Brazilian medicinal plants to treat upper respiratory tract and bronchial illness: systematic review and meta-analyses—study protocol

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ABSTRACT

Introduction: Respiratory illness, often associated with cough and sputum, is frequent. In Brazil, herbal medicines are often recommended as a first-line treatment for respiratory illness. There exists uncertainty regarding the effectiveness of these treatments. No systematic review has evaluated Brazilian medicinal plants (BMP) to treat upper respiratory tract and bronchial illness (URTI).

Methods and analysis: We will conduct a systematic review and, if appropriate, a series of meta-analyses evaluating the safety and effectiveness of BMP for URTI. Eligible randomised controlled trials and observational studies will enrol adult or paediatric patients presenting with URTI treated by BMP approved by the Brazilian Health Surveillance Agency compared with placebo, no treatment or an alternative therapy. Our search will include the Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Acute Respiratory Illness Group's Specialized Register; MEDLINE; EMBASE; CINAHL (Cumulative Index to Nursing and Allied Health Literature); Web of Science; AMED; LILACS; CAB abstracts; clinical trial.gov; the WHO Trial Register and the Brazilian thesis database (CAPES) without any language restrictions. Outcomes of interest are time to resolution of clinical symptoms and/or signs (cough, sputum production or activity limitations), severity of symptoms prior to resolution and major/minor adverse events. Teams of reviewers will, independently and in duplicate, screen titles and abstracts and the complete full text to determine eligibility. For eligible studies, reviewers will perform data abstraction and assess risk of bias of eligible trials. When appropriate, we will conduct meta-analyses. We will also assess the quality of body of evidence (confidence in estimates of effect) for each of the outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Ethics and dissemination: The systematic review will be published in a peer-reviewed journal. Brief reports of review findings will be disseminated directly to appropriate audiences via email and other modes of communication. The review will guide healthcare practice and policy in Brazil.

Strengths and limitations of this study

- This will be the first systematic review to assess Brazilian medicinal plants approved by the Brazilian Health Surveillance Agency (ANVISA) to treat upper respiratory tract and bronchial illness associated with cough and sputum.
- The results of this systematic review will help clinicians in making decisions in clinical practice and also help patients with cough and sputum seeking effective and safe treatment options.
- The methods of the review are state of the art, including explicit eligibility criteria, a comprehensive search, an independent duplicate assessment of eligibility and use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess confidence in estimates of effect including independent assessment of risk of bias, precision, consistency, directness and publication bias. We will make separate ratings for bodies of evidence from randomised trials and from observational studies.
- Since primary studies are likely to be limited to non-randomised studies and randomised trials with a high risk of bias confidence in estimates is likely to be low. Eligible studies will likely differ substantially in study design and outcome measures. The exact constituents of the plants being tested are likely to be associated with some uncertainty.

INTRODUCTION
Use of herbal medicines is frequent, particularly in Brazil
In high-income countries, there is increasing public interest in, and use of, a wide range of therapies that lie outside the mainstream of

traditional Western medical practice.[1] [2] Complementary and alternative medicine (CAM) has grown rapidly over the past two decades.[1] In the USA, approximately 38% of adults and approximately 12% of children are using some form of CAM.[3] In Brazil, of the total revenues of the pharmaceutical industry from sales of drugs in the period from 1996 to the present, up to 25% came from preparations derived from plants.[4] The government's decision to include herbal medicine in the list of publicly subsidised medicine in the Brazilian Health System (SUS) may have contributed to an increase in expenditures on herbal medicine in Brazil of 12% in 2012 over 2011, with a total of $1.147 billion.[5]

The license approval process for herbal medicines varies across countries, including wide variation in the evidence of effectiveness required for licensing.[6] [7] Licensing requirements in some countries, including Brazil, require only evidence of long-standing and widespread use of a plant. In such countries, the extent of pharmacovigilance of licensed products differs; relatively rigorous pharmacovigilance exists in Australia,[8] Canada, Germany, among others, but not in Brazil.[7] [9]

In many countries, traditional herbal medicines are available over the counter (OTC; ie, there is no need for a prescription for their purchase or use[3]). These medications are typically not recommended for serious medical conditions, but rather as adjunctive treatments and for short-term use in conditions that are not serious.[10] [11] Aside from Brazil, there is no country that provides public support for payment for herbal medicines approved only on the basis of long-standing and widespread prior use. Nowadays Brazil has a list of 12 such herbal medicines funded by the government.[12] [13]

Primary care physicians often recommend herbal medicines to their patients as the first line of treatment.[14] This is particularly the case in Brazil, perhaps encouraged by government funding for these drugs. Furthermore, people frequently self-prescribe OTC cough medications. One reason for concern about this widespread use is that patients are less likely to consult their general practitioner because of an adverse reaction to a herbal remedy than for a conventional medicine.[15]

Respiratory illness and herbal medicine
Respiratory illness, in particular upper respiratory tract and bronchial illness (URTI), often with associated cough and sputum, is frequent[16] and a major cause of morbidity, especially in children and the elderly.[17] Although in most cases benign,[18] respiratory illness is a cause for concern for parents[19] and a major cause of outpatient visits in most settings.[20–23] URTI can adversely impact on quality of life.[24] Patients spend billions of dollars annually on OTC medications for URTI and, in particular, for the frequently accompanying cough symptoms.[25]

Numerous OTC cough preparations are available, but a Cochrane review that does not address the plants that are the topic of the current review suggests that there is no conclusive evidence regarding their efficacy.[26] [27] In children, OTC medications may be associated with serious adverse events such as death, altered consciousness and arrhythmias.[28–32]

A search in the database of the Brazilian Health Surveillance Agency (ANVISA) revealed that 15 species of herbal medicines are approved for treatment of acute cough from a URTI. Of these, Public Health System (SUS) funding is available for two. There are no systematic reviews available that address the benefits and harms of the herbal medication approved by ANVISA for URTI. Identification of ineffective preparations could reduce costs for consumers and healthcare providers, and reduce the risk of adverse events from treatments with no benefit.[27] This current systematic review therefore aims to collect the evidence to evaluate the effectiveness and safety of 15 Brazilian herbal medicines currently approved for management of cough from a URTI.

OBJECTIVES
The primary objective is to address the safety and efficacy of 15 Brazilian herbal medicines approved by ANVISA for acute cough from a URTI.

METHODS AND ANALYSES
The systematic review will be performed according to the recommendations specified in the Cochrane Handbook for Intervention Reviews.[33] The reporting of the review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[34]

Protocol and registration
Our protocol is registered on PROSPERO (CRD42014007057), and is available from http://www.crd.york.ac.uk/PROSPERO

Eligibility criteria for considering studies for review
Inclusion criteria
Patients: Studies must include patients with adult (>18 years old) or paediatric (0–18 years old) patients with upper respiratory disease: the common cold, sinusitis, tonsillitis, otitis media, pharyngitis or laryngitis; or symptoms arising from the upper part of the lower respiratory tract (either secondary to upper respiratory tract symptoms—eg, postnasal drip—or to acute bronchitis or bronchiolitis).

Interventions: Studies must include an arm in which patients are taking one of the Brazilian herbal medicines from any of the following plant preparations (whole, powder, extract, standardised mixture) with one of the select plants:

Ananas comosus (L.) Merr., Bromeliaceae;
Echinacea purpurea (L.) Moench, Asteraceae;
Eucalyptus globulus Labill., Myrtaceae;
Glycyrrhiza glabra L., Fabaceae;
Hedera helix L., Araliaceae;

Malva sylvestris L., Malvaceae;

Mentha spp (Mentha x piperita L., Mentha x villosa Huds., or other hybrids), Lamiaceae;

Mikania glomerata Spreng.or Mikania laevigata Sch.Bip. ex Baker, Asteraceae;

Pelargonium sidoides DC., Geraniaceae;

Petasites hybridus (L.) G. Gaertn., B. Mey. & Scherb., Asteraceae;

Pimpinella anisum L., Apiaceae;

Polygala senega L., Polygalaceae;

Psychotria ipecacuanha (Brot.) Stokes or Cephaelis ipe-cacuanha (Brot.) A. Rich., Rubiaceae;

Sambucus nigra L., Adoxaceae.

Outcome measures

We will include studies that report any of the following outcomes:

- ▶ Time to resolution of clinical symptoms and/or signs (eg, cough, sputum production);
- ▶ Frequency and severity of symptoms prior to resolution;
- ▶ Minor and serious adverse effects of the intervention and the proportion of patients requiring discontinuation of the herbal medicine;
- ▶ Hospitalisation rates;
- ▶ Duration of hospital stay;
- ▶ Days receiving antibiotics;
- ▶ Functional status (including number of days of disability that may be defined as days in bed, days off work or days when patients were unable to undertake normal activities);
- ▶ Quality of life measured by a validated instrument. The score will be evaluated using the Cough-Specific Quality-of-Life Questionnaire,[24] the Leicester Cough Questionnaire[35] or other validated questionnaires.

Study design

We will include (1) any comparison (randomised controlled trials or observational study) including an arm in which patients received one of the herbal medicines listed above via any route of administration compared to an arm in which patients receive an inert (placebo) or no treatment or an active non-herbal medicine controls.

We will exclude studies in which more than 20% of participating patients suffered from one or more of the following conditions in which results from the eligible population were not separately reported: chronic obstructive pulmonary disease, pneumonia, bronchiectasis, cystic fibrosis, broncopulmonary dysplasia, asthma or tuberculosis; underlying immunodeficiency or respiratory tract anatomical defect; acute respiratory distress requiring mechanical ventilation. Also, we will exclude studies that investigate the simultaneous use of more than one of the eligible plants.

Search methods for primary studies
Electronic searches

We will search the following electronic databases irrespective of language or publication status: the Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Acute Respiratory Infections Group's Specialized Register; MEDLINE; EMBASE; CINAHL (Cumulative Index to Nursing and Allied Health Literature); Web of Science; Health Star (via OVID); AMED; the database of the Cochrane Complementary Medicine Field; LILACS; CAB abstracts; clinical trial.gov; the WHO Trial Register[36] and the Brazilian thesis database (CAPES).

Searching other resources

For every eligible study we identify and for studies, such as review articles, that may have citations including eligible studies, one reviewer will examine the reference list.

We will write to the principal authors of the identified trials and the pharmaceutical companies involved in the production of medicinal herbs and inquire about additional trials of which they are aware.

Unpublished studies will be identified by searching in the books including the list of references for evaluation of safety and efficacy of herbal medicines described in the Brazilian legislation for herbal medicines in Brazil and conference proceedings (Medicinal Symposium of Brazilian medicinal plants; International Congress of Ethnopharmacology).

The following Brazilian scientific journals will also be scanned manually for eligible studies: *Journal of Basic and Applied Pharmaceutical Sciences; Brazilian Journal of Pharmacy; Brazilian Journal of Pharmacognosy; Brazilian Journal of Medicinal Plants; Brazilian Journal of Pharmaceutical Sciences.*

Search strategy

We will restrict the search to human participants, but we will not restrict the searches or inclusion criteria to any specific languages. We stated the search strategy in online supplementary appendix section to search MEDLINE and CENTRAL. We will not combine the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE[37] because we think we will find only few results. We will adapt the search string to search EMBASE, CINAHL, LILACS and Web of Science.

The search will be conducted individually for each plant. The following terms will be used: (1) *intervention*: medicine, herbal; plants, plant; extracts; medicinal; medicine, traditional; herb$; phytomedicine; phytotherapy; complementary therap*; complementary Medicine*; alternative therap*; traditional medicine*; ethnomedicine*; ethnobotany; ethnopharmacology; oriental traditional medicine*; scientific name of plant, synonymies of each medicinal plants; popular name of each medicinal plant selected; (2) *Condition*: respiratory tract diseases, respirat*, cough*, sputum; bronchial illness. The complete search strategy is available in online supplementary appendix 1.

Eligibility determination

Four reviewers, working in pairs, will independently screen potentially relevant citations and, if available, abstracts and apply the selection criteria. We will obtain full texts of all articles that either reviewer feels might be eligible. Two reviewers will independently assess the eligibility of each full-text article and resolve disagreements by consensus.

To exclude duplicate articles, one reviewer will examine all eligible articles and identify those that have one or more authors in common. For such articles, a detailed review will determine if there is duplicate publication, and if there is, we will use the article with the more complete data.

Data extraction

The reviewers, working in pairs, will independently extract the data, recording information regarding patients, methods, interventions, outcomes, missing outcome data and results using standardised and pretested data extraction forms with accompanying instructions. For articles published in abstract form only, or for articles in which important information is missing, we will seek complete information regarding methods and results from authors. Individually, reviewers will evaluate two articles and then check agreement with one another. This process will continue for every two articles until reviewers are confident that they can achieve very high rates of agreement. Disagreements will be resolved through discussion with any unresolved issues referred to another reviewer.

Risk of bias in individual studies

For randomised trials, two reviewers will independently assess the risk of bias, including sequence generation, allocation concealment, blinding, number of patients with missing outcome data, selective outcome reporting and other sources of bias using a modified version of the Cochrane collaboration risk of bias tool.[38] We will assess the risk of bias of observational studies with a modified version of the Newcastle-Ottawa instrument that includes confidence in assessment of exposure and outcome, adjusted analysis for differences between groups in prognostic characteristics, accuracy of outcomes assessment, and missing data.[39]

Confidence in pooled estimates of effect

We will also independently rate the quality of evidence (confidence in effect estimates) for each of the outcomes by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[40–43] We will make separate ratings for bodies of evidence from randomised trials and from observational studies. In the GRADE approach, randomised trials begin as high-quality evidence but may be rated down by one or more of five categories of limitations: risk of bias, inconsistency, indirectness, imprecision and reporting bias. Observational studies begin as low-quality evidence but can be rated up for a large effect size, evidence of dose–response gradient observational studies, or for consideration of all plausible confounding.

Documentation of agreement

To measures agreement, we will use Kappa statistics. Values of kappa between 0.40 and 0.59 have been considered to reflect fair agreement, between 0.60 and 0.8 to reflect good agreement and 0.75 or more to reflect excellent agreement[44]

Data synthesis

Where meta-analysis is not appropriate (excessive heterogeneity of population, intervention, comparator, outcome or methodology), we will construct summary tables and provide a narrative synthesis. When meta-analysis is appropriate, we will conduct analyses for each herbal intervention separately for each outcome of interest. For interventions and outcomes for which there are randomised trials and observational studies available, we will determine the confidence in estimates for each body of evidence and conduct an analysis for the body of evidence that warrants greater confidence. If the two bodies of evidence warrant similar confidence, we will conduct analyses for both bodies of evidence.

Meta-analyses will be conducted using Comprehensive Meta-Analysis (Biostat, Englewood, New Jersey, USA). We will use random effects meta-analyses,[45] which are conservative in that they consider within-studies and between-studies differences in calculating the error term used in the analysis. For trials that report dichotomous outcomes, we will calculate the pooled relative risk with associated 95% CIs. In the cross-sectional and case–control studies, we will document the proportion of patients in the intervention and control groups who experience each of the outcomes of interest. For case–control studies, we will use ORs rather than relative risks.

When pooling across trials that report continuous outcomes using the same instrument, we will calculate the weighted mean difference (WMD), which maintains the original unit of measurement, with studies weighted by the inverse of their variance. Once the WMD has been calculated, we will contextualise this value by noting, when available, the corresponding minimally important difference (MID)—the smallest change in instrument score that patients perceive is important.

If studies reported the same construct using different measurement instruments, we will calculate the standardised mean difference (SMD). The SMD expresses the intervention effect in SD units, rather than the original units of measurement, with the value of an SMD depending on the size of the effect (the difference between means) and the SD of the outcomes (the inherent variability among participants). For outcome measures that have an established anchor-based MID, we will use this measure to convert the SMD into an OR and risk difference. We will complement this presentation by either converting the SMD into natural units of a widely accepted instrument used to measure changes in the domain of interest or, if such an instrument

is not available, we will substitute the MID for the SD (denominator) in the SMD equation, which will result in more readily interpretable MID units instead of SD units.[46] If an estimate of the MID is not available, we will use a statistical approach developed by Suissa[47] to provide a summary estimate of the proportion of patients who benefit from treatment across all studies. Statistical approaches to enhance the interpretability of results of continuous outcomes outlined in this paragraph will use methods cited as well as those described by Thorlund et al.[48]

Funnel plots will be created to explore possible publication bias.

We will use recently developed approaches to address missing participant data for dichotomous outcomes[49] and continuous outcomes.[50] We will only apply these approaches to patient-important outcomes that meet the following criteria: (1) show a significant treatment effect and (2) report sufficient missing participant data to potentially introduce clinically important bias. Thresholds for important missing participant data will be determined on an outcome-by-outcome basis.

Explaining heterogeneity

We hypothesise the following possible explanations for heterogeneity: (1) doses (higher vs lower) with an expected larger effect with higher doses; (2) risk of bias, with an expected larger effect in trials at high or unclear risk of bias versus trials at low risk of bias; (3) bacterial and viral illnesses, with a larger effect in viral than bacterial illnesses; (4) age (adult vs paediatric) with a postulated larger effect in paediatric patients. The presence of heterogeneity will be investigated with the use of a χ^2 test statistic and the I^2 statistic—the percentage of variability that is due to true differences between studies (heterogeneity) rather than sampling error (chance).[51 52]

Summarising evidence

We will present results in evidence profiles (EPs) as recommended by the GRADE Working Group.[53 54] EPs provide succinct, easily digestible presentations of quality of evidence and magnitude of effects. Our EPs will be constructed with the help of a software program, GRADEpro (http://ims.cochrane.org/gradepro) to include the following seven elements: (1) a list of all important outcomes, both desirable and undesirable; (2) a measure of the typical burden of these outcomes (eg, control group, estimated risk); (3) a measure of the difference between risks with and without intervention; (4) the relative magnitude of effect; (5) numbers of participants and studies addressing these outcomes, and follow-up time; (6) a rating of the overall confidence in estimate of effect for each outcome and (7) comments, which will include the MID if available.

DISCUSSION

Our review will evaluate Brazilian herbal intervention for respiratory illness associated with cough, provide estimates of the effectiveness of treatments and their associated harms and evaluate the quality of the evidence in a thorough and consistent manner using the GRADE approach.[55–57] We will prioritise patient important outcomes. The results of our systematic review will be of interest to public health and primary care practitioners in Brazil. Our review will inform these practitioners about the best estimates of effect and confidence in those estimates for effectiveness and safety of herbal medicines for URTI and identify key areas for future research.

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