated mechanisms such as visceral hypersensitivity, abnormal motility, dietary intolerance, enhanced pain perception, autonomic nervous system abnormality, and neural and immunological communication[4]. Primary treatment for IBS is the use of medications such as loperamide, tricyclic antidepressants, rifaximin, and selective serotonin receptor inhibitors[5]. However, there are some limitations to their efficacy and side effects such as dry mouth[6].

In Asia, herbal medicine has been used, which has fewer side effects than Western medicine[7]. *Yukgunja-tang* (YGT) is a traditional Korean herbal medicine (Rikkunshi-to in Japan and Liu-Jun-Zi-Tang in China) that is known to be effective in treating gastrointestinal symptoms in Asia[8]. Moreover, modified YGT (YGT added with specific herbs) can be used to treat gastric fullness and gastrointestinal symptoms[9] which are similar to the clinical manifestations of IBS. YGT consists of *Atractylodis lanceae* rhizoma (5.63 g), *Ginseng* radix (3.75 g), *Pinellia* tubers (5.63 g), Poria cocos (3.75 g), *Zizyphi fructus* (3.75 g), *Aurantii nobilis pericarpium* (3.75 g), *Glycyrrhizae* radix (1.88 g), and *Zingiberis* rhizoma (3.75 g). Several studies using YGT reported the positive effect on functional gastrointestinal diseases[8,10], however, there are still lack of studies on the use of YGT for IBS.

In this study, we will conduct a meta-analysis and systematic review of the efficacy and safety of YGT for IBS to provide evidence for using YGT as an alternative treatment for IBS.

Ⅱ. Methods

1. Study registration

A protocol has been registered on PROSPERO (ID: CRD42023400078).

2. Inclusion criteria for study selection

1) Types of studies

This systematic review will include published randomized controlled trials (RCTs) and quasi-RCTs. Case studies, commentaries, and animal research will be excluded.

2) Types of patients

Patients who fulfilled the Rome diagnostic criteria, including age, sex, and race, will be included in this study. As the first Rome criteria standard was established in 1992[11], studies before 1992 will be screened, and similar criteria (e.g., Manning and Kruis criteria)[12] will be included with agreement among researchers. Studies on IBS patients with other diseases, such as inflammatory bowel disease or colorectal cancer, will be excluded.

3) Types of interventions

Studies using YGT and modified YGT for IBS treatment will be included. The comparator groups will be conventional Western medicine, placebos with the same appearance and odor as YGT, and the waiting group with no treatment. Other Interventions will be excluded. Interventions in Western medicine group will include antidiarrheal agents, psychotropic agents, and smooth muscle relaxants.

4) Types of outcome measures

The Gastrointestinal System Rating Scale-IBS score will be the primary outcome, and IBS-quality of life score, World Health Organization-quality of life-brief score, and adverse events will be the

secondary outcomes[13,14].

3. Data source and data collection procedures

1) Database for searching

Eleven electronic databases will be searched up to April 2023. Four English databases, including Medline (via PubMed), EMBASE, Cochrane Central Register of Controlled Trials, and Allied and Complementary Medicine Database will be included. Five Korean databases, including the Korean Studies Information Service System, National Digital Science Library, Korean Medical Database, KoreaMed, and Oriental Medicine Advanced Searching Integrated System, will be searched. One Chinese database (China National Knowledge Infrastructure), and Japanese databases (Citation Information by NII) will be included. The researchers will use the term related to the disease and intervention. The search strategy for MEDLINE (via PubMed) is presented in Table 1. There will be no language restriction.

Table 1. Search Terms for Medline via PubMed

#1. Irritable Bowel Syndrome[MH] OR "Irritable Bowel Syndrome" OR "irritable Bowel Syndromes" OR "Syndrome, Irritable Bowel" OR "Syndromes, Irritable Bowel"
#2. "Colon, Irritable" OR "Irritable Colon"
#3. "Colitis, Mucous" OR "Colitides, Mucous" OR "Mucous Colitides" OR "Mucous Colitis"
#4. "Colonic disease, functional" OR "Irritable Bowel" OR "Spastic colon" OR "functional bowel disease" OR "functional colonic disease" OR Colonic Diseases, Functional[mh]
#5. "irritable bowel syndrome"[tw] OR irritable bowel syndrome*[tw] OR IBS[tw] OR "functional abdominal pain"[tw] OR "functional gastrointestinal disorders"[tw]
#6. #1 OR #2 OR #3 OR #4 OR #5
#7. *Yukgunja-tang* OR *Yukgunjatang* OR "*Yukgunja tang*"
#8. "*Liu Jun Zi Tang*" OR "*LiuJunZi Tang*" OR *Liujunzitang*
#9. *Gamiyukgunja-tang* OR *Gamiyukgunjatang* OR "*Gamiyukgunja tang*"
#10. "*Jiawei Liu Jun Zi Tang*" OR "*JiaweiLiuJunZi Tang*" OR *Jiaweiliujunzitang OR Jiawei-Liu-Jun-Zi-Tang*
#11. *Rikkunshito OR KamiRikkunshito*
#12. #7 OR #8 OR #9 OR #10 OR #11
#13. #6 AND #12

2) Data selection and exclusion

Two researchers (K-WL and S-JK) will independently screen for eligibility and review titles, abstracts, and full texts. The final studies will go through an agreement procedure between the two researchers, and if they disagreed, a third reviewer (JWP) will intervene and resolve it. The screening of the study will be done using the Endnote X7 (Clarivate Analytics, London, UK). This procedure will be illustrated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram (Fig. 1).

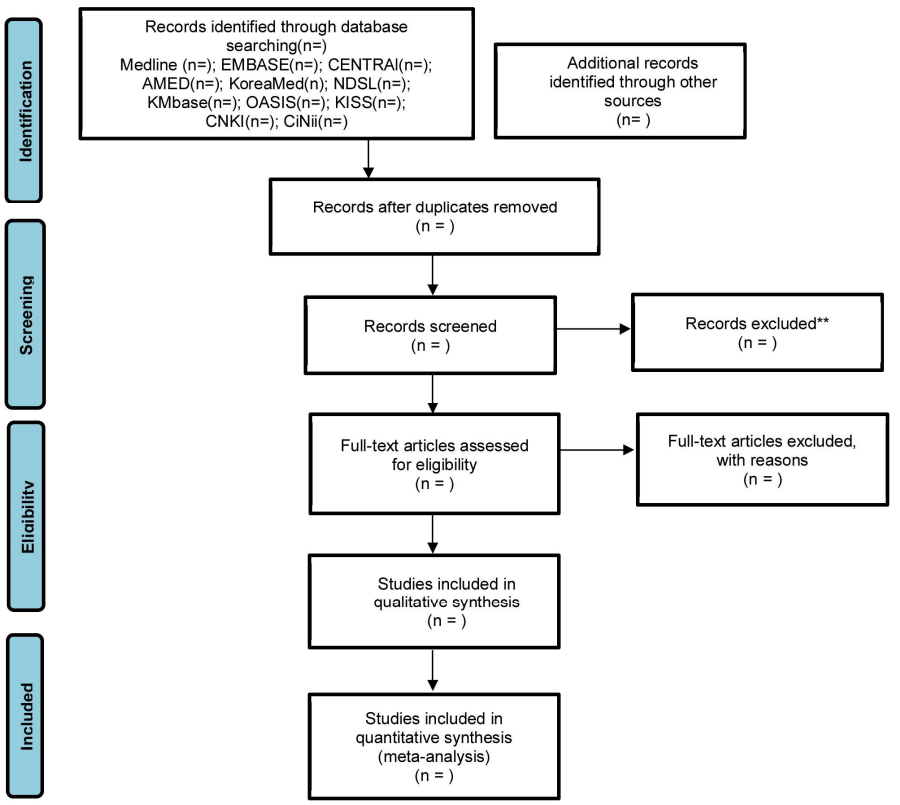

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram of literature screening and selection process.

AMED = Allied and Complementary Medicine Database, CENTRAL = Cochrane Central Register of Controlled Trials, CiNii = Citation Information by Nii, CNKI = China National Knowledge Infrastructure, KISS = Korean studies Information Service System, KMbase = Korean Medical Database, NDSL = National Digital Science Library, OASIS = Oriental Medicine Advanced Searching Integrated System.

3) Data extraction

Data extraction will be performed using the format "Consolidated Standards of Reporting Trials Extension for Chinese Herbal Medicine Formulas 2017." It contains various information about the title, abstract, keywords, introduction, trial method, result data, discussion, and others[15]. Missing or insufficient data will be requested from the corresponding authors of the studies.

4. Quality assessment

The studies will be evaluated using the Cochrane Collaboration's risk-of-bias tool, which is used to evaluate the bias of the domains, such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, completeness of outcome data, selective reporting, and other biases[16].

We will use the Grading of Recommendations Assessment, Development, and Evaluation approach

to score the quality of evidence. Two researchers will assess the risk of bias, inconsistency and imprecision of the results, indirectness of evidence, publication bias, large effects, and dose-dependent gradients[17].

5. Data analysis and synthesis

1) Analysis and synthesis strategy

The Review Manager version 5.3 software (Cochrane Collaboration, Oxford, UK) will be used to process the data. The dichotomous outcome is shown as a risk ratio with a 95% confidence interval (CI), whereas the continuous outcome is shown as a mean difference or standardized mean difference with a 95% CI. Statistical heterogeneity among pooled studies will be calculated using the I^2 statistic, and if the studies show significant heterogeneity ($I^2 \geq 50\%$), the random-effects model will be used. A sensitivity analysis will be performed, if needed.

2) Analysis of subgroups or subsets

A subgroup analysis will be conducted regarding the type or dose of treatment, treatment duration, or the subtype of IBS (diarrhea- or constipation-predominant IBS).

Ⅲ. Discussion

The global prevalence of IBS in Asia was 9.6%[18]. Western medicine has not provided the satisfactory results for IBS, leading to recurrent symptom-relapse and economic burden on society[19].

Although YGT has long been used to treat gastrointestinal symptoms[8], its efficacy and safety in IBS have not yet been fully investigated. A recent studies revealed that YGT showed significant better effect on IBS symptoms compared to that of Western medicine or probiotics[20,21]. According to Traditional Asian Medicine theory, IBS belongs to the spleen-deficiency and *qi*-stagnation syndromes; therefore, YGT which boosts the *qi* of the spleen can be a suitable treatment for IBS[22].

In this review, we aimed to determine the statistical efficacy of YGT in the treatment of IBS. This study will provide evidence on the efficacy and safety of YGT as an alternative treatment for IBS, and the results will be beneficial for both the patients with IBS and healthcare providers.

One expected limitation will be the poor quality of the studies including methodology. And another will be insufficient data. Despite above limitations, this review will expand our understanding using YGT for IBS. We hope this study will provide helpful guideline of Korean medicine for IBS.

Registration

PROSPERO ID: CRD42023400078 (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=400078)

Acknowledgments

This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. 2022R1C1C1004937) to S.J.K., and by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (No. 2022M3A9E4082682) to J.W.P..

Author contributions

Conceptualization: Seok-Jae Ko, Jae-Woo Park.

Funding acquisition: Jae-Woo Park.

Methodology: Kangwook Lee, Seok-Jae Ko, Minjeong Kim, Chaehyun Park, Min-Seok Cho.

Supervision: Jae-Woo Park.

Writing - original draft: Kangwook Lee.

Writing - review & editing: Seok-Jae Ko, Jae-Woo Park.

References

1. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features, and Rome IV. *Gastroenterology* 2016;150(6):1262-79.
2. Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable bowel syndrome. *The Lancet* 2020;396(10263):1675-88.
3. Oka P, Parr H, Barberio B, Black CJ, Savarino EV, Ford AC. Global prevalence of irritable bowel syndrome according to Rome III or IV criteria: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020;5(10):908-17.
4. Muscatello MR, Bruno A, Mento C, Pandolfo G, Zoccali RA. Personality traits and emotional patterns in irritable bowel syndrome. *World J Gastroenterol* 2016;22(28):6402-15.
5. Trinkley KE, Nahata MC. Treatment of irritable bowel syndrome. *J Clin Pharm Ther* 2011;36(3):275-82.
6. Ford AC, Moayyedi P, Chey WD, Harris LA, Lacy BE, Saito YA, et al. American college of gastroenterology monograph on management of irritable bowel syndrome. *Am J Gastroenterol* 2018;113(suppl 2):1-18.
7. Ko SJ, Han GJ, Kim SK, Seo JG, Chung WS, Ryu BH, et al. Effect of Korean herbal medicine combined with a probiotic mixture on diarrhea-dominant irritable bowel syndrome: a double-blind, randomized, placebo-controlled trial. *Evid Based Complement Alternat Med* 2013;2013:824605.
8. Sujuki H, Matsuzaki J, Fukushima Y, Suzaki F, Kasugai K, Nishizawa T, et al. Randomized clinical trial: *Rikkunshito* in the treatment of functional dyspepsia-a multicenter, double-blind, randomized, placebo-controlled study. *Neurogastroenterol Motil* 2014;26(7):950-61.
9. Wu Q. The Golden Book of the Medical Order. Great China Book Company; 1971, p. 107-8.
10. Ko SJ, Park JW, Lee JH, Lee JE, Ha NY, Nam SU, et al. An Herbal Medicine, *Yukgunja-Tang* is more Effective in a Type of Functional Dyspepsia Categorized by Facial Shape Diagnosis: A Placebo-Controlled, Double-Blind, Randomized Trial. *Evid Based Complement Alternat Med* 2018;2018:8546357.
11. Drossman DA, Hasler WL. Rome IV-functional GI disorders: disorders of gut-brain interaction. *Gastroenterology* 2016;150(6):1257-61.
12. Lacy BE, Patel NK. Rome criteria and a diagnostic approach to irritable bowel syndrome. *J Clin Med* 2017;6(11):99.
13. Li B, Liang L, Deng H, Guo J, Shu H, Zhang L. Efficacy and safety of probiotics in irritable bowel syndrome: A systematic review and meta-analysis. *Front Pharmacol* 2020;11:332.
14. Shih YS, Tsai CH, Li TC, Lai HC, Wang KT, Liao WL, et al. The effect of *Xiang-Sha-Liu-Jun-Zi tang* (XSLJZT) on irritable bowel syndrome: A randomized, double-blind, placebo-controlled trial. *J Ethnopharmacol* 2019;238:111889.
15. Cheng CW, Wu TX, Shang HC, Li YP, Altman DG, Moher D, et al. CONSORT extension for Chinese herbal medicine formulas 2017: Recommendations, explanation, and elaboration.

Ann Intern Med 2017;167(2):112-21.
16. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
17. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE Handbook. 2013. Available at http://gdt.gradepro.org/app/handbook/handbook.html. Accessed December 15, 2022.
18. Sperber AD, Dumitrascu D, Fukudo S, Gerson C, Ghoshal UC, Gwee KA, et al. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. *Gut* 2017;66(6):1075-82.
19. Wang Y, Huang YQ, Zhu SL, Zhang CR, Chen XL, Hou QK, et al. Efficacy of *Tong-Xie-Yao-Fang* granule and its impact on whole transcriptome profiling in diarrhea-predominant irritable bowel syndrome patients: study protocol for a randomized controlled trial. *Trials* 2020;21(1):908.
20. Xu JP. Effect of *Xiangsha Liu-Jun-Zi-Tang* Decoction on Irritable Bowel Syndrome. *Journal of health for all* 2018;02:141.
21. Gou YC. Clinical Observation on the treatment of Diarrhea-type Irritable Bowel Syndrome with *Si-ni-san* plus *Xiangsha Liu-Jun-Zi-Tang* Decoction in Liver Depression and Spleen Deficiency syndrome. *Journal of traditional Chinese internal medicine* 2013;5:56.
22. Xiao Y, Liu YY, Yu KQ, Ouyang MZ, Luo R, Zhao XS. Chinese herbal medicine *liu jun zi tang* and *Xiang sha liu jun zi tang* for functional dyspepsia: meta-analysis of randomized controlled trials. *Evid Based Complement Altern Med* 2012;2012:936459.

【부 록】

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1, 6, 7
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	6
Sponsor	5b	Provide name for the review funder and/or sponsor	6
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	6
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3, 4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4, 5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Table 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	3, 4, 5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5, 6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	5, 6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5, 6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	5

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015 Jan 2;349(jan02 1):g7647.