The herbal drug, Bu-Zhong-Yi-Qi-Tang, for the treatment of atopic dermatitis
Protocol for a systematic review

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Abstract

Introduction: Bu-Zhong-Yi-Qi-Tang (BZYQT) is an herbal drug that is widely used to treat various diseases, including gastrointestinal diseases, allergic rhinitis, and atopic dermatitis (AD) in East Asian countries. BZYQT has been shown to have anti-allergic, anti-inflammatory, and immunoregulatory properties in experimental studies, and there is substantial clinical evidence of its effect on AD. This review will systematically assess the evidence of BZYQT for the treatment of AD.

Methods/design: Eleven databases will be searched from their inception without language restriction. Randomized controlled trials that examined BZYQT or modified BZYQT for AD will be included. The selection of the studies, data abstraction, and validations will be performed independently by 2 researchers. The methodological qualities of the randomized controlled trials will be assessed using the Cochrane Collaboration tool for assessing the risk of bias.

Ethics and dissemination: This systematic review will be published in a peer-reviewed journal and will also be disseminated electronically or in print. It will be useful to inform and guide healthcare practitioners.

Trial register number: CRD42018105173.

Abbreviations: AD = atopic dermatitis, BZYQT = Bu-Zhong-Yi-Qi-Tang, CI = confidence interval, IgE = immunoglobulin E, MD = mean difference, RCT = randomized controlled trial, RR = relative risk, Th1/Th2 = T-helper 1/T-helper 2.

Keywords: atopic dermatitis, Bojungikki-tang, Bu-Zhong-Yi-Qi-Tang, eczema, herbal medicine, Hochu-ekki-to, systematic review

1. Introduction

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease that affects approximately 15% to 30% of children and 2% to 10% of adults.\textsuperscript{[1]} The onset of AD usually occurs in childhood, with 60% of patients experiencing an eruption in the first year.\textsuperscript{[2]} Major symptoms of AD are characterized by itching or pruritus and chronic recurrent morphology and distribution. Although clinical features differ with each age group, eczematous rashes, loss of sleep, and impact on the psychosocial wellbeing of patients are common in all age groups.\textsuperscript{[3,4]} The causes of AD are still uncertain; however, interactions among genetic factors are a probable cause, which are associated with skin barrier function and altered cutaneous immune responses, as well as environmental factors, such as early-life gut bacteria, humidity, microbes, and allergens.\textsuperscript{[5,6]}

Topical administration of corticosteroids or calcineurin inhibitors are regarded as a standard first-line treatment for AD.\textsuperscript{[7]} However, long-term application of topical corticosteroids has been associated with adverse cutaneous effects including atrophy, rebound flares, and increased percutaneous absorption with the potential for adverse systemic effects.\textsuperscript{[8]} In addition, the use of topical calcineurin inhibitors has been associated as a potential risk factor for cancer. Likewise, systemic medications including oral corticosteroids or immunosuppressive drugs, which are used for refractory AD, have also been reported to have adverse systemic effects such as hepatosplenic T-cell lymphomas.\textsuperscript{[9–11]} Due to these adverse effects of conventional medical treatment, many AD patients prefer herbal medicine in the form of complementary and alternative medicine for improving AD symptoms.\textsuperscript{[12]}

Bu-Zhong-Yi-Qi-Tang (BZYQT), also known as “Hochuekki-to” in Japan, and “Bojungikki-tang” in Korea, is an herbal drug extensively used for treatment of various diseases, such as gastrointestinal diseases, allergic rhinitis, and AD, in East Asian countries. It has been reported that BZYQT has anti-allergic properties through suppression of serum immunoglobulin E (IgE) levels and eosinophil infiltration, and controlling T-helper 1/T-helper 2 (Th1/Th2) balance.\textsuperscript{[13–17]} Moreover, BZYQT also has immunomodulatory effects that prevent serum IgE level increase and correct the Th1/Th2 balance skewed to Th2 in atopic NC/Nga mice.\textsuperscript{[18,19]} In addition, studies have reported on the protective effect of BZYQT against oxidative skin stress.\textsuperscript{[20]}
Likewise, many studies have been reported BZYQT to be effective in treating AD patients.[21–24] However, there is no evident critical appraisal, such as a systematic review or meta-analysis of the potential benefits and harms of BZYQT on AD. Therefore, in this present study, we aim to conduct a systematic review of randomized controlled trials (RCTs) to assess the evidence on the effectiveness of BZYQT for treating AD.

2. Methods

2.1. Study registration and ethics

The protocol for this systematic review has been registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO) under the number CRD42018105173 and was written in accordance with the preferred reporting items for systematic reviews and meta-analysis protocol (PRISMA-P) guidelines.[25] This systematic review is not necessary for ethical approval because individual patient data cannot be identified.

2.2. Type of studies

All RCTs and quasi-RCTs will be included and any trials without parallel comparisons or control groups will be excluded.

2.3. Type of participants

This study will include AD patients of any age with the following criteria: diagnosis of AD (or atopic eczema) using clinical diagnosis or validated diagnostic criteria.

2.4. Type of interventions

In this study, both BZYQT and modified BZYQT will be included. BZYQT is composed of 8 medical plants, Astragali radix, Atractylodis Rhizoma Alba, Ginseng radix, Angelicae Gigantis Radix, Citri Unshiu Pericarpium, Glycyrrhizae Radix et Rhizoma, Cimicifugae Rhizoma, and Bupleuri radix. Modified BZYQT is added or removed medicinal plants according to pattern identification, or syndrome differentiation, resulting in nearly the same actions as the original BZYQT. If orally administered, any formulation of BZYQT will be included. There is no limitation on the number of herbs, dosage, or duration of treatment.

2.5. Type of comparisons

All types of controls such as placebo, conventional treatment, or no treatment will be included. Trials in which BZYQT was used as the only treatment or as an adjunct to other treatments, as well as those in which the control group received the same treatment as the intervention group will be included.

2.6. Outcome measures

2.6.1. Primary outcomes.

1. Symptom severity assessment tools that evaluate the extent and intensity of skin lesions, such as the SCORing atopic dermatitis index (SCORAD) and eczema area severity index (EASI).
2. Total effectiveness rate.
3. Percentage of trial participants with the sum of “recovery” and “significant improvement” reported by the trial investigators itching visual analogue scale.

2.7. Secondary outcomes

1. Adverse effects measured by any relevant incidence and duration of any side effects.
2. Validated quality of life assessment tools such as the dermatology life quality index (DLQI).
3. Concurrent therapies: the dosage of topical agents expressed as the total equivalent amount and assessment of the add-on effect of BZYQT combined with topical agents.

2.8. Data sources

We will search for trials from the following electronic databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), AMED, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). We will also search 4 Korean medical databases (Oriental Medicine Advanced Searching Integrated System [OASIS], Korean studies Information Service System [KISS], National Digital Science Library [NDSL], and KoreaMed), 1 Chinese database (China Network Knowledge Infrastructure [CNKI]), and 1 Japanese Database (CiNii). For ongoing trials, trials will be searched on the metaRegister of Controlled Trials (mRCT; http://www.controlled-trials.com/mRCT/), Clinical trials.gov (http://www.ClinicalTrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/). We will also check the reference lists of reviews and the retrieved articles for additional studies. The search strategies that will be applied to the MEDLINE and CNKI are presented in Appendix 1, http://links.lww.com/MD/C738. Similar search strategies will be applied for all databases. All bibliographic information and articles will be managed using EndNote (X8.2; Clarivate Analytics, Philadelphia).

2.9. Selection of studies

Three reviewers will review and screen the titles and abstracts to identify eligible trials based on the inclusion criteria. Disagreements will be resolved by discussion, and if required, by the arbiter. Details of the study selection procedure are summarized in a PRISMA-compliant flow diagram.[26]

2.10. Data extraction

We will extract the following information from the included systematic reviews: bibliographic information (e.g., author, publication date, and country), population demographics and setting (e.g., age, sex, and sample size), type of intervention (e.g., dosage, regimen, administration method, and herbal composition of prescription), outcome measures, and adverse events. Two authors will perform data extraction using a predefined data extraction form to record descriptive characteristics of the included reviews. Disagreements will be resolved by discussion among all of the authors, and another author will act as an arbiter for unresolved disagreements. Extracted data will be presented as included study summary table.

2.11. Quality assessment

The risk of bias will be assessed in accordance with criteria from the Cochrane Handbook version 5.2.0, which includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.[27] The quality of each trial will be categorized on the basis
of low/unclear/high risk of bias. We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess confidence in estimates of effect.[28]

2.12. Data synthesis
Differences between the intervention and control groups will be assessed in this study. For continuous data, we will use the mean difference (MD) with 95% confidence interval (CI) to measure the treatment effects. We will convert other forms of data into MD. For outcome variables on different scales, we will use the standard MD with 95% CI. For dichotomous data, we will present treatment effect as a relative risk (RR) with 95% CI; other binary data will be converted into RR. All statistical analyses will be conducted using Cochrane Collaboration's software program, Review Manager (RevMan), version 5.3 for Windows (Copenhagen, Denmark, The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). If appropriate, we will pool data across studies for a meta-analysis using fixed-effects and random-effects models with 95% CI.

2.13. Unit of analysis issue
For crossover trials, the data from the first treatment period will be used. For trials in which more than 1 control group is assessed, the primary analysis will combine the data from each control group. Subgroup analyses of the control groups will be conducted. Each patient will be counted only once in the analyses.

2.14. Dealing with missing data
If we find that data is missing when we include the data, we will consider the reason for the loss of data. And then, we will contact the corresponding authors to acquire and verify data wherever possible. If it is not possible to do this, we will only analyze the available data.

2.15. Assessment of heterogeneity
If meta-analysis is possible, the I² tests will be used to evaluate the heterogeneity of the included studies, where I² > 50 will indicate high heterogeneity. In the case of heterogeneity, we will conduct subgroup analyses to explore the possible causes.[29] We will use the random or fixed-effects model in this study for meta-analysis according to the data analysis.

2.16. Assessment of reporting biases
If a sufficient number of included studies (at least 10 trials) are available, we will use funnel plots to detect reporting bias. However, as funnel plot asymmetry is not identical to publication bias, we will attempt to distinguish the possible reasons for any asymmetries, such as small-study effects, poor methodological qualities, and true heterogeneities.[30,31]

3. Discussion
Recently, there has been an increase in the use of complementary and alternative medicine for treating AD worldwide.[12,32] A Cochrane systematic review evaluating the effects of herbal medicine on AD showed that oral application of herbal medicine was superior to conventional medicine in total effectiveness rate (RR 1.43, 95% CI 1.27–1.61) and itching visual analogue scale (standard MD, 95% CI 1.43–0.22).[33] Furthermore, herbal medicine treatment for AD was recommended in the Korean Medicine Clinical Practice Guideline as grade B, which states that herbal medicine must be considered before conventional medicine based on the clinician's opinion.[34]

BZYQT is a widely used herbal medicine in Asian countries, such as China, Japan, and Korea. BZYQT, which is referred to as a decoction to tonify the middle and augment the Qi formula, was first recorded in Dong Yuan Ten Medical Books, a medical text written by Li Dong-yuan in the year 1249.[35] It is known as a herbal treatment for gastrointestinal diseases, cancer, and chronic fatigue syndrome associated with the syndrome of “sinking of qi due to spleen deficiency,” a concept of traditional medicine.[36–38] Furthermore, the Chinese Clinical Guidelines for AD reported deficiency of the spleen with accumulation of dampness to be the most common syndrome of childhood AD, and recommended using BZYQT for the treatment of pediatric AD.[39,40] The pathogenesis of AD is complex and multifactorial; however, the systemic immune response plays a major role in pathogenesis in AD patients. Most patients with AD have eosinophilia and increased serum IgE concentrations.[5,6] Many studies using various experimental models have shown that BZYQT has immunoregulatory effects.[13–19] These properties are also beneficial for alleviating AD symptoms in clinical practice.

Thus, in this study, we will investigate the clinical evidence related to the effectiveness of BZYQT for treating AD. All BZYQT formulations, such as decoctions, pills, capsules, and tablets, will be considered in this study. Furthermore, trials for which the assessed BZYQT involved a different ratio of ingredients or missing herbs compared to the original BZYQT will be included if similar to the original BZYQT. Detailed information about variants of BZYQT will be provided, including their composition, ingredient ratio, type of formulation, and prescription based on the pattern identification. Thus, this systematic review will provide evidence for the use of BZYQT in the treatment of AD. Moreover, as our systematic review will involve an unbiased search of various databases including Asian databases without language restrictions, readers will obtain the opportunity to access studies originally published in East Asian languages that they would otherwise be unable to read.

Author contributions
M.K.J. and M.J.S. conceived the study, developed the study criteria, and wrote the protocol. M.K.J. and Y.E.K. conducted the preliminary search. A.K. examined the relevance of the protocol in clinical practice. M.J.S. and J.J. revised the manuscript. All authors have read and approved the final manuscript.

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