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Herbal Medicine for the Treatment of Non-Erosive Reflux Disease: A Systematic Review and Meta-Analysis Protocol

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ABSTRACT

Introduction: Non-erosive reflux disease (NERD) is the most common subtype of gastroesophageal reflux disease (GERD). This study aims to synthesize evidence on the efficacy and safety of various herbal medicines for the treatment of NERD.

Methods and analysis: Ten electronic databases will be examined: MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials, Embase, Allied and Complementary Medicine Database, China National Knowledge Infrastructure Database, Citation Information by Nii, Korean Medical Database, Korean Studies Information Service System, National Digital Science Library, and Oriental Medicine Advanced Searching Integrated System. All randomized controlled trials published from inception to May 2023 that meet the eligibility criteria will be selected. Two independent researchers will extract data, such as publication year, study design, intervention details, outcome measures, main results, and adverse events. The risk of bias and quality of evidence will be assessed, and subgroup analyses will be performed according to the type of control intervention and herbal medicine. The analysis process will be conducted using Review Manager 5.4 software.

Discussion: This review will present a summary and rationale for herbal medicine's effectiveness in treating NERD. The findings of this review can help those who want to apply herbal medicine to the treatment of NERD.

Systematic review registration: PROSPERO registration number CRD42023423052.

Key words: Non-erosive reflux disease, Herbal Medicine, Systematic Review, Meta-Analysis

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Ⅰ. Introduction

Gastroesophageal reflux disease (GERD) is one of the most commonly diagnosed chronic gastrointestinal disorders and is characterized by regurgitation of

stomach contents back into the esophagus. Based on the endoscopic and histopathological appearance, there are several phenotypes of GERD, such as non-erosive reflux disease (NERD), erosive esophagitis, and Barrett's esophagus. NERD accounts for the most prevalent type among them[1]. Symptoms induced by the regurgitation of gastric juice associated with NERD, even without inflammatory lesions on the mucous membrane of the esophagus, can contribute to lowering the patients' quality of life and generating severe heartburn[2,3]. Conventional treatment options currently include lifestyle modifications, medical, surgical, and endoluminal therapy[4]. Proton pump inhibitor (PPI) therapy is the most widely used method that can be tried in medical therapy. However, evidence for the effectiveness of PPIs in the treatment of NERD has not been sufficiently established[5,6]. Herbal medicine can serve as a viable alternative for treating NERD, particularly when Western medicine fails to provide desired results, such as in cases of PPI-refractory reflux disease or when dose reduction is preferred. There have been various types of reports, such as case reports, randomized controlled trials (RCT), and systematic reviews that confirmed the efficacy and safety of herbal medicine treatment on GERD and NERD[7-10]. A meta-analysis confirming the efficacy and safety of traditional treatment of NERD was conducted in 2018[11]. However, the databases searched were limited to English and Chinese, and trials involving Western medicine in the intervention group were excluded. Therefore, we aimed to search for more recent and extensive trials relevant to herbal medicine treatment of NERD and conduct subgroup analyses to synthesize the current state of evidence on the efficacy of herbal medicine in treating NERD.

Ⅱ. Methods and analysis

This systematic review and meta-analysis aimed to identify, synthesize, and analyze the evidence on the efficacy and safety of herbal medicines for NERD. The systematic review and meta-analysis will be conducted according to the Cochrane Handbook for Systematic Reviews of Interventions[12]. The protocol for this systematic review is based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guideline[13], and is registered in the International Prospective Register of Systematic Review (PROSPERO) with registration number CRD42023423052.

1. Search strategy

We will search the following 10 electronic databases from inception to May 2023 without language or publication date restrictions: MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Allied and Complementary Medicine Database (AMED), China National Knowledge Infrastructure Database (CNKI), Citation Information by Nii (CiNii), Korean Medical Database (Kmbase), Korean Studies Information Service System (KISS), National Digital Science Library (NDSL), Oriental Medicine Advanced Searching Integrated System (OASIS). The search term will consist of a combination of controlled terms such as Medical Subject Headings (MeSH) and free text words related to "non-erosive reflux disease", "herbal medicine", or "traditional medicine". The search strategy for MEDLINE is shown in Table 1.

Table 1. Search strategy for Medline via PubMed

No.	Search strategy
#1.	gastroesophageal reflux[MeSH Terms]
#2.	gastric acid reflux[tiab] OR acid reflux, gastric[tiab] OR reflux, gastric acid[tiab] OR gastric acid reflux disease[tiab]
#3.	gastro-esophageal reflux disease[tiab] OR gastro esophageal reflux disease[tiab] OR gastro-esophageal reflux diseases[tiab] OR reflux disease, gastro-esophageal[tiab]
#4.	gastro-oesophageal reflux[tiab] OR gastro oesophageal reflux[tiab] OR reflux, gastro-oesophageal[tiab]
#5.	gastroesophageal reflux disease[tiab]
#6.	GERD[tiab] OR reflux, gastroesophageal[tiab] OR esophageal reflux[tiab] OR gastro-esophageal reflux[tiab] OR gastro esophageal reflux[tiab] OR reflux, gastro-esophageal[tiab]
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8.	non erosive[tiab] OR non-erosive[tiab] OR nonerosive[tiab] OR non erosion[tiab] OR non-erosion[tiab] OR NERD[tiab] OR non erosive reflux disease[tiab] OR non-erosive reflux disease[tiab] OR nonerosive reflux disease[tiab] OR non erosion reflux disease[tiab] OR non-erosion reflux disease[tiab]
#9.	#7 OR #8
#10.	herbal medicine[MeSH Terms]
#11.	medicine, herbal[tiab] OR herb*[tiab]
#12.	plants, medicinal[MeSH Terms] OR plant extracts[MeSH Terms]
#13.	medicine, traditional[MeSH Terms] OR medicine, korean traditional[MeSH Terms] OR medicine, chinese traditional[MeSH Terms] OR medicine, east asian traditional[MeSH Terms]
#14.	korean[tiab] OR chinese[tiab] OR east asian[tiab] OR japanese[tiab]
#15.	tradition*[tiab]
#16.	#14 AND #15
#17.	traditional[tiab] OR chinese[tiab] OR herbal[tiab]
#18.	medicine[tiab]
#19.	#17 AND #18
#20.	medicine, kampo[MeSH Terms]
#21.	complementary therapies[MeSH Terms]
#22.	drugs, chinese herbal[MeSH Terms]
#23.	tang[tiab] OR decoction[tiab] OR formula*[tiab] OR herbal formula[tiab] OR granule[tiab] OR syrup[tiab] OR san[tiab] OR hwan[tiab] OR capsule[tiab] OR powder[tiab] OR tablet[tiab]
#24.	#10 OR #11 OR #12 OR #13 OR #16 OR #19 OR #20 OR #21 OR #22 OR #23
#25.	randomized controlled trial[pt]
#26.	controlled clinical trial[pt]
#27.	randomized[tiab] OR randomised[tiab]
#28.	randomly[tiab]
#29.	clinical[tiab]
#30.	trial*[tiab]
#31.	clinical trial[tiab]
#32.	#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
#33.	#9 AND #24 AND #32

MeSH : medical subject headings, tiab : title/abstract, GERD : gastroesophageal reflux disease, NERD : non-erosive reflux disease, pt : publication type

2. Eligibility criteria

The following eligibility criteria will be applied to select the appropriate studies for inclusion in this review.

1) Types of studies

RCTs and quasi-RCTs in humans will be included. Other than RCTs, such as case reports, retrospective studies, reviews, and animal studies will be excluded.

2) Types of participants

Patients diagnosed with NERD will be included, and those diagnosed with any organic disease associated with symptoms other than GERD or NERD will be excluded. There will be no restriction on demographic characteristics, such as race or gender, but studies involving only non-adults under the age of 19 years will be excluded.

3) Types of interventions

Studies involving any type of herbal medicine, such as a decoction, pill, tablet, capsule, or powder administered orally as an intervention, will be included. There will be no restrictions on the number of herbs that comprise the formula, and studies using herbal medicines consisting of only one herb as an intervention will also be included. Studies comparing herbal medicine with any type of control intervention will be included: herbal medicine alone, herbal medicine combined with Western medicine versus Western medicine alone, herbal medicine versus placebo formulation, and herbal medicine versus no treatment. However, studies that involved other traditional treatment methods, such as acupuncture or moxibustion with herbal medicine as the main intervention in the treatment group and studies that included herbal medicine as an intervention in both the control and treatment groups, will be excluded.

4) Types of outcome measures

The primary outcome will be the total efficacy rate. Symptom scores and quality of life examined by self-response questionnaires such as reflux diagnostic questionnaire score, gastroesophageal reflux disease questionnaire, short-form 36 health survey score, and recurrence rates will be secondary outcomes.

3. Study selection

Two researchers (MK and CP) will independently examine the titles and abstracts of all retrieved studies in the first phase of screening. In the second phase, researchers will undergo a full-text screening process. Disagreements between the two researchers will be resolved through a discussion with a senior researcher (S-JK). Duplicates among the studies will be identified by study characteristics such as author names, publication year, trial registration number, intervention, or participants during the screening process, and multiple reports will be removed. The selection process will be shown in the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) flow diagram (Fig. 1). Selected studies that meet the eligibility criteria above will undergo data extraction process. Data management will be performed using Endnote X20 software program.

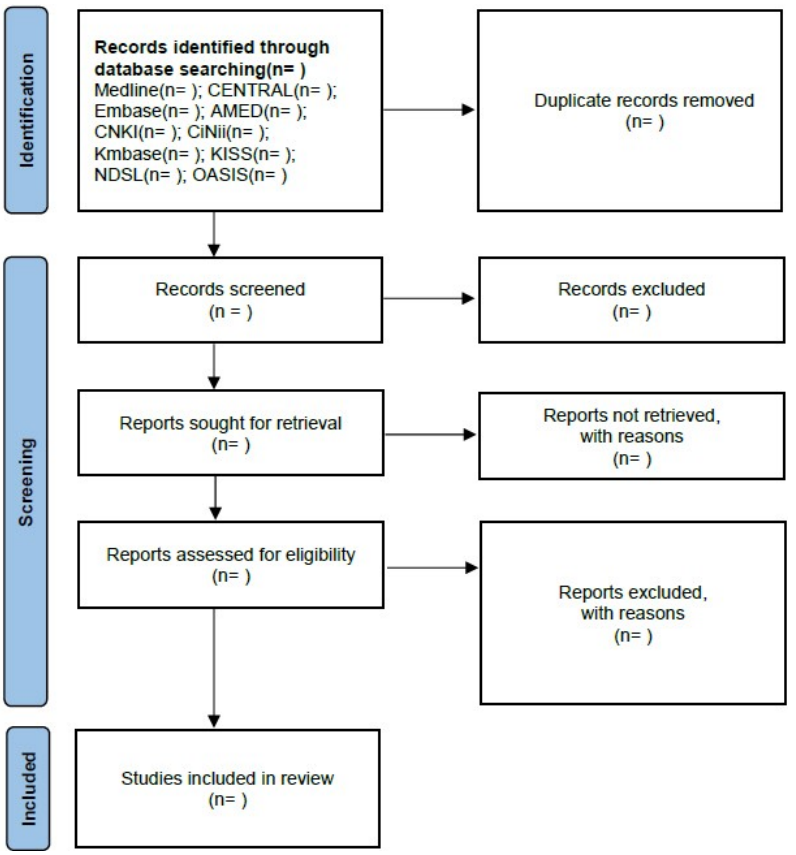

Fig. 1. Flow chart of the search process.

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

4. Data extraction

Data extraction will be performed by two independent researchers (MK and CP), and data will be recorded in a pre-defined form. The extracted data will include the basic characteristics of the study, such as authors' name, year of publication, study design, information about participants, details of the intervention, outcome measures, main results, and adverse events. Details of the intervention will include the type of herbal medicine, and duration and frequency of treatment.

Ⅲ. Meta-analysis

1. Assessment of the risk of bias

The quality of all selected studies will be assessed using the Cochrane risk-of-bias tool for randomized trials individually[14]. Biases in the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome

assessment, incomplete outcome data, and selective reporting will be checked. Each domain will be judged as low, uncertain, or high.

2. Data synthesis and analysis

Results such as the overall efficacy rate from the treatment and control groups will be compared. Dichotomous data will be presented as risk ratios (RR) with a 95% confidence intervals (CI); continuous data will be presented as mean difference (MD) or standardized mean difference (SMD) with a 95% CI[15]. Statistical analyses will be conducted using Review Manager program (RevMan) version 5.4.. A narrative summary will be provided if the studies are not appropriate for quantitative synthesis.

Statistical heterogeneity of the studies will be measured using I^2 statistics; if it is over 50%, it will be considered to have significant heterogeneity[16]. Fixed- or random- effects models will be used for the meta-analysis. In addition, a funnel plot will be used to assess publication bias in terms of the primary outcome.

3. Assessment of meta-biases

The quality of evidences from the included studies will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. The risks of bias, imprecision, inconsistency, indirectness, and publication bias will be assessed and graded as high, moderate, low, or very low[17].

4. Subgroup analyses

A subgroup analysis will be performed based on the type of control intervention or type of herbal medicine used. Differences will be compared according to the type of Western medicine and whether herbal medicine is combined with Western medicine or used alone.

Ⅳ. Discussion

NERD is the most common type of GERD. It is defined as the absence of mucosal lesions confirmed by endoscopy and represents up to 60% of all patients with reflux symptoms[18]. Medical treatment of patients with NERD is based on gastric acid-suppressive drugs such as PPIs. Although PPI therapy is the most effective method for treating GERD, the response rates to PPIs are lower in patients than in those with other phenotypes of GERD[19]. This systematic review and meta-analysis will assess the efficacy and safety of herbal medicines for the treatment of NERD.

Herbal medicines can be a helpful option for the treatment of reflux disease, especially in cases that do not respond to conventional medical treatments, including proton pump inhibitors. Various herbal medicines can alleviate the symptoms of non-erosive reflux disease in patients with symptoms such as heartburn[20,21]. In this study, we will investigate clinical trials published from the inception of herbal medicine treatment for NERD, and synthesize recent evidence of its efficacy.

Ethics and dissemination

Since this study do not include individual patient data, ethical approval is not required. The results of this systematic review will be disseminated via peer-reviewed journal publication or conference presentations.

Acknowledgements

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Contributors

Both MK and CP contributed to the conceptualization of the review. Both J-WP and JK contributed to the development of the search strategy and design of the analysis plan. MK wrote the initial draft of the manuscript. S-JK reviewed and edited the final manuscript. All the authors have read and approved the final version of the manuscript.

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【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
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	11
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	12
Sponsor	5b	Provide name for the review funder and/or sponsor	12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12
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	3-7
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	3-4
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	5-6
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
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)	7-8
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	10
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	10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
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	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	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)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias (es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

* 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.

Pre-defined Data Extraction Form

No.	First author (year)	Language	Participants (n)	M:F / Age	Diagnosis criteria	Invervention (n) / Content	Control (n) / Content	Treatment period	Outcome measure	Main results / Main statistics	Side effects
1											