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Herbal Medicine (Gyejibongneyong-hwan) for treating primary dysmenorrhoea: A protocol for a systematic review of controlled trials

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Running title: A protocol for a systematic review of Gyejibongneyong-hwan for dysmenorrhoea

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Strengths and limitations of this study

- The strength of this protocol of systematic review is unbiased search of various databases without a language restriction.
- The trial screening and data extraction will be conducted independently by two authors.
- We will use of the GRADE approach to assess confidence in estimates of effect
- In complementary and alternative medicine field, there are not insufficient number of randomized controlled trials.

Abstract

Introduction: Gyejibongneyong-hwan (GH) is also known as Guizhi Fuling formula and is widely applied for uterine fibroids in China. Many clinical trials have been reported. The present study assessed the efficacy and safety of GH formula for the treatment of dysmenorrhoea. This review will assess the clinical evidence for and against the use of GH formula as a treatment for dysmenorrhoea. This review will also discuss the proposed mechanism(s) that could link herbal medicine to improvements in dysmenorrhoea.

Methods and analysis: Eleven databases will be searched until Janurary2016. We will include randomized controlled trials (RCTs) examining GH decoctions for any type of dysmenorrhoea. All RCTs of decoctions or modified decoctions will be included. The methodological qualities of the RCTs will be assessed with Cochrane's risk of bias assessments.

Ethics and dissemination: This systematic review will be published in a peer-reviewed journal. The review will also be disseminated electronically and in print. Updates of the review will be conducted to inform and guide healthcare practices.

Registration number: CRD42015023419

Keywords: dysmenorrhoea, herbal medicine, Gyejibongneyong-hwan, Guizhi Fuling formula

Introduction

Dysmenorrhoea can be primary or secondary and is among the most painful menstrual problems of women of reproductive age [1]. This study focuses on primary dysmenorrhoea (PD), which is defined as painful menses in women without any uterine abnormalities [2].

The prevalence of PD varies from 20 to 90% depending on the pain measurements employed and ethnicities examined [3]. PD interferes with women's daily performances and school girls' activities. In Korea, 78.3% of adolescent girls have been reported to suffer from PD during their menstrual periods, and this is the main cause of short-term school absences [4]. The main symptoms of PD are abdominal and lower back pain before and during menstruation. Fifteen per cent of girls require analgesics to relieve these symptoms [5].

The current knowledge about the aetiology of PD is that the hormone prostaglandin triggers uterine muscle contractions that result in cramping and pain [6 7]. In Korean medicine, PD is thought to be caused by the stagnation of the blood or Qi in the lower abdomen during menstruation [8]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered the first-line treatment for PD [9]. Other treatments, such as oral contraceptives and β-blockers, are also prescribed [10]. However, these are ineffective and can even elicit adverse events, such as digestive disorders, that have occurred in up to 25% of women [11]. Thus, a large number of patients suffering from PD seek complementary and alternative approaches, such as acupuncture [12], moxibustion [13 14], and herbal medicine [15 16]. Among the alternative approaches, Gyejibongneyong-hwan (GH, 桂枝茯苓丸), which is also known as Guizhi-Fuling-Wan (pill), is a widely used remedy for PD that has been employed since ancient times in East Asia [17 13 18]. GH was first prescribed in the Essential Prescriptions from the Golden Cabinet (Jin Gui Yao Lue, 金匱要略) by Zhang Zhongjing (張仲景) of the Han Dynasty (206 BC – 220 AD) [19]. The 5 ingredients of GH are Ramulus Cinnamomi Cassiae, Sclerotium

Poriae Cocos, Cortex Moutan Radicis, Semen Pruni Persicae, and Radix Paeoniae Lactiflorae, and these ingredients are combined in a ratio of 1:1:1:1:1. GH is applied to remove blood stasis and masses in the abdominal region to promote blood circulation [15 20]. There are various forms of GH that not only include pills but also include capsules, tablets, and decoctions. All types of GH will be included in this study.

Methods

Study registration

The protocol for this systematic review has been registered on PROSPERO 2015 under the number CRD42015023419.

Data sources

The following databases will be searched from their inceptions to the current date: Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), AMED, and CINAHL. We will also search 6 Korean medical databases (i.e., OASIS, the Korean Traditional Knowledge Portal, the Korean Studies Information Service System, KoreaMed, the Korean Medical Database and DBPIA) and 3 Chinese databases including CNKI (i.e., the China Academic Journal, the China Doctoral Dissertations and Master's Theses Full-text Database, the China Proceedings of Conference Full Text Database and the Century Journal Project), Wanfang and VIP. Furthermore, we will conduct non-electronic searches of conference proceedings, of our own article files, and of 9 Korean traditional medical journals (the Journal of Korean Medicine, the Journal of the Korean Acupuncture and Moxibustion Society, the Korean Journal of Acupuncture, the Journal of Acupuncture and Meridian Studies, the Journal of Pharmacopuncture, the Journal of Oriental Rehabilitation Medicine, the Journal of Korea Chuna Manual Medicine for Spine and Nerves, the Korean Journal of Oriental Physiology and Pathology and the Journal of Korean Oriental Internal Medicine). The search strategy that will be applied to the MEDLINE database is presented in Supplement 1. Similar search strategies will be applied to the other databases.

Study selection will be documented and summarized in a PRISMA-compliant flow chart (http://www.prisma-statement.org) (*Fig. 1*).

Types of studies

All prospective randomized controlled clinical trials (RCTs) will be included if they are randomized studies of GH formula as the sole treatment or as an adjunct to other treatments, as well as if the control group received the same treatment as the intervention group. Trials comparing GH formula with any type of control intervention will also be included. No language restrictions will be imposed. Hard copies of all articles will be obtained and read in full.

Data extraction and quality assessment

Hard copies of all articles will be obtained and read in full. Two authors (SJP and JAL) will perform the data extraction and quality assessment using a predefined data extraction form. The risk of bias will be assessed using the assessment tool for the risk of bias of the Cochrane Handbook version 5.1.0, which includes random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of the outcome assessments, incomplete outcome data, selective reporting and other sources of bias [21].Our review will use 'L', 'U', and 'H' to indicate the results of the assessments; 'L' indicates a low risk of bias, 'U' indicates that the risk of bias was unclear, and 'H' indicates a high risk of bias. Disagreements will be resolved by discussion between all of the authors. When disagreements regarding selection cannot be resolved through discussion, the arbiter (MSL) will make the final decision.

Data collection and synthesis

Data extraction and management

The data extraction and quality assessment will be conducted by two authors (JAL and JHJ) using a predefined data extraction form. Any disagreement among the authors will be resolved by discussion between all of the authors. When the data are insufficient or ambiguous, MSL will

contact the corresponding authors by e-mail or telephone to request additional information or clarification. The data screening and selection process will be performed independently by an author (JHJ) who is fluent in Chinese. We will use the GRADEpro software of the Cochrane Systematic Reviews to create a Summary of Findings table. When disagreements regarding the selections cannot be resolved through discussion, the arbiter (MSL) will make the final decision.

Outcome measures

Primary outcomes

Change in symptom as indicated on a 100-mm visual analogue scale (VAS)

Pain duration (h) according to the McGill questionnaire

Total treatment efficacy, i.e., the number of patients whose PD symptoms improved

Secondary outcomes

Quality of life as measured using a validated questionnaire

Impact of symptoms measured as measured with validated questionnaires

Adverse events

Assessment of bias in the included studies

We will independently assess the bias of the included studies according to the criteria of the Cochrane Handbook, version 5.1.0, which include random sequence generation, allocation concealment, the blinding of participants and personnel, the blinding of outcome assessments, incomplete outcome data, selective reporting and other sources of bias. [21]

Data synthesis

The differences between the intervention and control groups will be assessed. For continuous data, we will use the mean differences (MDs) with the 95% confidence intervals (CIs) to measure the treatment effects. We will convert other forms of data into MDs. In case of outcome variables with different scales, we will use the standard mean difference (SMD) with the 95% CIs. For dichotomous data, we will present the treatment effects as relative risks (RRs) with 95% CIs. We will convert other binary data into RR values.

All of the statistical analyses will be conducted using the Cochrane Collaboration's software program Review Manager (RevMan) version 5.2.7 (Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration, 2012) for Windows. For studies with insufficient information, we will contact the corresponding authors to acquire and verify the data whenever possible. When appropriate, we will pool the data across studies for a meta-analysis using fixed- or random-effects.

Unit of analysis issues

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

Addressing the missing data

Intention-to-treat analyses that include all of the randomized patients will be performed. For patients with missing outcome data, carry-forward of the last observed response procedure will be employed. The individual patient data will be sought from the original source or the published trial reports when the individual patient data are initially unavailable.

Assessment of heterogeneity

We will use the random- or fixed-effect model for the meta-analysis according to the data analysis. Chi-squared and I-squared tests will be used to evaluate the heterogeneities of the included studies, and I^2 >50 will be considered indicative of high heterogeneity. When heterogeneity is observed, we will conduct subgroup analyses to explore the possible causes. [22]

Assessment of reporting biases

If a sufficient number of the included studies (at least 10 trials) are available, we will use funnel plots to detect reporting biases.[23] However, funnel plot asymmetries are not identical to publication biases; therefore, we will attempt to determine the possible reasons for any asymmetries, such as small-study effects, poor methodological qualities and true heterogeneities in the included studies. [23 24]

Discussion

Currently, no systematic reviews of the effects of GH formula on PD have been published. This systematic review will provide a summary of the current evidence related to the effectiveness of GH formula in the treatment of the symptoms of patients with PD. This evidence will be useful to practitioners, patients and health policy-makers regarding the use of acupuncture in PD treatment.

Contributions

JAL and SJP conceived the study, developed the criteria, searched the literature, performed the data analysis and wrote the protocol. JAL, JJ and JC conducted the preliminary search. JJH and MSL assisted in searching the Chinese literature and extracting the data. All authors have read and approved the final manuscript.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

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Supplement 1. MEDLINE OvidSP Search Strategy

1. Dysmenorrhoea
2. Period pain
3. menstrual pain
4. cramps
5. Gyejibongneyong-hwan
6. Guizhi-Fuling-Wan
7. Keishibukuryo-gan
8. randomized controlled trial.pt.
9. controlled clinical trial.pt.
10. randomized.ab.
11. placebo.tw.
12. clinical trials as topic.sh.
13. randomly.ab
14. trial.ti.
15. (crossover or cross-over or cross over).tw.
16. 8-15/or
17. exp animals/ not humans.sh.
18. 16 not 17
19. 21, and 18

Supplement 2. CNKI search strategy

1. Dysmenorrhoea
2. Period pain
3. menstrual pain
4. cramps
5. Gyejibongneyong-hwan
6. Guizhi-Fuling-Wan
7. Keishibukuryo-gan
8. random
9. control
10. clinical trial
11. blind procedure
12. placebo
13. 16-20/or

Supplement 3. Summary of randomized clinical studies form.

First author (year) Country	Patients No. (M/F); Age, mean (I/C); Diagnosis; Duration of disease;	Intervention Group (Regime)	Control group (Regime)	Duration of treatment (total times)	Main outcomes	Intergroup differences	Adverse events
Study 1							
Study 2							
Study 3							
……							

Supplement 4. Summarized interventions in the included studies.

First author (year)	Herbal type Method (Fixed/Partially Individualized/ Individualized)[1]	Treatment rationale	Regimen	Acupuncture Points	Response Sought[2]	Co-intervention
Study 1						
Study 2						
Study 3						
……						

1. Herbal type was classified into 3 categories on the basis of the types "pill", "decoction" and means.

Supplement 5. Risks of bias in the included RCTs.

First author (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Study 1							
Study 2							
Study 3							
……							

'L' indicates a low risk of bias; 'U' indicates that the risk of bias is uncertain; 'H' indicates a high risk of bias.

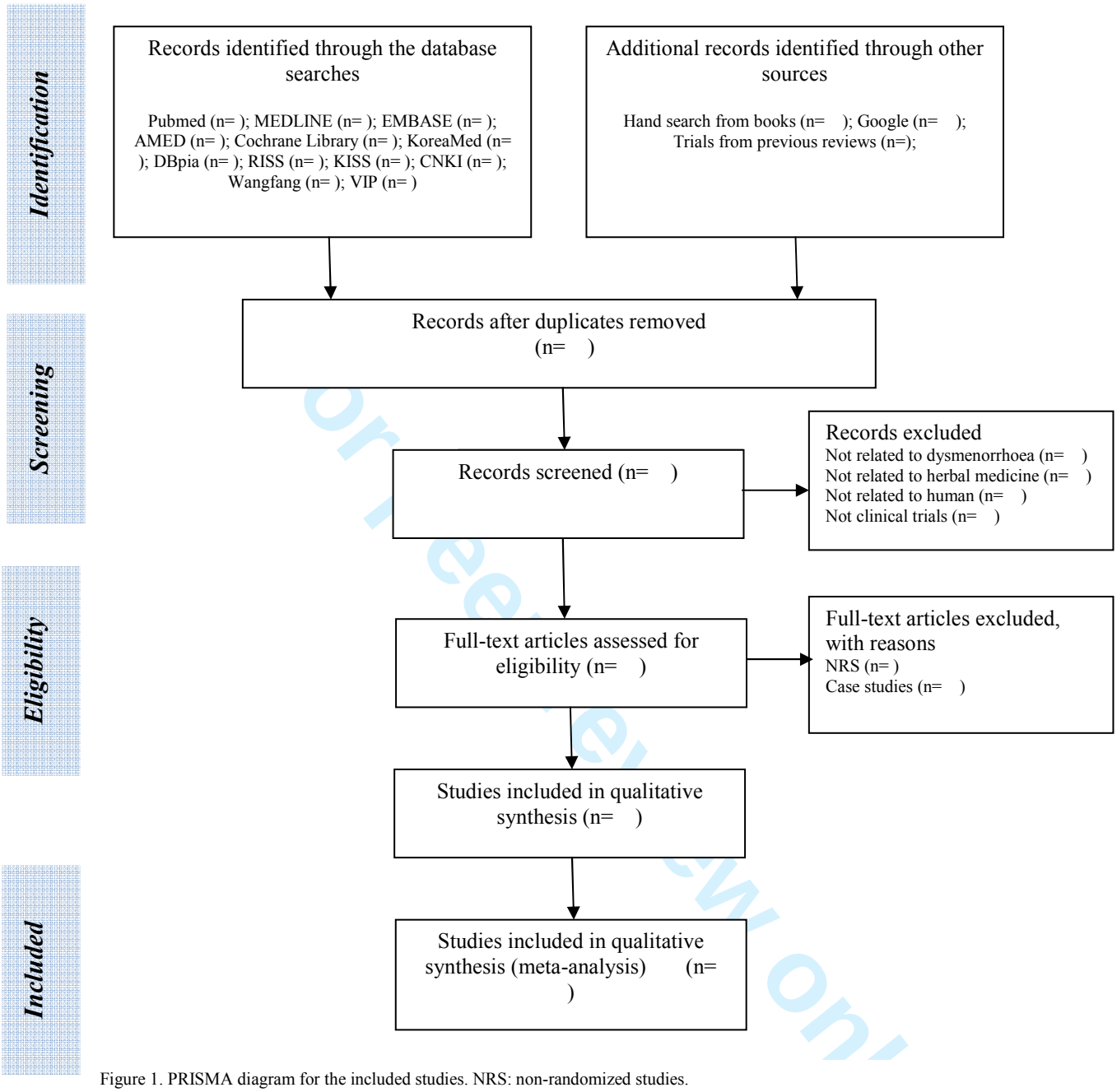

Figure 1. PRISMA diagram for the included studies. NRS: non-randomized studies.

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	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	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
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	10
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	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
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	6
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	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	14,15

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
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)	6-7
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	6-7
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	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
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	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	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 I^2, Kendall's τ)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

*** 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.**

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In this review, we will investigate evidence related to the effectiveness of GH formula in the treatment of the symptoms of patients with PD which is widely used in traditional Korean medicine (TKM) and traditional Chinese Medicine (TCM).

Methods

Study registration

The protocol for this systematic review has been registered on PROSPERO 2015 under the number CRD42015023419.

Data sources

The following databases will be searched from their inceptions to the current date: Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), AMED, and CINAHL. We will also search 6 Korean medical databases (i.e., OASIS, the Korean Traditional Knowledge Portal, the Korean Studies Information Service System, KoreaMed, the Korean Medical Database and DBPIA) and 3 Chinese databases including CNKI (i.e., the China Academic Journal, the China Doctoral Dissertations and Master's Theses Full-text Database, the China Proceedings of Conference Full Text Database and the Century Journal Project), Wanfang and VIP. Furthermore, we will conduct non-electronic searches of conference proceedings, of our own article files, and of 9 Korean traditional medical journals (the Journal of Korean Medicine, the Journal of the Korean Acupuncture and Moxibustion Society, the Korean Journal of Acupuncture, the Journal of Acupuncture and Meridian Studies, the Journal of Pharmacopuncture, the Journal of Oriental Rehabilitation Medicine, the Journal of Korea Chuna Manual Medicine for Spine and Nerves, the Korean Journal of Oriental Physiology and Pathology and the Journal of Korean Oriental Internal Medicine). The search strategies that will be applied to the MEDLINE database and CNKI

are presented in Supplement 1, 2. Similar search strategies will be applied to the other databases.

Study selection will be documented and summarized in a PRISMA-compliant flow chart (http://www.prisma-statement.org) (*Fig. 1*).

Types of studies

All prospective randomized controlled clinical trials (RCTs) will be included if they are randomized studies of GH formula as the sole treatment or as an adjunct to other treatments, as well as if the control group received the same treatment as the intervention group. Trials comparing GH formula with any type of control intervention will also be included. No language restrictions will be imposed. Hard copies of all articles will be obtained and read in full.

Data extraction and quality assessment

Hard copies of all articles will be obtained and read in full. Two authors (SJP and JAL) will perform the data extraction and quality assessment using a predefined data extraction form (Supplement 3, 4, 5). Any disagreement among the authors will be resolved by discussion between all of the authors. When the data are insufficient or ambiguous, MSL will contact the corresponding authors by e-mail or telephone to request additional information or clarification. The data screening and selection process will be performed independently by an author (JHJ) who is fluent in Chinese. The risk of bias will be assessed using the assessment tool for the risk of bias of the Cochrane Handbook version 5.1.0, which

includes random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of the outcome assessments, incomplete outcome data, selective reporting and other sources of bias [17].Our review will use 'L', 'U', and 'H' to indicate the results of the assessments; 'L' indicates a low risk of bias, 'U' indicates that the risk of bias was unclear, and 'H' indicates a high risk of bias. Disagreements will be resolved by discussion between all of the authors. When disagreements regarding selection cannot be resolved through discussion, the arbiter (MSL) will make the final decision.

Data collection and synthesis

Outcome measures

Primary outcomes

Change in symptom as indicated on a 100-mm visual analogue scale (VAS)

Pain duration (h) according to the McGill questionnaire

Improve effectiveness including total treatment efficacy, i.e., the number of patients whose PD symptoms improved

Secondary outcomes

Quality of life as measured using a validated questionnaire

Impact of symptoms measured as measured with validated questionnaires

Adverse events

Information related GH usage

Pattern type in response based on TKM or TCM theory

Range of dosage of GH in each study

Duration of treatment

The details of the formula compositions

Assessment of bias in the included studies

We will independently assess the bias of the included studies according to the criteria of the Cochrane Handbook, version 5.1.0, which include random sequence generation, allocation concealment, the blinding of participants and personnel, the blinding of outcome assessments, incomplete outcome data, selective reporting and other sources of bias. [17]

Data synthesis

The differences between the intervention and control groups will be assessed. For continuous data, we will use the mean differences (MDs) with the 95% confidence intervals (CIs) to measure the treatment effects. We will convert other forms of data into MDs. In case of outcome variables with different scales, we will use the standard mean difference (SMD) with the 95% CIs. For dichotomous data, we will present the treatment effects as relative risks (RRs) with 95% CIs. We will convert other binary data into RR values.

We will use the GRADEpro software of the Cochrane Systematic Reviews to create a Summary of Findings table. When disagreements regarding the selections cannot be resolved through discussion, the arbiter (MSL) will make the final decision.

All of the statistical analyses will be conducted using the Cochrane Collaboration's software program Review Manager (RevMan) version 5.2.7 (Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration, 2012) for Windows. For studies with

insufficient information, we will contact the corresponding authors to acquire and verify the data whenever possible. When appropriate, we will pool the data across studies for a meta-analysis using fixed- or random-effects.

Unit of analysis issues

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

Addressing the missing data

Intention-to-treat analyses that include all of the randomized patients will be performed. For patients with missing outcome data, carry-forward of the last observed response procedure will be employed. The individual patient data will be sought from the original source or the published trial reports when the individual patient data are initially unavailable.

Assessment of heterogeneity

We will use the random- or fixed-effect model for the meta-analysis according to the data analysis. I-squared tests will be used to evaluate the heterogeneities of the included studies, and I^2 >50 will be considered indicative of high heterogeneity. When heterogeneity is observed, we will conduct subgroup analyses to explore the possible causes. [18]

Assessment of reporting biases

If a sufficient number of the included studies (at least 10 trials) are available, we will use funnel plots to detect reporting biases.[19] However, funnel plot asymmetries are not identical to publication biases; therefore, we will attempt to determine the possible reasons for any asymmetries, such as small-study effects, poor methodological qualities and true heterogeneities in the included studies. [19 20]

Discussion

Among the alternative approaches, Gyejibongneyong-hwan (GH, 桂枝茯苓丸), which is also known as Guizhi-Fuling-Wan (pill), is a widely used remedy for PD that has been employed since ancient times in East Asia [21 13 22]. GH was first prescribed in the Essential Prescriptions from the Golden Cabinet (Jin Gui Yao Lue, 金匱要略) by Zhang Zhongjing (張仲景) of the Han Dynasty (206 BC – 220 AD) [23]. The 5 ingredients of GH are *Ramulus Cinnamomi Cassiae, Sclerotium Poriae Cocos, Cortex Moutan Radicis, Semen Pruni Persicae,* and *Radix Paeoniae Lactiflorae*, and these ingredients are combined in a ratio of 1:1:1:1:1. GH is applied to remove blood stasis and masses in the abdominal region to promote blood circulation [15 24]. There are various forms of GH such as pills, capsules, tablets, and decoctations. All types of GH will be included in this study. Currently, no systematic reviews of the effects of GH formula on PD have been published. This systematic review will provide a summary of the current evidence related to the effectiveness of GH formula in the treatment of the symptoms of patients with PD. Especially, we will consider the special features of intervention in full review of GH for PD. Although many SR have been done for herbal medicine, important information for HM usage were not extracted and missed [25]. Therefore, we will identify subtypes that this remedy is particularly useful for (e.g. certain pattern type based on TKM or TCM theory), identifying a range of dosages, modifications used to improve effectiveness, or comparing duration of treatment in full review of this protocol. Original GH are composed of five herbs mentioned above, however, the primary studies show high heterogeneity in ingredients of GH. Therefore, we will investigate the composition of each formula of the

primary studies. This evidence will be useful to practitioners, patients and health policy-makers regarding the use of acupuncture in PD treatment.

Contributions

JAL and SJP conceived the study, developed the criteria, searched the literature, performed the data analysis and wrote the protocol. JAL, JJ and JC conducted the preliminary search. JJH and MSL assisted in searching the Chinese literature and extracting the data. All authors have read and approved the final manuscript.

Figure legend

Figure 1. PRISMA diagram for the included studies. NRS: non-randomized studies.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

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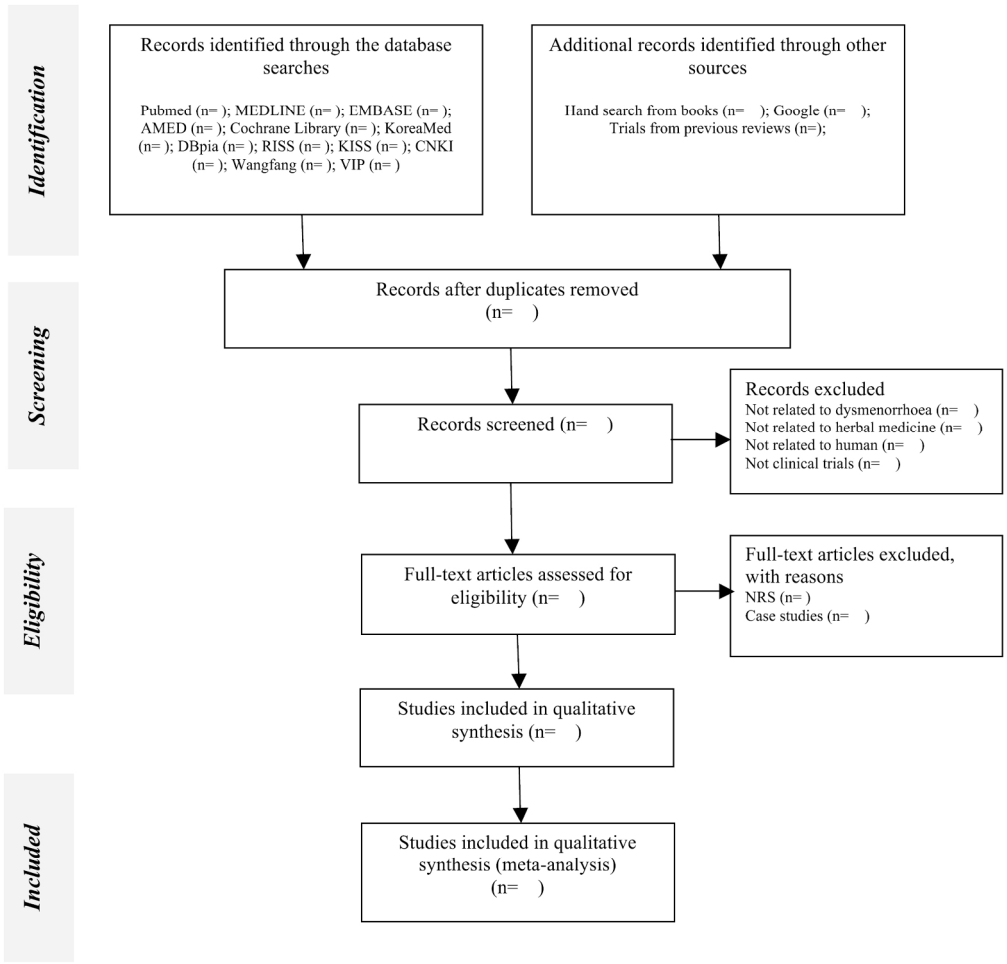

180x172mm (300 x 300 DPI)

Supplement 1. MEDLINE OvidSP Search Strategy

1. Dysmenorrhoea
2. Period pain
3. menstrual pain
4. cramps
5. Gyejibongneyong-hwan
6. Guizhi-Fuling-Wan
7. Keishibukuryo-gan
8. randomized controlled trial.pt.
9. controlled clinical trial.pt.
10. randomized.ab.
11. placebo.tw.
12. clinical trials as topic.sh.
13. randomly.ab
14. trial.ti.
15. (crossover or cross-over or cross over).tw.
16. 8-15/or
17. exp animals/ not humans.sh.
18. 16 not 17
19. 21, and 18

Supplement 2. CNKI search strategy

1. Dysmenorrhoea
2. Period pain
3. menstrual pain
4. cramps
5. Gyejibongneyong-hwan
6. Guizhi-Fuling-Wan
7. Keishibukuryo-gan
8. random
9. control
10. clinical trial
11. blind procedure
12. placebo
13. 16-20/or

Supplement 3. Summary of randomized clinical studies form.

First author (year) Country	Patients No. (M/F); Age, mean (I/C); Diagnosis; Duration of disease;	Intervention Group (Regime)	Control group (Regime)	Duration of treatment (total times)	Main outcomes	Intergroup differences	Adverse events
Study 1							
Study 2							
Study 3							
……							

Supplement 4. Summarized interventions in the included studies.

First author (year)	*Herbal type Method (Fixed/Partially Individualized/ Individualized)*[1]	*Treatment rationale*	*Regimen*	*Response Sought*	*Co-intervention*
Study 1					
Study 2					
Study 3					
……					

1. Herbal type was classified into 3 categories on the basis of the types "pill", "decoction" and means.

Supplement 5. Risks of bias in the included RCTs.

First author (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Study 1							
Study 2							
Study 3							
……							

'L' indicates a low risk of bias; 'U' indicates that the risk of bias is uncertain; 'H' indicates a high risk of bias.

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	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	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
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	10
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	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
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	6
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	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	14,15

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
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)	6-7
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	6-7
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	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
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	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	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 I^2, Kendall's τ)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

*** 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.**

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