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Herbal medicines for the treatment of otitis media with effusion: Protocol for a systematic review

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Article focus

- The aim of the proposed systematic review is to analyse trial data concerning the effectiveness of herbal medicines for otitis media with effusion.

Key messages

- This systematic review will be performed using a comprehensive search strategy and will establish the current status of the evidence using unbiased methods.

Strengths and limitations of this study

- The strength of this systematic review is its extensive, unbiased search of various databases without a language restriction.
- The trial screening and data extraction will be conducted independently by two of the authors.

Abstract

Introduction: The purpose of this systematic review is to investigate the effectiveness of herbal medicines for otitis media with effusion (OME) through analysing trial data.

Methods and analysis: Electronic searches of the following eleven databases will be performed: MEDLINE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, the Allied and Complementary Medicine Database (AMED), the Cochrane Central Register of Controlled Trials (CENTRAL), the China Network Knowledge Infrastructure (CNKI) and five Korean databases [Oriental Medicine Advanced Searching Integrated System (OASIS), DBPIA, Korea-Med, Research Information Service System (RISS) and the Korean Studies Information Service System (KISS)]. The selection of the studies, data abstraction, and validations will be performed independently by two researchers.

Dissemination: The 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 practice and policy.

Trial registration number: PROSPERO 2013: CRD42013005430.

Introduction

Description of the condition

Otitis media with effusion (OME) is characterised as the presence of middle-ear effusion without the signs and symptoms of an acute ear infection and a disease course of months until recovery [1-4]. OM affects nearly every child at least once, and approximately 90% of children experience an episode of OME before school age due to incomplete Eustachian tube functioning or inflammation following acute otitis media (AOM) [5 6]. Approximately 35% to 50% of OME patients have chronic or recurrent states. When inadequately treated, OME can cause major functional limitations such as permanent hearing loss, which may delay language, speech and cognitive development [7-9].

Description of the intervention

OME has high socioeconomic consequences, and the annual cost of OME was $4 billion.[4 5] Patients with OME are treated with antibiotics, antihistamines, steroids and the insertion of ventilation tubes. However, antibiotics and steroids have been suggested to provide only a marginal benefit, and antihistamines are not recommended in systematic reviews.[10-12] A review of randomised controlled trials revealed that the insertion of ventilation tubes reduced the proportion of time spent with effusion compared with watchful waiting. However, ventilation tubes lead to adverse effects, such as tympanosclerosis and tympanic membrane abnormalities [13 14].

How the intervention might work

Currently, many patients who are seeking ways to relieve the symptoms associated with chronic OME or to avoid the side effects of conventional treatment have chosen complementary and alternative medicine (CAM) [15]. Herbal medicine, a part of CAM, is the

use of medicinal plants, minerals and animal parts for preventing or treating clinical conditions. Many types of herbal medicines are known to have an anti-inflammatory effects and have been to reduce swelling and prevent endotoxin-induced OME in experimental investigations [16-20].

Why it is important to perform this review

Herbal medicine has been approved by the World Health Organization as a therapy for the treatment of OME [15 21]. However, no systematic reviews assessing the intervention of herbal drugs treatment in OME have been conducted to date. Understanding the effectiveness and safety of herbal medicines will allow the appropriate recommendation of an herbal drug treatment for patients.

Objectives

Thus, we will undertake a systematic review to assess the safety and efficacy of herbal drugs for the treatment of OME.

Methods

Criteria for considering studies for this review

Types of studies

The review will include randomised controlled trials, including cluster randomised trials. Quasi-randomised trials, in which the group allocation was not purely random but rather determined by a factor such as a birth date, a hospital record number or alternation, will be included. Any trials without parallel comparisons or control groups will be excluded.

Types of participants

The review will include studies evaluating patients who had a diagnosis of OME. The diagnostic criteria for OME should be based on the criteria of the WHO, the American Academy of Pediatrics (AAP) and the American Academy of Otolaryngology and Head and Neck Surgery (AAOHNS), but if necessary, trials for which the definition of OME used by the authors is in question will also be included. We will exclude studies of patients with ventilation tubes present, patients with an anatomical deformity or patients with other chronic immune-compromised states.

Types of interventions

The review will include those trials using herbal medicine alone or as a combined therapy of herbal medicine with a conventional therapy versus the same conventional therapy. Herbal medicine is defined as a single herb, an individually prescribed herbal formula or herbal products extracted from natural herbs. There is no limitation on the number of herbs used, the dosage, the forms of medication or the duration of the treatment. We will include only the oral administration of the medication.

Types of outcome measures

The following outcome measures will be assessed based on analyses of the data obtained in the included trials.

Primary Outcome

Resolution of symptoms or signs (however measured)

Secondary Outcomes

1. Duration of effusion
2. Hearing level
3. Language and speech development
4. Cognitive development
5. Insertion of ventilation tubes
6. New AOM
7. Tympanic membrane sequelae
8. Quality of life
9. Adverse effects likely to be related to treatment

Search methods for identifying the studies

Electronic searches

The electronic searches will be performed using MEDLINE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, the Allied and Complementary Medicine Database (AMED) and the Cochrane Central Register of Controlled Trials (CENTRAL). We will also search one Chinese database [China Network Knowledge Infrastructure (CNKI)] and five Korean databases [Oriental Medicine Advanced Searching

Integrated System (OASIS), DBPIA, Korea-Med, the Research Information Service System (RISS) and the Korean Studies Information Service System (KISS)].

Searching other resources

The reference lists of review articles and the retrieved articles will be examined to find additional studies. Additional trials will be sought in the meta-Register of Controlled Trials (m RCT) (www.controlled-trials.com/mrct), Clinical trials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry platform (ICTRP) (http://apps.who.int/trialsearch/) for all of which list ongoing trials.

Search strategy

The strategies for searching The Cochrane Library, MEDLINE, and EMBASE databases are presented in Appendix 1. These strategies will be modified for use with other databases.

Data collection and analysis

Selection of studies

Two of the review's authors (Son MJ and Kim YH) will independently screen the titles and abstracts of the searched studies, perform the study selection and record their decisions on a standard eligibility form. The arbitrator (Lee MS) will decide upon the study selection when a consensus cannot be reached.

Inclusion Criteria

1. In randomised cross-over trials, only the data from the first period will be included to avoid the carry-over effect

2. No language limitation

3. No publication status restriction

Exclusion Criteria

1. Animal experiments

2. Non-randomised clinical trials

3. Case report/series, news items, and letters

4. Qualitative studies

Data extraction and management

Two of the authors (Son MJ and Kim YH) will independently extract the data using a standard data extraction form and resolve disagreements through discussion before analysis. When the reported data are insufficient or ambiguous, two of the authors (Kim YE and Lee HW) will contact the corresponding authors of the clinical trials by e-mail or telephone to request additional information or clarification.

Assessment of risk of bias in the included studies

We will independently assess the risk of bias in the eligible studies according to the criteria in the Cochrane Handbook version 5.1.0, which include random sequence generation, allocation concealment, the blinding of participants and personnel, the blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias [22]. The quality of the study will be classified as low, unclear or high risk of bias. If necessary, we will contact the authors of eligible trials for clarification. Any differences in opinion will be resolved by discussion or arbitration involving a third author.

Assessment of reporting biases

We will prepare funnel plots to assess the reporting biases if sufficient studies are available (at least 10 trials) [23]. However, funnel plot asymmetry is not the same as publication bias; therefore, we will attempt to distinguish the different possible reasons for the asymmetry, such as small-study effects, poor methodological quality and true heterogeneity of the included studies [23 24].

Measurement of the treatment effect

For continuous data, we will use the mean difference (MD) to measure the treatment effect with 95% confidence intervals (CIs). We will convert other forms of data into MDs. In the case of outcome variables with different scales, we will use the standard mean difference (SMD) with 95% CIs. For dichotomous data, we will present the treatment effects as a relative risk (RR) with 95% CIs. We will convert other binary data into the RR form.

Strategy for missing data

We will conduct intention-to-treat analyses that include all of the randomised patients. A carry-forward of the last observed response will be used for patients with missing outcome data. We will seek the individual patient data from the original source or the published trial reports when the individual patient data are unavailable.

Assessment of heterogeneity

If a meta-analysis is possible, we will use the I^2 statistic to quantify the inconsistencies among the included studies. An I^2 value >50% will be considered indicative of substantial heterogeneity [25]. If heterogeneity is observed, we will conduct subgroup analysis to explore the possible causes [25].

Data synthesis

Data synthesis will be performed using Review Manager (RevMan), Version 5.0, for Windows software. The primary meta-analyses will be performed using random effects models due to the expected inter-trial heterogeneity.

Subgroup analysis and investigation of heterogeneity

If there is a sufficient number of studies, subgroup analyses will be conducted to assess the heterogeneity between the studies, including the following:

1. Type of herbal medicine
2. Type of control
3. Type of age group.

Sensitivity analysis

If an adequate number of studies are available, sensitivity analyses will be performed to determine whether the findings are robust. The following aspects will be considered.

1. Sample size (e.g., more or less than 30 participants in each group)
2. Methodological qualities (e.g., allocation concealment or the blinding of participants/assessors)
3. Analysis-related issues (e.g., processes for handling missing data)

Discussion

Because no primary data collection will be undertaken, no additional formal ethical assessment or informed consent is required. The systematic review will be published in a peer-reviewed journal. It will also be disseminated electronically and in print. Updates of the review will be conducted to provide a summary of the current state of the evidence for the effectiveness of interventions utilising herbal drugs on OME and to guide healthcare practice and policy.

Contributors

The protocol was drafted by all authors. It was revised and the final version approved by all authors.

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Conflicts of interest

None known

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Appendix 1. Search strategies

Table 1 The Cochrane Library (Wiley Online Library)

#1	MeSH descriptor: [Otitis Media with Effusion] explode all trees
#2	glue NEXT ear OR otitis NEXT media NEAR effusion* OR middle NEXT ear NEAR effusion* OR nonsuppurative NEXT otitis OR non NEXT suppurative NEXT otitis
#3	tympanitis OR serous NEXT otitis OR secretory NEXT otitis OR otitis NEXT serosa
#4	mucoid NEAR otitis OR mucous NEAR otitis OR seromuco* NEAR otitis OR sero NEXT muco* NEAR otitis
#5	mucoid NEAR middle NEXT ear OR mucous NEAR middle NEXT ear OR seromuc* NEAR middle NEXT ear
#6	adhesive NEAR otitis OR exudative NEAR otitis
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	MeSH descriptor: [Medicine, Traditional] explode all trees
#9	MeSH descriptor: [Medicine, African Traditional] explode all
#10	MeSH descriptor: [Medicine, Arabic] explode all trees
#11	MeSH descriptor: [Medicine, Ayurvedic] explode all trees
#12	MeSH descriptor: [Medicine, Chinese Traditional] explode all trees
#13	MeSH descriptor: [Medicine, East Asian Traditional] explode all trees
#14	MeSH descriptor: [Medicine, Kampo] explode all trees
#15	MeSH descriptor: [Medicine, Korean Traditional] explode all trees
#16	MeSH descriptor: [Medicine, Mongolian Traditional] explode all trees
#17	MeSH descriptor: [Medicine, Tibetan Traditional] explode all trees
#18	MeSH descriptor: [Plants] explode all trees
#19	MeSH descriptor: [Plants, Medicinal] explode all trees
#20	MeSH descriptor: [Phytotherapy] explode all trees
#21	MeSH descriptor: [Ethnopharmacology] explode all trees
#22	MeSH descriptor: [Ethnobotany] explode all trees
#23	herb* OR plant* OR plant* extract
#24	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
#25	#7 and #24

Table 2 Medline(PubMed)

#1 otitis media with effusion[MeSH Terms]
#2 glue ear
#3 otitis AND media AND effusion*
#4 middle AND ear AND effusion*
#5 nonsuppurative AND otitis
#6 nonsuppurative otitis
#7 tympanitis
#8 serous otitis
#9 secretory otitis
#10 otitis serosa
#11 mucoid AND otitis
#12 mucous AND otitis
#13 seromuco* AND otitis
#14 mucoid AND middle ear
#15 mucous AND middle ear
#16 seromuc* AND middle ear
#17 adhesive AND otitis
#18 exudative AND otitis
#19 or/#1-18
#20 medicine, african traditional[MeSH Terms]
#21 medicine, arabic[MeSH Terms]
#22 medicine, ayurvedic[MeSH Terms]
#23 medicine, traditional[MeSH Terms]
#24 medicine, korean traditional[MeSH Terms]
#25 medicine, kampo[MeSH Terms]
#26 medicine, chinese traditional[MeSH Terms]
#27 Medicine, Tibetan Traditional[MeSH Terms]
#28 Drugs, Chinese Herbal[MeSH Terms]
#29 Medicine, Mongolian Traditional[MeSH Terms]
#30 herb, medicinal[MeSH Terms]

#31 herbal therapy[MeSH Terms]
#32 medicinal plants[MeSH Terms]
#33 plant extracts[MeSH Terms]
#34 ethnobotany[MeSH Terms]
#35 ethnopharmacology[MeSH Terms]
#36 phytotherapy[MeSH Terms]
#37 Plants[MeSH Terms]
#38 herb*[Title/Abstract]
#39 or/#20-38
#40 #19 and #39

Table 3. EMBASE

#1	'secretory otitis media'/exp
#2	'glue'/exp OR glue AND ('ear'/exp OR ear)
#3	'otitis'/exp OR otitis AND media AND ('effusion'/exp OR effusion)
#4	middle AND ('ear'/exp OR ear) AND effusion*
#5	nonsuppurative AND ('otitis'/exp OR otitis)
#6	non AND suppurative AND ('otitis'/exp OR otitis)
#7	'tympanitis'/exp OR tympanitis
#8	serous AND ('otitis'/exp OR otitis)
#9	'serous otitis media'/exp OR 'serous otitis media'
#10	'secretory otitis media'/exp OR 'secretory otitis media'
#11	'otitis'/exp OR otitis AND ('serosa'/exp OR serosa)
#12	mucoid AND ('otitis'/exp OR otitis)
#13	mucous AND ('otitis'/exp OR otitis)
#14	seromuco* AND ('otitis'/exp OR otitis)
#15	sero AND muco* AND ('otitis'/exp OR otitis)
#16	mucoid AND middle AND ('ear'/exp OR ear)
#17	mucous AND middle AND ('ear'/exp OR ear)
#18	seromuc* AND middle AND ('ear'/exp OR ear)
#19	'adhesive'/exp OR adhesive AND ('otitis'/exp OR otitis)

#20	exudative AND ('otitis'/exp OR otitis)
#21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#22	'traditional medicine'/exp OR 'traditional medicine'
#23	'african medicine'/exp OR 'african medicine'
#24	'ayurvedic medicine'/exp OR 'ayurvedic medicine'
#25	'kampo'/exp OR kampo
#26	'korean medicine'/exp OR 'korean medicine'
#27	'latin american medicine'/exp OR 'latin american medicine'
#28	'mongolian medicine'/exp OR 'mongolian medicine'
#29	'oriental medicine'/exp OR 'oriental medicine'
#30	'tibetan traditional medicine'/exp OR 'tibetan traditional medicine'
#31	'traditional chinese medicine'/exp OR 'traditional chinese medicine'
#32	'herbal medicine'/exp OR 'herbal medicine'
#33	'herbal medicinal product'/exp OR 'herbal medicinal product'
#34	'herbaceous agent'/exp OR 'herbaceous agent'
#35	'medicinal plant'/exp OR 'medicinal plant'
#36	'plant'/exp OR plant
#37	'plant extract'/exp OR 'plant extract'
#38	'phytotherapy'/exp OR phytotherapy
#39	'ethnopharmacology'/exp OR ethnopharmacology
#40	'ethnobotany'/exp OR ethnobotany
#41	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
#42	#21 AND #41

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Dissemination: The systematic review will be published in a peer-reviewed journal. The review will also be disseminated electronically and in print. The review will be updated to inform and guide healthcare practice and policy.

Trial registration number: PROSPERO 2013: CRD42013005430.

Keywords: Herbal medicine, complementary and alternative medicine, otitis media, effusion, systematic review, protocol

Article focus

- The aim of the proposed systematic review is to analyse trial data concerning the efficacy of the oral administration of herbal medicines for otitis media with effusion.

Key messages

- This systematic review will be performed using a comprehensive search strategy and will establish the current status of the evidence using unbiased methods.

Strengths and limitations of this study

- The strength of this systematic review is its extensive, unbiased search of various databases without a language restriction.
- The trial screening and data extraction will be conducted independently by two of the authors.

Introduction

Description of the condition

Otitis media with effusion (OME) is characterised by the presence of middle-ear effusion without the signs and symptoms of an acute ear infection and a disease course of months until recovery. [1-4] Otitis media affects nearly every child at least once, and approximately 90% of children experience an episode of OME before reaching school age. [5 6] The aetiology of OME is uncertain, but poor clearance due to poor Eustachian tube function, local inflammatory reactions, low-grade infection, allergic reactions and adenoidal infection or hypertrophy have been implicated.[7] Many episodes resolve spontaneously within three months, but approximately 35% to 50% of OME patients experience chronic or recurrent states of this disease. Persistent, symptomatic and untreated OME may lead to major functional limitations such as permanent hearing loss, which may delay language, speech and cognitive development. [8-10] The high prevalence and potential complications of OME cause high socioeconomic consequences, the loss of the caregivers' income and working time and the children's time in addition to the medical costs. The combined direct and indirect annual cost of OME was $4 billion in the United States.[4 5]

Description of the intervention

Antibiotics and steroids have been suggested to provide only a marginal benefit, and antihistamines are not recommended in systematic reviews. Thus, based on the current evidence regarding the efficacy of treatments for OME, the recommendation is to not administer medications but instead follow an observational policy for at least three months from its onset. [11-13] The decision to provide surgical treatment is to be considered after 3 months of observation with evaluation of hearing. A review of randomised controlled trials

revealed that the insertion of ventilation tubes reduced the proportion of time spent with effusion compared with watchful waiting. However, surgical treatment may lead to adverse effects, such as tympanosclerosis and tympanic membrane abnormalities. [14 15]

Currently, many patients who are seeking ways to relieve the symptoms associated with chronic OME or to avoid the side effects of conventional treatment have chosen complementary and alternative medicine (CAM). Herbal medicine, a part of CAM, is the medical utilisation of medicinal plants, minerals and animal parts to prevent or treat clinical conditions. [16] According to the survey data, herbal medicine was commonly used to treat respiratory problems, digestive problems, allergies and insomnia. A US survey indicated that 16.4% of patients visiting an internal medicine clinic currently used herbal medicines. [17 18]

How the intervention might work

Many types of herbal medicines are known to have immunomodulatory properties and to show anti-inflammatory efficacy in clinical research. [19-21] In experimental research, herbal medicines reduced swelling and prevented endotoxin-induced otitis media through stimulating the mucociliary system for pathogen clearance. Additionally, many types of herbal medicines had anti-inflammatory and anti-bacterial effects in experiments using an otitis media animal model. [22-26] However, the mechanisms underlying the observed immunomodulatory properties of herbal medicines are currently unclear.

Why it is important to perform this review

Notwithstanding the increased use of herbal medicines in the treatment of otitis media, no systematic reviews assessing the intervention of herbal drugs treatment for OME have been

conducted to date. [16 27] Understanding the efficacy and safety of herbal medicines will allow the appropriate recommendation of an herbal drug treatment for patients.

Objectives

Thus, we propose to undertake a systematic review to assess the safety and efficacy of herbal drugs for the treatment of OME.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs (the group allocation was not purely random but rather determined by a factor such as a birth date, a hospital record number or an alternation) will be included. Cluster RCTs, case studies, case series, qualitative studies and uncontrolled trials will be excluded. Trials that do not provide detailed results will also be excluded. Dissertations and abstracts will be included if these contain sufficient details for critical evaluation. No language restriction will be imposed. If we encounter languages other than English, Koran, and Chinese, we will either contact the original authors or obtain a translation of the manuscript from professional service.

Types of participants

The studies that evaluated patients who had a diagnosis of OME will be included. The diagnostic criteria for OME should be based on the criteria of the American Academy of Pediatrics (AAP) and the American Academy of Otolaryngology and Head and Neck Surgery (AAOHNS).[5] We will exclude studies of patients with ventilation tubes present, patients with an anatomical deformity or patients with other chronic immune-compromised states.

Types of interventions

We will include those trials using the oral administration of herbal medicine alone or as a combined therapy of the oral administration of herbal medicine with a conventional therapy versus the same conventional therapy. Herbal medicine is defined as a single herb, an individually prescribed herbal formula or herbal products extracted from natural herbs. There

is no limitation on the number of herbs used, the dosage, the forms of medication or the duration of the treatment. We will include only the oral administration of the medication.

Types of outcome measures

The following outcome measures will be assessed based on analyses of the data obtained in the included trials:

Primary Outcome

Complete resolution of OME (however measured) at two or three months post-randomisation (resolution in the affected ear in participants with unilateral OME at randomisation and resolution in both ears of those with bilateral OME)

Secondary Outcomes

1. Partial or complete resolution of OME at all possible time points
2. Duration of hearing loss as defined by pure-tone audiometric loss of more than 20 dB
3. Language and speech development
4. Cognitive development
5. Insertion of ventilation tubes
6. Tympanic membrane sequelae
7. Reduction of complication of OME
8. Quality of life
8. Adverse effects likely to be related to treatment

Search methods for identifying the studies

Electronic searches

The electronic searches will be performed using MEDLINE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, the Allied and Complementary Medicine Database (AMED) and the Cochrane Central Register of Controlled Trials (CENTRAL). We will also search three Chinese databases (China Network Knowledge Infrastructure (CNKI), Wangfang Data and VIP Information) and five Korean databases (KoreaMed, the Research Information Service System (RISS), Oriental Medicine Advanced Searching Integrated System (OASIS), DBPIA, and the Korean Studies Information Service System (KISS)).

Searching other resources

Ongoing studies will be sought in the meta-Register of Controlled Trials (mRCT) (www.controlled-trials.com/mrct), Clinical trials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry platform (ICTRP) (http://apps.who.int/trialsearch/), all of which list ongoing trials. The bibliographic references of all of the included trials will be reviewed to identify other relevant studies. We will also contact the authors of the trial studies and experts in the field.

Search strategy

The strategies for searching The Cochrane Library, MEDLINE, and EMBASE databases are presented in Appendix 1. These strategies will be modified for use with other databases.

Data collection and analysis

Selection of studies

Two of the review's authors (Son MJ and Kim YH) will independently screen the titles and abstracts of the searched studies, perform the study selection and record their decisions on a standard eligibility form. The arbitrator (Lee MS) will decide upon the study selection when a consensus cannot be reached. The details of selection process will be shown in PRISMA flow diagram (Figure 1).

Data extraction and management

Two of the authors (Son MJ and Kim YH) will independently extract the data using a standard data extraction form and resolve disagreements through discussion before analysis. When the reported data are insufficient or ambiguous, two of the authors (Kim YE and Lee HW) will contact the corresponding authors of the clinical trials by e-mail or telephone to request additional information or clarification.

Assessment of risk of bias in the included studies

We will independently assess the risk of bias in the eligible studies according to the criteria described in the Cochrane Handbook version 5.1.0, which include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of the outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.[28] The quality of the study will be classified as low, unclear or high risk of bias. If necessary, we will contact the authors of eligible trials for clarification. Any differences in opinion will be resolved by discussion or arbitration involving a third author.

Measures of the treatment effect

For continuous data, we will use the mean difference (MD) to measure the treatment effect at a 95% confidence interval (CI). We will convert other forms of data into MDs. In the case of outcome variables with different scales, we will use the standard mean difference (SMD) with a 95% CI. For dichotomous data, we will present the treatment effects as a relative risk (RR) or risk difference (RD) with 95% CIs. Based on these results, we will calculate the associated numbers needed to treat (NNT).

Unit of analysis issues

Data from parallel-group studies will be included for meta-analysis. If there are cross-over trials, the first phase of the data will be adopted for analysis.

Managing missing data

We will request missing data from the original authors, whenever possible. If it is not possible to do this, we will only analyse the available data.

Assessment of heterogeneity

If a meta-analysis is possible, we will use the I^2 statistic to quantify the inconsistencies among the included studies. An I^2 value of >50% will be considered indicative of substantial heterogeneity.[31] If heterogeneity is observed, we will conduct a subgroup analysis to explore its possible causes.[31]

Assessment of reporting biases

We will prepare funnel plots to assess the reporting biases if sufficient studies are available (at least 10 trials).[29] However, funnel plot asymmetry is not the same as publication bias;

therefore, we will attempt to distinguish the different possible reasons for the asymmetry, such as small-study effects, poor methodological quality and the true heterogeneity of the included studies. [29 30]

Data synthesis

Data synthesis for comparable trials with comparable outcomes will be performed using Review Manager (RevMan), Version 5.2.6.

Subgroup analysis and investigation of heterogeneity

If the data are available, a predefined subgroup analysis will be conducted to assess the heterogeneity of different studies, including the following:

1. Laterality of OME: bilateral OME versus unilateral OME

2. Duration of OME: any duration of OME versus persistent OME (lasting for more than two or three months)

3. Duration of treatment

4. Type of herbal medicine

5. Type of control

6. Type of age group (participants aged over 18 years versus children aged two years or more versus children younger than two years)

Sensitivity analysis

Sensitivity analysis will principally be performed as follows:

1. Sample size (e.g., more or less than 40 participants in each group)

2. Low risk of bias (e.g., allocation concealment or the blinding of participants/assessors)

Discussion

Because no primary data collection will be undertaken, no additional formal ethical assessment or informed consent is required. The systematic review will be published in a peer-reviewed journal. It will also be disseminated electronically and in print. The review will be updated, and a GRADE evaluation of the quality of evidence will be conducted to provide summaries of the future state of the evidence for the efficacy of interventions utilising herbal drugs on OME. The review may guide healthcare practices and policies regarding the oral administration of herbal medicines to treat OME.

Contributors

The protocol was drafted by all authors. It was revised and the final version approved by all authors.

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Conflicts of interest

None known

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Figure legends

Figure 1. Study selection flow diagram

Appendix 1. Search strategies

Table 1 The Cochrane Library (Wiley Online Library)

#1	MeSH descriptor: [Otitis Media with Effusion] explode all trees
#2	glue NEXT ear OR otitis NEXT media NEAR effusion* OR middle NEXT ear NEAR effusion* OR nonsuppurative NEXT otitis OR non NEXT suppurative NEXT otitis
#3	tympanitis OR serous NEXT otitis OR secretory NEXT otitis OR otitis NEXT serosa
#4	mucoid NEAR otitis OR mucous NEAR otitis OR seromuco* NEAR otitis OR sero NEXT muco* NEAR otitis
#5	mucoid NEAR middle NEXT ear OR mucous NEAR middle NEXT ear OR seromuc* NEAR middle NEXT ear
#6	adhesive NEAR otitis OR exudative NEAR otitis
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	MeSH descriptor: [Medicine, Traditional] explode all trees
#9	MeSH descriptor: [Medicine, African Traditional] explode all
#10	MeSH descriptor: [Medicine, Arabic] explode all trees
#11	MeSH descriptor: [Medicine, Ayurvedic] explode all trees
#12	MeSH descriptor: [Medicine, Chinese Traditional] explode all trees
#13	MeSH descriptor: [Medicine, East Asian Traditional] explode all trees
#14	MeSH descriptor: [Medicine, Kampo] explode all trees
#15	MeSH descriptor: [Medicine, Korean Traditional] explode all trees
#16	MeSH descriptor: [Medicine, Mongolian Traditional] explode all trees
#17	MeSH descriptor: [Medicine, Tibetan Traditional] explode all trees
#18	MeSH descriptor: [Plants] explode all trees
#19	MeSH descriptor: [Plants, Medicinal] explode all trees
#20	MeSH descriptor: [Phytotherapy] explode all trees
#21	MeSH descriptor: [Ethnopharmacology] explode all trees
#22	MeSH descriptor: [Ethnobotany] explode all trees
#23	herb* OR plant* OR plant* extract
#24	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
#25	#7 and #24

Table 2 Medline(PubMed)

#1 otitis media with effusion[MeSH Terms]
#2 glue ear
#3 otitis AND media AND effusion*
#4 middle AND ear AND effusion*
#5 nonsuppurative AND otitis
#6 nonsuppurative otitis
#7 tympanitis
#8 serous otitis
#9 secretory otitis
#10 otitis serosa
#11 mucoid AND otitis
#12 mucous AND otitis
#13 seromuco* AND otitis
#14 mucoid AND middle ear
#15 mucous AND middle ear
#16 seromuc* AND middle ear
#17 adhesive AND otitis
#18 exudative AND otitis
#19 or/#1-18
#20 medicine, african traditional[MeSH Terms]
#21 medicine, arabic[MeSH Terms]
#22 medicine, ayurvedic[MeSH Terms]
#23 medicine, traditional[MeSH Terms]
#24 medicine, korean traditional[MeSH Terms]
#25 medicine, kampo[MeSH Terms]
#26 medicine, chinese traditional[MeSH Terms]
#27 Medicine, Tibetan Traditional[MeSH Terms]
#28 Drugs, Chinese Herbal[MeSH Terms]
#29 Medicine, Mongolian Traditional[MeSH Terms]
#30 herb, medicinal[MeSH Terms]

#31 herbal therapy[MeSH Terms]
#32 medicinal plants[MeSH Terms]
#33 plant extracts[MeSH Terms]
#34 ethnobotany[MeSH Terms]
#35 ethnopharmacology[MeSH Terms]
#36 phytotherapy[MeSH Terms]
#37 Plants[MeSH Terms]
#38 herb*[Title/Abstract]
#39 or/#20-38
#40 #19 and #39

Table 3. EMBASE

#1	'secretory otitis media'/exp
#2	'glue'/exp OR glue AND ('ear'/exp OR ear)
#3	'otitis'/exp OR otitis AND media AND ('effusion'/exp OR effusion)
#4	middle AND ('ear'/exp OR ear) AND effusion*
#5	nonsuppurative AND ('otitis'/exp OR otitis)
#6	non AND suppurative AND ('otitis'/exp OR otitis)
#7	'tympanitis'/exp OR tympanitis
#8	serous AND ('otitis'/exp OR otitis)
#9	'serous otitis media'/exp OR 'serous otitis media'
#10	'secretory otitis media'/exp OR 'secretory otitis media'
#11	'otitis'/exp OR otitis AND ('serosa'/exp OR serosa)
#12	mucoid AND ('otitis'/exp OR otitis)
#13	mucous AND ('otitis'/exp OR otitis)
#14	seromuco* AND ('otitis'/exp OR otitis)
#15	sero AND muco* AND ('otitis'/exp OR otitis)
#16	mucoid AND middle AND ('ear'/exp OR ear)
#17	mucous AND middle AND ('ear'/exp OR ear)
#18	seromuc* AND middle AND ('ear'/exp OR ear)
#19	'adhesive'/exp OR adhesive AND ('otitis'/exp OR otitis)

#20	exudative AND ('otitis'/exp OR otitis)
#21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#22	'traditional medicine'/exp OR 'traditional medicine'
#23	'african medicine'/exp OR 'african medicine'
#24	'ayurvedic medicine'/exp OR 'ayurvedic medicine'
#25	'kampo'/exp OR kampo
#26	'korean medicine'/exp OR 'korean medicine'
#27	'latin american medicine'/exp OR 'latin american medicine'
#28	'mongolian medicine'/exp OR 'mongolian medicine'
#29	'oriental medicine'/exp OR 'oriental medicine'
#30	'tibetan traditional medicine'/exp OR 'tibetan traditional medicine'
#31	'traditional chinese medicine'/exp OR 'traditional chinese medicine'
#32	'herbal medicine'/exp OR 'herbal medicine'
#33	'herbal medicinal product'/exp OR 'herbal medicinal product'
#34	'herbaceous agent'/exp OR 'herbaceous agent'
#35	'medicinal plant'/exp OR 'medicinal plant'
#36	'plant'/exp OR plant
#37	'plant extract'/exp OR 'plant extract'
#38	'phytotherapy'/exp OR phytotherapy
#39	'ethnopharmacology'/exp OR ethnopharmacology
#40	'ethnobotany'/exp OR ethnobotany
#41	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
#42	#21 AND #41

~~Herbal~~Oral administration of herbal medicines for the treatment of otitis media with effusion: Protocol for a systematic review

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~~Runing~~**Running title:** ~~Herbal~~Oral administration of herbal medicines for otitis media with effusion

~~**Keywords:** Herbal medicine, complementary and alternative medicine, otitis media, effusion, systematic review, protocol~~

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Article focus

- The aim of the proposed systematic review is to analyse trial data concerning the ~~effectiveness~~efficacy of the oral administration of herbal medicines for otitis media with effusion.

Key messages

- This systematic review will be performed using a comprehensive search strategy and will establish the current status of the evidence using unbiased methods.

Strengths and limitations of this study

- The strength of this systematic review is its extensive, unbiased search of various databases without a language restriction.
- The trial screening and data extraction will be conducted independently by two of the authors.

Abstract

Introduction: The purpose of this systematic review is to investigate the ~~effectiveness~~efficacy of the oral administration of herbal medicines for otitis media with effusion (OME) through analysing trial data.

Methods and analysis: Electronic searches of the following eleven databases will be performed: MEDLINE, ~~the Cumulative Index to Nursing and Allied Health Literature (~~CINAHL~~),~~ EMBASE, ~~the Allied and Complementary Medicine Database (~~AMED~~),~~ the Cochrane ~~Central Register of Controlled Trials (~~CENTRAL~~), the China Network Knowledge Infrastructure ~~, three Chinese databases (CNKI, Wangfang Data and VIP Information) and five Korean databases ~~[~~(KoreaMed, Research Information Service System, Korea Studies Information System, Oriental Medicine Advanced Searching Integrated System (OASIS~~),~~ ~~DBPIA, Korea Med, Research Information Service System (RISS) and the Korean Studies Information Service System (KISS)]~~.) and DBpia). The selection of the studies, data abstraction, and validations will be performed independently by two researchers.

Dissemination: The systematic review will be published in a peer-reviewed journal. The review will also be disseminated electronically and in print. ~~Updates of the~~The review will be ~~conducted~~updated to inform and guide healthcare practice and policy.

Trial registration number: PROSPERO 2013: CRD42013005430.

Keywords: Herbal medicine, complementary and alternative medicine, otitis media, effusion, systematic review, protocol

Introduction

Description of the condition

Otitis media with effusion (OME) is characterised ~~as~~by the presence of middle-ear effusion without the signs and symptoms of an acute ear infection and a disease course of months until recovery~~ [1-4]. OM~~. [1-4] Otitis media affects nearly every child at least once, and approximately 90% of children experience an episode of OME before reaching school age. [5 6] The aetiology of OME is uncertain, but poor clearance due to ~~incomplete~~poor Eustachian tube ~~functioning~~function, local inflammatory reactions, low-grade infection, allergic reactions and adenoidal infection or ~~inflammation following acute otitis media (AOM) [5 6]. Approximately~~hypertrophy have been implicated.[7] Many episodes resolve spontaneously within three months, but approximately 35% to 50% of OME patients ~~have~~experience chronic or recurrent states~~. When inadequately treated, OME can cause~~ of this disease. Persistent, symptomatic and untreated OME may lead to major functional limitations such as permanent hearing loss, which may delay language, speech and cognitive development~~ [7-9]. .~~ [8-10] The high prevalence and potential complications of OME cause high socioeconomic consequences, the loss of the caregivers' income and working time and the children's time in addition to the medical costs. The combined direct and indirect annual cost of OME was $4 billion in the United States.[4 5]

Description of the intervention

~~OME has high socioeconomic consequences, and the annual cost of OME was $4 billion.[4 5] Patients with OME are treated with antibiotics, antihistamines, steroids and the insertion of ventilation tubes. However, antibiotics~~Antibiotics and steroids have been suggested to

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provide only a marginal benefit, and antihistamines are not recommended in systematic reviews~~.[10-12]~~. Thus, based on the current evidence regarding the efficacy of treatments for OME, the recommendation is to not administer medications but instead follow an observational policy for at least three months from its onset. [11-13] The decision to provide surgical treatment is to be considered after 3 months of observation with evaluation of hearing. A review of randomised controlled trials revealed that the insertion of ventilation tubes reduced the proportion of time spent with effusion compared with watchful waiting. However, ~~ventilation tubes~~surgical treatment may lead to adverse effects, such as tympanosclerosis and tympanic membrane abnormalities~~.[13-14].~~ [14 15]

~~***How the intervention might work***~~

Currently, many patients who are seeking ways to relieve the symptoms associated with chronic OME or to avoid the side effects of conventional treatment have chosen complementary and alternative medicine (CAM~~) [15].~~ Herbal medicine, a part of CAM, is the ~~use~~medical utilisation of medicinal plants, minerals and animal parts ~~for preventing~~ to prevent or ~~treating~~treat clinical conditions. [16] According to the survey data, herbal medicine was commonly used to treat respiratory problems, digestive problems, allergies and insomnia. A US survey indicated that 16.4% of patients visiting an internal medicine clinic currently used herbal medicines. [17 18]

How the intervention might work

Many types of herbal medicines are known to have ~~an~~immunomodulatory properties and to show anti-inflammatory ~~effects and have been to reduce~~efficacy in clinical research. [19-21] In

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experimental research, herbal medicines reduced swelling and ~~prevent~~prevented endotoxin-induced ~~OME in experimental investigations [16 20].~~ otitis media through stimulating the mucociliary system for pathogen clearance. Additionally, many types of herbal medicines had anti-inflammatory and anti-bacterial effects in experiments using an otitis media animal model. [22-26] However, the mechanisms underlying the observed immunomodulatory properties of herbal medicines are currently unclear.

Why it is important to perform this review

~~Herbal medicine has been approved by~~Notwithstanding the ~~World Health Organization as a therapy for~~ increased use of herbal medicines in the treatment of ~~OME [15 21]. However~~otitis media, no systematic reviews assessing the intervention of herbal drugs treatment ~~in~~for OME have been conducted to date. [16 27] Understanding the ~~effectiveness~~efficacy and safety of herbal medicines will allow the appropriate recommendation of an herbal drug treatment for patients.

Objectives

Thus, we ~~will~~propose to undertake a systematic review to assess the safety and efficacy of herbal drugs for the treatment of OME.

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Methods

Criteria for considering studies for this review

Types of studies

~~The review will include randomised~~Randomised controlled trials~~, including cluster randomised trials. Quasi randomised trials, in which~~ (RCTs) and quasi-RCTs (the group allocation was not purely random but rather determined by a factor such as a birth date, a hospital record number or ~~alternation, will be included. Any trials without parallel comparisons or control groups will be excluded.~~an alternation) will be included. Cluster RCTs, case studies, case series, qualitative studies and uncontrolled trials will be excluded. Trials that do not provide detailed results will also be excluded. Dissertations and abstracts will be included if these contain sufficient details for critical evaluation. No language restriction will be imposed. If we encounter languages other than English, Koran, and Chinese, we will either contact the original authors or obtain a translation of the manuscript from professional service.

Types of participants

The ~~review will include~~ studies ~~evaluating~~that evaluated patients who had a diagnosis of OME~~.~~ will be included. The diagnostic criteria for OME should be based on the criteria of ~~the WHO,~~ the American Academy of Pediatrics (AAP) and the American Academy of Otolaryngology and Head and Neck Surgery (AAOHNS~~), but if necessary, trials for which the definition of OME used by the authors is in question will also be included.~~).[5] We will exclude studies of patients with ventilation tubes present, patients with an anatomical deformity or patients with other chronic immune-compromised states.

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Types of interventions

~~The review~~We will include those trials using the oral administration of herbal medicine alone or as a combined therapy of the oral administration of herbal medicine with a conventional therapy versus the same conventional therapy. Herbal medicine is defined as a single herb, an individually prescribed herbal formula or herbal products extracted from natural herbs. There is no limitation on the number of herbs used, the dosage, the forms of medication or the duration of the treatment. We will include only the oral administration of the medication.

Types of outcome measures

The following outcome measures will be assessed based on analyses of the data obtained in the included trials~~.~~:

Primary Outcome

~~Resolution of symptoms or signs (however measured)~~

Complete resolution of OME (however measured) at two or three months post-randomisation (resolution in the affected ear in participants with unilateral OME at randomisation and resolution in both ears of those with bilateral OME)

Secondary Outcomes

1. Partial or complete resolution of OME at all possible time points

2. Duration of ~~effusion~~

~~2. Hearing level~~hearing loss as defined by pure-tone audiometric loss of more than 20 dB

3. Language and speech development

4. Cognitive development

5. Insertion of ventilation tubes

6. ~~New AOM~~Tympanic membrane sequelae

~~7. Tympanic membrane sequelae~~

7. Reduction of complication of OME

8. Quality of life~~.~~

~~9~~8. Adverse effects likely to be related to treatment

Search methods for identifying the studies

Electronic searches

The electronic searches will be performed using MEDLINE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, the Allied and Complementary Medicine Database (AMED) and the Cochrane Central Register of Controlled Trials (CENTRAL). We will also search ~~one~~three Chinese ~~database [~~databases (China Network Knowledge Infrastructure (CNKI~~)~~), Wangfang Data and VIP Information) and five Korean databases ~~[~~(KoreaMed, the Research Information Service System (RISS), Oriental Medicine Advanced Searching Integrated System (OASIS), DBPIA, ~~Korea Med, the Research Information Service System (RISS) and~~ and the Korean Studies Information Service System (KISS~~)]~~.)).

Searching other resources

~~The reference lists of review articles and the retrieved articles will be examined to find additional~~Ongoing studies~~. Additional trials~~ will be sought in the meta-Register of Controlled Trials (~~m RCT~~mRCT) (www.controlled-trials.com/mrct), Clinical trials.gov

(www.clinicaltrials.gov) and the WHO International Clinical Trials Registry platform (ICTRP) (http://apps.who.int/trialsearch~~/) for all of which list ongoing trials~~/), all of which list ongoing trials. The bibliographic references of all of the included trials will be reviewed to identify other relevant studies. We will also contact the authors of the trial studies and experts in the field.

Search strategy

The strategies for searching The Cochrane Library, MEDLINE, and EMBASE databases are presented in Appendix 1. These strategies will be modified for use with other databases.

Data collection and analysis

Selection of studies

Two of the review's authors (Son MJ and Kim YH) will independently screen the titles and abstracts of the searched studies, perform the study selection and record their decisions on a standard eligibility form. The arbitrator (Lee MS) will decide upon the study selection when a consensus cannot be reached. The details of selection process will be shown in PRISMA flow diagram (Figure 1).

~~Inclusion Criteria~~

~~1. In randomised cross-over trials, only the data from the first period will be included to avoid the carry-over effect~~

~~2. No language limitation~~

~~3. No publication status restriction~~

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~~Exclusion Criteria~~

~~1. Animal experiments~~

~~2. Non-randomised clinical trials~~

~~3. Case report/series, news items, and letters~~

~~4. Qualitative studies~~

Data extraction and management

Two of the authors (Son MJ and Kim YH) will independently extract the data using a standard data extraction form and resolve disagreements through discussion before analysis. When the reported data are insufficient or ambiguous, two of the authors (Kim YE and Lee HW) will contact the corresponding authors of the clinical trials by e-mail or telephone to request additional information or clarification.

Assessment of risk of bias in the included studies

We will independently assess the risk of bias in the eligible studies according to the criteria described in the Cochrane Handbook version 5.1.0, which include random sequence generation, allocation concealment, ~~the blinding of participants and personnel, the blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias [22].~~ blinding of participants and personnel, blinding of the outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.[28] The quality of the study will be classified as low, unclear or high risk of bias. If necessary, we will contact the authors of eligible trials for clarification. Any differences in opinion will be resolved by discussion or arbitration involving a third author.

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~~Assessment of reporting biases~~

~~We will prepare funnel plots to assess the reporting biases if sufficient studies are available (at least 10 trials) [23]. However, funnel plot asymmetry is not the same as publication bias; therefore, we will attempt to distinguish the different possible reasons for the asymmetry, such as small study effects, poor methodological quality and true heterogeneity of the included studies [23 24].~~

~~Measurement~~Measures of the treatment effect

For continuous data, we will use the mean difference (MD) to measure the treatment effect ~~with~~at a 95% confidence ~~intervals (CIs~~interval (CI). We will convert other forms of data into MDs. In the case of outcome variables with different scales, we will use the standard mean difference (SMD) with a 95% ~~CIs~~CI. For dichotomous data, we will present the treatment effects as a relative risk (RR) or risk difference (RD) with 95% CIs. ~~We~~Based on these results, we will ~~convert other binary data into~~calculate the ~~RR form~~associated numbers needed to treat (NNT).

~~Strategy for missing data~~

~~We will conduct intention-to-treat analyses that include all~~Unit of ~~the randomised patients. A carry-forward of the last observed response~~analysis issues

Data from parallel-group studies will be ~~used~~included for meta-analysis. If there are cross-over trials, the first phase of the data will be adopted for ~~patients with~~analysis.

Managing missing data

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We will request missing ~~outcome data. We will seek the individual patient~~ data from the original ~~source or the published trial reports when the individual patient~~authors, whenever possible. If it is not possible to do this, we will only analyse the available data ~~are unavailable.~~

Assessment of heterogeneity

If a meta-analysis is possible, we will use the I^2 statistic to quantify the inconsistencies among the included studies. An I^2 value of >50% will be considered indicative of substantial heterogeneity.[31] If heterogeneity is observed, we will conduct a subgroup analysis to explore its possible causes.[31]

Assessment of reporting biases

We will prepare funnel plots to assess the reporting biases if sufficient studies are available (at least 10 trials).[29] However, funnel plot asymmetry is not the same as publication bias; therefore, we will attempt to distinguish the different possible reasons for the asymmetry, such as small-study effects, poor methodological quality and the true heterogeneity of the included studies. [29 30]

~~Assessment of heterogeneity~~

~~If a meta-analysis is possible, we will use the I^2 statistic to quantify the inconsistencies among the included studies. An I^2 value >50% will be considered indicative of substantial heterogeneity [25]. If heterogeneity is observed, we will conduct subgroup analysis to explore the possible causes [25].~~

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Data synthesis

Data synthesis for comparable trials with comparable outcomes will be performed using Review Manager (RevMan), Version 5.~~0, for Windows software. The primary meta-analyses will be performed using random effects models due to the expected inter-trial heterogeneity.~~2.6.

Subgroup analysis and investigation of heterogeneity

If ~~there is~~the data are available, a ~~sufficient number of studies,~~predefined subgroup ~~analyses~~analysis will be conducted to assess the heterogeneity ~~between the~~of different studies, including the following:

1. Laterality of OME: bilateral OME versus unilateral OME

2. Duration of OME: any duration of OME versus persistent OME (lasting for more than two or three months)

3. Duration of treatment

4. Type of herbal medicine

~~2~~5. Type of control

~~3. Type of age group.~~

6. Type of age group (participants aged over 18 years versus children aged two years or more versus children younger than two years)

Sensitivity analysis

~~If an adequate number of studies are available, sensitivity analyses will be performed to determine whether the findings are robust. The following aspects will be considered.~~

Sensitivity analysis will principally be performed as follows:

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1. Sample size (e.g., more or less than ~~30~~40 participants in each group)

2. ~~Methodological qualities~~Low risk of bias (e.g., allocation concealment or the blinding of participants/assessors)

~~3. Analysis related issues (e.g., processes for handling missing data)~~

Discussion

Because no primary data collection will be undertaken, no additional formal ethical assessment or informed consent is required. The systematic review will be published in a peer-reviewed journal. It will also be disseminated electronically and in print. ~~Updates of the~~ The review will be updated, and a GRADE evaluation of the quality of evidence will be conducted to provide ~~a summary~~summaries of the ~~current~~future state of the evidence for the ~~effectiveness~~efficacy of interventions utilising herbal drugs on OME ~~and to~~. The review may guide healthcare ~~practice~~practices and ~~policy~~policies regarding the oral administration of herbal medicines to treat OME.

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Contributors

The protocol was drafted by all authors. It was revised and the final version approved by all authors.

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Conflicts of interest

None known

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Figure legends

Figure 1. Study selection flow diagram

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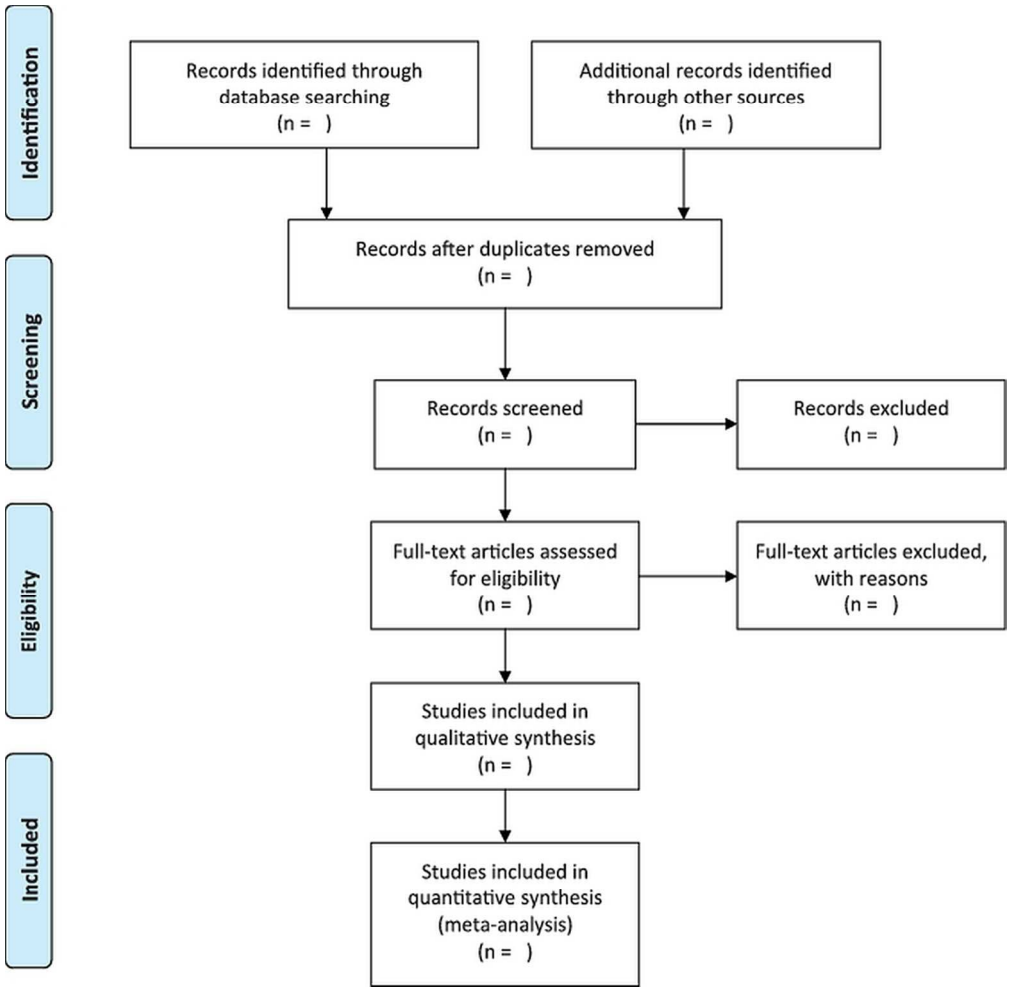

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