

BMJ Open Oral administration of herbal medicines for the treatment of otitis media with effusion: protocol for a systematic review

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ABSTRACT

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

Methods and analysis: Electronic searches of the following 11 databases will be performed: MEDLINE, CINAHL, EMBASE, AMED, the Cochrane CENTRAL, 3 Chinese databases (CNKI, Wangfang Data and VIP Information) and 5 Korean databases (KoreaMed, Research Information Service System, Korea Studies Information System, Oriental Medicine Advanced Searching Integrated System (OASIS) 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. The review will be updated 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 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 3 months, but approximately 35–50% of patients with OME

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.
- Our systematic review may pertain to the potential incompleteness of the evidence reviewed, including publication and location bias, poor quality of the primary data and poor reporting of results.

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 medical costs. The combined direct and indirect annual cost of OME was US\$4 billion in the USA.^{4 5}

Description of the intervention

Antibiotics and steroids have been suggested to provide only a marginal benefit, and anti-histamines 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 3 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



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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 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 antibacterial 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, Korean 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 immunocompromised 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 2 or 3 months postrandomisation (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
9. Adverse effects likely to be related to treatment

Search methods for identifying the studies

Electronic searches

Electronic search will be conducted 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; <http://www.controlled-trials.com/mrct>), Clinical trials.gov (<http://www.clinicaltrials.gov>) and the WHO International Clinical Trials Registry platform (ICTRP; <http://apps.who.int/trialsearch/>), 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 online supplementary 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 (MJS and YHK) 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 (MSL) will decide on 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 (MJS and YHK) 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 (Y-EK and HWL) will contact the corresponding authors of the clinical trials by email 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 V.5.1.0, which include random

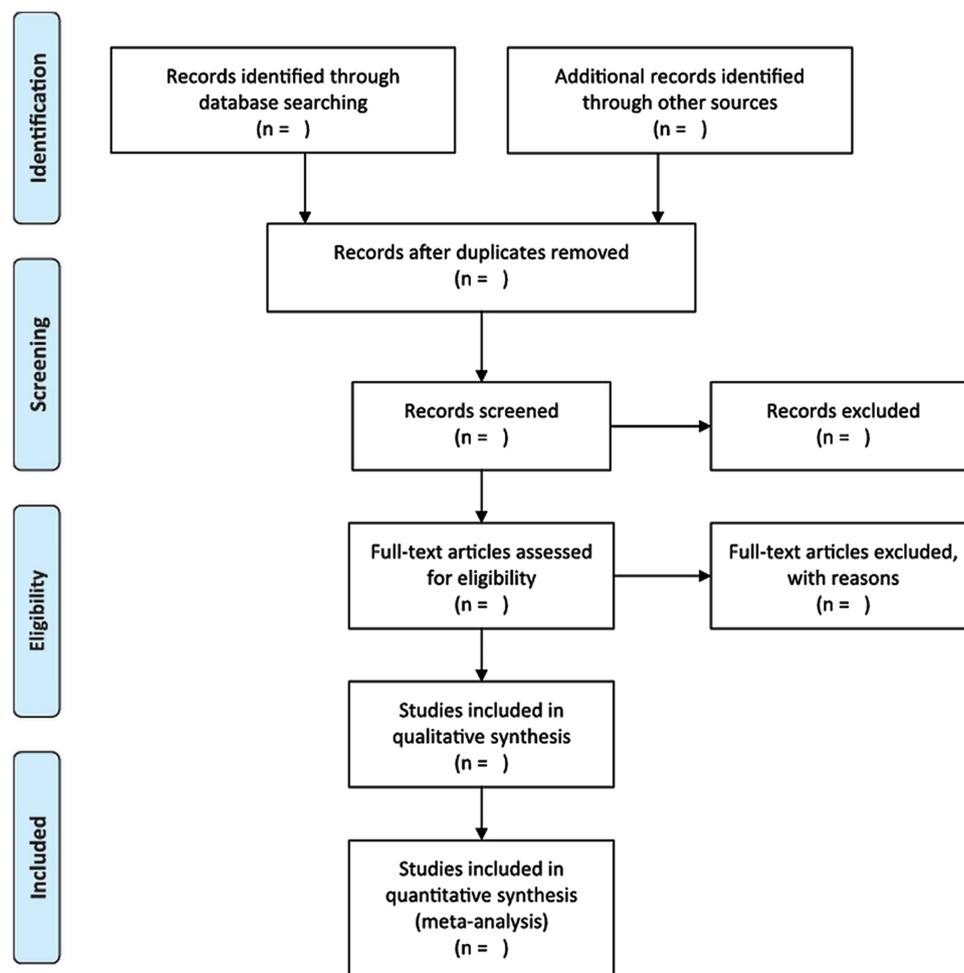


Figure 1 Study selection flow diagram.

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% CI. We will convert other forms of data into MDs. In the case of outcome variables with different scales, we will use the standard MD with a 95% CI. For dichotomous data, we will present the treatment effects as a relative risk or risk difference with 95% CIs. Based on these results, we will calculate the associated numbers needed to treat.

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.²⁹ If heterogeneity is observed, we will conduct a subgroup analysis to explore its possible causes.²⁹

Assessment of reporting biases

We will prepare funnel plots to assess the reporting biases if sufficient studies are available (at least 10 trials).³⁰ 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.^{30 31}

Data synthesis

Data synthesis for comparable trials with comparable outcomes will be performed using Review Manager (RevMan), V.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 2 or 3 months);
3. Duration of treatment;
4. Type of herbal medicine;
5. Type of control;
6. Type of age group (participants aged over 18 years vs children aged 2 years or more vs children younger than 2 years).

Sensitivity analysis

Sensitivity analysis will principally be performed as follows:

1. Sample size (eg, more or less than 40 participants in each group);
2. Low risk of bias (eg, allocation concealment or the blinding of participants/assessors).

DISCUSSION

As primary data collection will not 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.

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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
