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Brazilian medicinal plants to treat respiratory disease: systematic review and meta-analyses- Study Protocol

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ABSTRACT

Introduction: Respiratory illness, often associated with cough, 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 to treat the common cold, lower and upper respiratory tract infection and associated cough.

Methods and analysis: We will conduct a systematic review and if appropriate a series of meta-analyses evaluating the safety and effectiveness of Brazilian medicinal plants for the common cold and upper respiratory tract infection and associated cough. We will acquire eligible randomized controlled trials and observational studies in adult or pediatric patients with such illness treated by any form of Brazilian herbal compared with placebo, no treatment, or an alternative therapy through a systematic search of CINAHL, EMBASE, MEDLINE, AMED, Web of Science, Ovid Health star, Cochrane Library, Pubmed and Scielo and the Cochrane Central Registry of Controlled Trials. Teams of reviewers will, independently and in duplicate, screen titles and abstracts and complete full text reviews to determine eligibility, and subsequently perform data abstraction and assess risk of bias of eligible trials. When appropriate, we will conduct meta-analyses to establish the effect of all reported therapies on patient-important outcomes.

Discussion: Our review will be the first to evaluate all Brazilian medicinal plants to treat the common cold, upper respiratory tract infection and associated cough and establish best estimates of the safety and effectiveness of treatments. Our review will facilitate evidence-based management of patients in primary care and identify key areas for future research.

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.

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ARTICLE FOCUS:

Will a systematic review of Brazilian medicinal plants to treat the common cold, lower and upper respiratory tract infection and associated cough reveal effectiveness of these agents?

Do Brazilian medicinal plants lead to symptom improvement and cough control in common cold, lower and upper respiratory tract infection in patients?

KEY MESSAGE:

This study will investigate the effects of all marketed Brazilian medicinal plants indicated to use in respiratory disease: *Ananas comosus, Echinacea purpurea Moench, Eucalyptus globules, Glycyrrhiza glabra L., Hedera helix L., Malva sylvestris L., Mentha spp* (M. piperita or M. villosa), Mikania spp* (M. glomerata or M. laevigata), Pelargonium sidoides D.C., Petasites hybridus L., Pimpinella anisum L., Polygala senega L., Psychotria ipecacuanha (Brot.) Stokes, Sambucus nigra L.*

Outcomes of interest will include time to resolution of clinical symptoms and/or signs (where clinical symptoms and signs include cough, sputum production or activity limitations). Also of interest will be severity of symptoms prior to resolution. Other important outcomes will include hospitalization rates and duration of hospital stay, and days receiving antibiotics

STRENGTHS AND LIMITATIONS OF THIS STUDY

This will be the first systematic review to assess specifically the Brazilian medicinal plants to treat the common cold, lower and upper respiratory tract infection and associated cough. The methods of the review are state-of-art, including explicit eligibility criteria, a comprehensive search, independent duplicate assessment of eligibility, and use of the GRADE approach to assessing confidence in estimates of effect including independent duplicate assessment of risk of bias, precision, consistency, directness and publication bias. We will make separate ratings for bodies of evidence from randomized trials and bodies of evidence from observational studies.

Our results are likely to be limited by limitations in the primary studies include non-randomized studies and randomized trials with a high risk of bias. Eligible studies will differ substantially in study design and outcome measures.

INTRODUCTION

Respiratory illness is common and important

Respiratory illness, including the common cold and upper respiratory tract infection (URTI), and associated cough, are frequent[1] and a major cause of morbidity, especially in children and the elderly [2]. Although in most cases benign, respiratory illness results in many consultations to primary care [3 4].

Acute URTIs are the most common reason for people to seek medical care in the United States [5] and at least one billion colds occur there per year, with a frequency of two to six colds per person [6]. Symptoms of the common cold typically include a runny nose, congestion, sneezing, weakened sense of taste and smell, scratchy throat and cough. These start developing in the first three days following infection. Infants and young children are more likely than adults and teens to also develop fever. Symptoms usually abate within seven to 10 days but some colds last longer, especially in children, the elderly and those with generally poor health [7]. The most common symptom of respiratory tract infection, cough, is also the most common symptom presenting to general practitioners [5 8].

Cough may arise from at least three mechanisms. One is virus-induced postnasal drip. Alternatively, it has been proposed that a viral upper respiratory tract infection produces inflammatory mediators that result in an increase in the sensitivity of the afferent sensory nerves in the upper airway[9]. Third, the infection may spread from the upper to the lower respiratory tract with a resulting bronchitis. This third mechanism is often associated with sputum production.

Cough can be characterized based on time frame (ie, duration of cough), quality (eg, dry or wet, brassy, or staccato), or suggested etiology (ie, specific and nonspecific)[10]. Cough can be designated as acute (<3 weeks in duration), prolonged acute cough (3 to 8 weeks in duration) or chronic (> 8 weeks in duration) [11 12].

In adults, although there is no prospective study of the causes of acute cough, it has long been considered that the common cold is the single most common cause of acute cough (ie, cough < 3 weeks in duration)[9].

In most children acute coughing is usually due to a viral upper respiratory tract infection such as a simple head cold with bronchitis or croup. Less often, but still common, pathogens can involve the lower respiratory tract system causing bronchiolitis,

whooping cough, or pneumonia. Symptomatic URTI with cough in school children typically occurs around 7–10 times per year[13].

Non-herbal medication use to treat respiratory infection is common

Worldwide, the desire to reduce the symptom of cough is reflected in the billions of dollars spent on over-the-counter (OTC) products, mostly cough and cold medications (CCMs) [1]. The preparations are usually a combination of several medications including antitussives, expectorants, antibiotic, antihistamines, decongestants and antipyretics [14].

Current systematic reviews addressing the use of CCMs show insufficient evidence to decide whether OTC medications for cough beneficial[14]. It has been suggested that zinc can inhibit viral growth[15]. As such, the treatment of cough and cold with zinc was tested in several studies[16]. While some of them showed benefits, especially if used within 24 h of the onset of common cold symptoms [17][18], others failed to show the same effect[18]. At the present time, the use of zinc in children with cough and cold is not recommended[1]. The available evidence does not support the use of high doses of vitamin C for treating the common cold [19]. Likewise, there is insufficient evidence to support the treatment of upper respiratory tract infections with antibiotics, and an increased adverse effects associated with antibiotic use in adult patients [20].

Antihistamines in monotherapy - in children as well as in adults - do not alleviate nasal congestion, rhinorrhea and sneezing, or produce subjective improvement of the common cold[21]. First generation antihistamines also cause more side-effects than placebo, in particular they increase sedation in cold sufferers. Combinations of antihistamines with decongestives are not effective in small children. In older children and adults most trials show a beneficial effect on general recovery as well as on nasal symptoms. However, the extent to which improvement is important to patients remains unclear [22].

There are no effective licensed antiviral drugs for the common cold. Of the mucolytic drugs available to treat acute upper and lower URTI, the cysteine derivatives (that is, acetylcysteine and carbocysteine) are the most commonly prescribed in many European [23 24] and African countries[25] and in Brazil [8 26] and seem to have a limited efficacy and also appear to be safe in children older than two years.

Herbal medicines represent an alternative for treatment of respiratory illness

The synonyms of herbal medicines include herbal remedies, herbal medications, herbal products, herbal preparations, medicinal herbs and phytopharmaceuticals. Patients and physicians may be unaware that products with the same label differ appreciably in their composition, mainly due to the use of variable plant material, extraction methods and the addition of other components.

In high-income countries there is increasing public interest in, and use of, a wide range of therapies that lie outside the main stream of traditional Western medical practice[27 28]. Complementary and alternative medicine (CAM) has grown rapidly over the last two decades[27]. The Cochrane Collaboration defines complementary and alternative medicine as a broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health systems of a particular society or culture in a given historical period. In the United States, approximately 38 percent of adults (about 4 in 10) and approximately 12 percent of children (about 1 in 9) are using some form of CAM.

In Brazil, up to 25% of the $ 8 billion of revenues of the pharmaceutical industry, in 1996, may come from sales of drugs derived from plants [29]. United States and Germany are among the largest consumers of Brazilian natural products. Between 1994 and 1998, imported, respectively, 1,521 and 1,466 tons plants that follow for these countries under the generic label "Plant material of Brazil," according to Brazilian Institute of Environment and Renewable Natural Resources[30].

Herbal medicines have been widely used in cough[31]. Antitussives act either centrally on the cough center of the brain or peripherally on the cough receptors in the respiratory passages. The putative antitussive effect of many herbs may result from the content of mucilage, which exerts protective and demulcent activity[31].

Expectorant herbs containing saponins may reduce the surface tension of the secretions, facilitating their separation from the mucous membranes. This induces reflex stimulation which leads to an increase in the secretion of bronchial glands. Volatile-oil type expectorant herbs exert a direct stimulatory effect on the bronchial glands by means of local irritation. They may also have antibacterial activity. In colds and

influenza, herbs containing volatile oil can be used; also, volatile oils are ingredients of syrups and liquids as well as external phytomedicines in the form of liniments, ointments, and inhalations[32].

Both limited research into possible mechanisms of action, and widespread use with many testimonials to success, suggest that treatment with herbal medicines may have great potential to treat respiratory diseases. The effectiveness of such treatment, however, needs to be reviewed systematically and appraised critically to inform current practice and direct future research.

In 2008, the Ministry of Health of Brazil has built a list (Renisus), with 71 species, pre-selected by regions that alluded to its use for indications of use and according to the categories of the International Classification of Diseases (ICD-10), with the potential to advance the productive chain and generate products of interest to the public health system in Brazil[33]. Moreover, in this same year, 36 species were recorded as herbal medicines simplified registration (IN05) ie not need to prove through clinical trials the effectiveness or safety record of its clinical indications only considered data from tradition of popular use[34].

A search in the database of the Brazilian Health Surveillance Agency, for herbal medicines registered for commercialization indicated for the treatment of respiratory diseases resulted in 15 species currently registered for this indication. Of these, six belong to Renisus and nine to IN05.

Therefore, this study will investigate the effects of all marketed Brazilian medicinal plants indicated to use in respiratory disease: *Ananas comosus, Echinacea purpurea Moench, Eucalyptus globules, Glycyrrhiza glabra L., Hedera helix L., Malva sylvestris L., Mentha spp* (M. piperita or M. villosa), Mikania spp* (M. glomerata or M. laevigata), Pelargonium sidoides D.C., Petasites hybridus L., Pimpinella anisum L., Polygala senega L., Psychotria ipecacuanha (Brot.) Stokes, Sambucus nigra L.*

OBJECTIVES

The primary objective is to address the safety and efficacy of Brazilian medicinal plants to treat the common cold and upper respiratory tract infection and associated cough.

METHODS/DESIGN

Protocol and registration

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

Our review will conform to the PRISMA guidelines for reporting systematic reviews.

Inclusion criteria

Our eligibility criteria are as follows:

Patients: Studies must include patients with adult or pediatric 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 - e.g. post-nasal drip - or to acute bronchitis, bronchiolitis).

Interventions: study must include an arm in which patient are taking one of Brazilian herbal medicine from any of the following plant preparation (whole, powder, extract, standardized mixture) with one of select plants (*Ananas comosus, Echinacea purpurea Moench, Eucalyptus globules, Glycyrrhiza glabra L., Hedera helix L., Malva sylvestris L., Mentha spp* (M. piperita or M. villosa), Mikania spp* (M. glomerata or M. laevigata), Pelargonium sidoides D.C., Petasites hybridus L., Pimpinella anisum L., Polygala senega L., Psychotria ipecacuanha (Brot.) Stokes, Sambucus nigra L.*)

Type of study and design: We will include (1) any comparison (randomized controlled trials or observational study) including in an arm patients taking one of herbal medicine listed above compared with an inert (placebo) or active control and open label, via any route of administration.

Exclusion criteria

Trials that included more than 20% of patients with any of the following conditions will exclude: chronic obstructive pulmonary disease (COPD), pneumonia, bronchiectasis, cystic fibrosis, bronco-pulmonary dysplasia, asthma or tuberculosis; underlying immunodeficiency or respiratory tract anatomical defect; acute respiratory distress requiring mechanical ventilation, and in which results from the clearly eligible population were not separately reported. Also if the population of study uses two of the eligible plants we will exclude.

Search methods for primary studies:

We will search the CENTRAL MEDLINE, EMBASE, CINAHL, AMED, Web of Science, Ovid Healthstar, Pubmed, Scielo and The Cochrane Central Register of Controlled Trials (CENTRAL), which includes the Cochrane Airways Group Specialized Trials Register.

We will restrict the search to human subjects but we will not restrict the searches or inclusion criteria to any specific languages.

For every eligible study we identify and for studies such as other review articles that we identify that may have citations including eligible studies, one reviewer will examine the reference list. We will obtain and evaluate the full text of any potentially eligible studies thus identified and determine their eligibility as described below.

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.

Outcome Measures

Outcomes

Outcomes of interest will include time to resolution of clinical symptoms and/or signs (where clinical symptoms and signs include cough, sputum production or activity limitations). Also of interest will be severity of symptoms prior to resolution. Other important outcomes will include hospitalization rates and duration of hospital stay, and days receiving antibiotics. Finally, we will summarize data addressing quality of life or functional status (including number of days of disability that may be defined as days in bed, days off work or days where patients were unable to undertake normal activities during the illness), and adverse events.

Eligibility determination

We will also record minor and serious adverse effects of the intervention and the proportion of patients requiring discontinuation of the herbal medicine. Four reviewers authors, working in pairs (MC/MW; AM/LL) 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 (MC/CB) will independently assess the eligibility of each full-text article and resolve disagreements by consensus.

To exclude duplicate articles, one member (MCS) will look through all eligible articles and identify those in which one more authors are common. For such articles, detailed review will determine if there is duplicate publication and, if there is, MCS will decide which has the more complete data and. We will record the less complete as a duplicate and abstract data only for the more complete.

Data extraction

The reviewers, working in pairs (MCS-MW and MCS-LL), will independently extract the data, recording information regarding patients, methods, interventions, outcomes, missing outcome data, and results using standardized, 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 2 articles and then check agreement with one another. This process will continue every 2 articles until reviewers are confident they can achieve very high rates of agreement. Disagreements will be resolved through discussion with any unresolved issues referred to another reviewer (GG).

Risk of bias in individual studies

For randomized trials, two reviewers independently will 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[35]. 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, prognostic stratification, accuracy of outcomes assessment, and missing data.[36]

Confidence in pooled estimates of effect

We also independently rated the overall quality of evidence (confidence in effect estimates) for each of the outcomes by using the Grading of Recommendations

Assessment, Development and Evaluation (GRADE) approach [37-40]. We will make separate ratings for bodies of evidence from randomized trials and bodies of evidence from observational studies. In the GRADE approach, randomized trials begin as high-quality evidence but may be rated down by 1 or more of 5 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 a dose-response gradient observational studies, or for consideration of all plausible confounding.

Documentation of agreement

We will document chance-corrected agreement for i) eligibility and ii) risk of bias of individual studies and iii. all GRADE rating (precision, consistency, directness, and publication bias). To measures of agreement we will use Kappa statistical. Values of kappa between 0.40 and 0.59 have been considered to reflect fair agreement, between 0.60 and 0.74 to reflect good agreement and 0.75 or more to reflect excellent agreement [41].

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. We will conduct an analysis for each outcome of interest. For interventions and outcomes for which there are both randomized 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, NJ, USA). We will use random effects meta-analyses[42], which are conservative in that they consider both within 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% confidence intervals.

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 and represents the average difference between groups, with studies weighted by the inverse of their variance. Once the WMD has been calculated, we will contextualize 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 standardized mean difference (SMD). The SMD expresses the intervention effect in SD units, rather than the original units of measurement, with the value of a SMD depending on both 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 odds ratio (OR). 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[43]. If an estimated of the MID is not available we will use a statistical approach developed by Suissa [44]to provide a summary estimate of the proportion of patients who benefit from treatment across all studies. The statistical approaches to enhancing the interpretability of results of continuous outcomes outlined in this paragraph will use methods cited as well as those described by Thorlund et. al.[45] Funnel plots will be created to explore possible publication bias.

We will use recently developed approaches to address missing participant data for dichotomous outcomes[46] and continuous outcomes[47]. 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 hypothesize the following possible explanations for heterogeneity: (1) Doses (higher vs lower) with expected larger effect with higher than lower 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 larger effect in viral illnesses than bacterial; (4) Age (adult versus pediatric) with postulated larger effect in pediatric. The presence of heterogeneity will be investigated with the use of likelihood ratio test statistic. Any heterogeneity between the study results would have been described and tested to determine if it reached statistical significance using a chi-squared test.

Summarizing evidence

We will present results in Evidence Profiles (EP) as recommended by the GRADE Working Group[48 49]. 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 called GRADEpro (http://ims.cochrane.org/gradepro) to include the following 7 elements: 1. A list of all important outcomes, both desirable and undesirable; 2. a measure of the typical burden of these outcomes (e.g. control group, estimated risk); 3. a measure of the difference between the 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 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 [[50-52]. We will prioritize patient important outcomes. The results of our systematic review will be of interest to of interest to public health and primary care practitioners in Brazil. Our review will inform these practitioners about best estimates of effect and confidence in those estimates for both effectiveness and safety of herbal medicines and identify key areas for future research.

List of abbreviations

CAM = Complementary and alternative medicine

CCMs = Cough and cold medications

COPD = Chronic obstructive pulmonary disease

EP = Evidence Profiles

GRADE = Assessment, Development and Evaluation

IN05 = Herbal medicines simplified registration

MID = Minimally important difference

OR = Odds ratio

OTC =Over-the-counter

RENISUS = Ministry of Health of Brazil has built a list

SMD = Standardized mean difference

URTI = Upper respiratory tract infection

WMD = Weighted mean difference

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Contributorship Statement:

LCL is Principal Investigator and led the writing of the manuscript. GG is project manager and co-investigator and contributed to the writing and revision of the manuscript. MCOS, MW, CBM, JCO and AMQ are co-investigators and contributed to the writing and revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Supplementary Material

Additional file 1: Search Strategy.

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Appendix A: Search Strategy

We will acquire eligible studies through a systematic search of CINAHL, EMBASE, MEDLINE, AMED, Web of Science, Ovid Health Star, Cochrane Library, Pubmed and Scielo and the Cochrane Central Registry of Controlled Trials.

Searches were conducted individually for each plant. Thus the descriptors for the plants were:
Ananas comosus = *Ananas comosus*
Echinacea purpurea Moench = *Echinacea purpurea*
Eucalyptus globules = *Eucalyptus globules*
Glycyrrhiza glabra L. = *Glycyrrhiza glabra*
*Mentha spp** (*M. piperita* or *M. villosa*) = *Mentha piperita AND Mentha villosa*
*Mikania spp** (M. *glomerata* or *M. laevigata*) = *Mikania*. *glomerata AND Mikania laevigata*
Pimpinella anisum L. = *Pimpinella anisum*
Polygala senega L. = *Polygala senega*
Sambucus nigra L. = *Sambucus nigra*

Database: CINAHL <1982 to 2014 Week >

1. (Name of the plant).mp
2. Select LIMITS “Human”
3. exp (NAME OF THE PLANT (Search as Keyword))

Database: EMBASE <1980 to 2014 Week ->

1. (Name of the plant).mp
2. Select “Human”
3. exp (NAME OF THE PLANT (Search as Keyword))

Database: Ovid MEDLINE(R) <1946 to 2014 Week>

1. (Name of the plant).mp
2. Select “Human”
3. exp (NAME OF THE PLANT (Search as Keyword))

Database: AMED (Allied and Complementary Medicine) <1985 to 2013 Week 12>

1. (Name of the plant). mp
2. exp (NAME OF THE PLANT (Search as Keyword))
3. human
4. exp HUMAN.mp. *search as Keyword*
5. and/ 1-2

Database: Web of Science < 1976 to 2014 Week>

1. (Name of the plant). Mp
2. Refine Results: HUMAN

Database: Ovid Health star <1966 to 2014 Week>

1. (Name of the plant)
2. Select LIMITS “Human”
3. exp (NAME OF THE PLANT (Search as Keyword))

Database: Cochrane Library < to 2014 Week>

1. (Name of the plant)

Database: Pubmed <1950 to 2014 Week>

1. (Name of the plant)
2. Select Species: "Humans"

Database: Scielo < to 2014 Week>

1. Ananas comosus AND humans

Database: Cochrane Central Registry of Controlled Trials <1980 to 2014 Week >

1. (Name of the plant)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A 9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10-11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12-13
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	12-13

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	NA
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	NA
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Brazilian medicinal plants to treat upper respiratory tract and bronchial illness: systematic review and meta-analyses- Study Protocol

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Brazilian medicinal plants to treat upper respiratory tract and bronchial illness: systematic review and meta-analyses- Study Protocol

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Keywords: Common cold, upper respiratory disease, Sputum, bronchial illness, Cough, Systematic review, Meta-analysis, Brazilian medicinal plants

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 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 Brazilian medicinal plants (BMP) for URTI. Eligible randomized controlled trials and observational studies will enroll adult or pediatric patients presenting with upper respiratory tract and bronchial illness treated by BMP approved in Brazilian Health Surveillance Agency compared with placebo, no treatment, or an alternative therapy. Our search will include Cochrane Central Register of Controlled Trials (CENTRAL) which contains the Cochrane Acute Respiratory Illness Group's Specialized Register; MEDLINE, EMBASE; CINAHL; Web of Science; AMED; LILACS, CAB abstracts, clinical trial.gov, WHO Trial Register and 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 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 also assess the quality of body of evidence (confidence in estimates of effect) for each of the outcomes using the 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 health care practice and policy in Brazil.

Register Protocol: Prospero CRD42014007057

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This will be the first systematic review to assess Brazilian medicinal plants approved in 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 help patients with cough and sputum seeking effective and safe treatment options.
- The methods of the review are state-of-art, including explicit eligibility criteria, a comprehensive search, independent duplicate assessment of eligibility, and use of the 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 randomized trials and bodies of evidence from observational studies.
- Because primary studies are likely to be limited to non-randomized studies and randomized 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 main stream of traditional Western medical practice[1 2]. Complementary and alternative medicine (CAM) has grown rapidly over the last two decades[1]. In the United States, approximately 38 percent of adults and approximately 12 percent of children are using some form of CAM[3]. In Brazil, of 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 subsidized 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 total of $ 1.147 billion dollars[5].

The license approval process for herbal medicines vary across countries, including wide variation in evidence of effectiveness required for licensing .[6 7]. Some countries, including Brazil, demand for licensing 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 (ie 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 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 over-the-counter 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 an 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, are 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 21 22 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 did not address the plants that are the topic of the current review suggests 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 an URTI. Of these, Public Health System (SUS) funding is available for two. There are no systematic reviews available addressing 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 to management cough from an upper respiratory tract and bronchial illness.

OBJECTIVES

The primary objective is to address the safety and efficacy of 15 Brazilian herbal medicines approved by ANVISA for acute cough from upper respiratory tract and bronchial illness.

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 pediatric (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 - e.g. post-nasal drip - or to acute bronchitis or bronchiolitis).

Interventions: Studies must include an arm in which patient are taking one of Brazilian herbal medicine from any of the following plant preparation (whole, powder, extract, standardized mixture) with one of 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 ipecacuanha* (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 (e.g. 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
- hospitalization 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 Cough-Specific Quality-of-Life Questionnaire [24] , Leicester Cough Questionnaire [35] or other validated questionnaires.

Study Design

We will include (1) any comparison (randomized controlled trials or observational study) including in an arm in which patients are taking one of the herbal medicines listed above via any route of administration compared to an arm in which patients receive with an inert (placebo) or no treatment or an active non-herbal medicine control, or case-control studies comparing the frequency of use of herbal medicine in patients with better versus poorer outcomes of their respiratory illness.

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 (COPD), pneumonia, bronchiectasis, cystic fibrosis, bronco-pulmonary 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 the eligible plants.

Search methods for primary studies:

Electronic searches

We will search the following electronic databases irrespective of language or publication status: 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, WHO Trial Register[36] and 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 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 subjects but we will not restrict the searches or inclusion criteria to any specific languages. We stated the search strategy in in Appendix section to search MEDLINE and CENTRAL. We will not combine the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE[37] because we think 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 using individually for each plant. The following terms will be used to: 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 **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, 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 standardized, 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 2 articles and then check agreement with one another. This process will continue every 2 articles until reviewers

are confident 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 randomized 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 randomized trials and bodies of evidence from observational studies. In the GRADE approach, randomized trials begin as high quality evidence but may be rated down by 1 or more of 5 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

We will document chance-corrected agreement for i) eligibility and ii) risk of bias of individual studies. To measures of agreement we will use Kappa statistical. 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 both randomized 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, NJ, USA). We will use random effects meta-analyses[45], which are conservative in that they consider both within 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% confidence intervals. 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 odds ratios 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 contextualize 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 standardized mean difference (SMD). The SMD expresses the intervention effect in SD units, rather than the original units of measurement, with the value of a SMD depending on both 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 odds ratio (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. The statistical approaches to enhancing 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 hypothesize the following possible explanations for heterogeneity: (1) Doses (higher vs lower) with 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 larger effect in viral illnesses than bacterial; (4) Age (adult versus pediatric) with postulated larger effect in pediatric patients. The presence of heterogeneity will be investigated with the use of chi-squared 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]

Summarizing evidence

We will present results in Evidence Profiles (EP) 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 7 elements: 1. A list of all important outcomes, both desirable and undesirable; 2. a measure of the typical burden of these outcomes (e.g. control group, estimated risk); 3. a measure of the difference between the 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 prioritize patient important outcomes. The results of our systematic review will be of interest to of interest to public health and primary care practitioners in Brazil. Our review will inform these practitioners about best estimates of effect and confidence in those estimates for both effectiveness and safety of herbal medicines for URTI and identify key areas for future research.

List of abbreviations

CAM = Complementary and alternative medicine

COPD = Chronic obstructive pulmonary disease

EP = Evidence Profiles

GRADE = Assessment, Development and Evaluation

MID = Minimally important difference

OR = Odds ratio

OTC =Over-the-counter

SMD = Standardized mean difference

URTI = Upper respiratory tract and bronchial illness

WMD = Weighted mean difference

Authors' contributions

LCL is Principal Investigator and led the writing of the manuscript. GG is project manager and co-investigator and contributed to the writing and revision of the manuscript. MCOS, MW, CBM and AMQ are co-investigators and contributed to the writing and revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Brazilian medicinal plants to treat upper respiratory ~~disease~~tract and bronchial illness: systematic review and meta-analyses- Study Protocol

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Keywords: Common cold, upper respiratory disease, Sputum, bronchial illness, Cough, Systematic review, Meta-analysis, Brazilian medicinal plants

ABSTRACT

~~Background~~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 to treat ~~the common cold, lower and~~ upper respiratory tract ~~infection~~ and ~~associated cough.~~bronchial illness (URTI).

Methods~~/design~~ and analysis: We will conduct a systematic review and if appropriate a series of meta-analyses evaluating the safety and effectiveness of Brazilian medicinal plants (BMP) for ~~the common cold and upper respiratory tract infection and associated cough. We will acquire eligible~~URTI. Eligible randomized controlled trials and observational studies ~~in~~will enroll adult or pediatric patients presenting with ~~such~~upper respiratory tract and bronchial illness treated by ~~any form of~~ BMP approved in Brazilian ~~herbal~~Health Surveillance Agency compared with placebo, no treatment, or an alternative therapy ~~through a systematic~~. Our search ~~of CINAHL, EMBASE, MEDLINE, AMED, Web of Science, Ovid Health star, Cochrane Library, Pubmed and Scielo and the Cochrane~~ will include Cochrane Central ~~Registry~~Register of Controlled Trials (CENTRAL) which contains the Cochrane Acute Respiratory Illness Group's Specialized Register; MEDLINE, EMBASE; CINAHL; Web of Science; AMED; LILACS, CAB abstracts, clinical trial.gov, WHO Trial Register and 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 complete full text ~~reviews~~ to determine eligibility~~, and subsequently~~. For eligible studies, reviewers will perform data abstraction and assess risk of bias of eligible trials. When appropriate, we will conduct meta-analyses ~~to establish~~. We also assess the quality of body of evidence (confidence in estimates of effect ~~of all reported therapies on patient important~~) for each of the outcomes ~~using~~ using the GRADE approach.

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~~**Discussion:** Our review will be the first to evaluate all Brazilian medicinal plants to treat the common cold, upper respiratory tract infection and associated cough and establish best estimates of the safety and effectiveness of treatments. Our review will facilitate evidence based management of patients in primary care and identify key areas for future research.~~

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~~health care practice and policy in Brazil.

Register Protocol: Prospero CRD42014007057

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Keywords: Common cold, upper respiratory disease, Cough, Systematic review, Meta-analysis, Brazilian medicinal plants

ARTICLE FOCUS:

Will a systematic review of Brazilian medicinal plants to treat the common cold, lower and upper respiratory tract infection and associated cough reveal effectiveness of these agents?

Do Brazilian medicinal plants lead to symptom improvement and cough control in common cold, lower and upper respiratory tract infection in patients?

KEY MESSAGE:

This study will investigate the effects of all marketed Brazilian medicinal plants indicated to use in respiratory disease: *Ananas comosus, Echinacea purpurea Moench, Eucalyptus globules, Glycyrrhiza glabra L., Hedera helix L., Malva sylvestris L., Mentha spp* (M. piperita or M. villosa), Mikania spp* (M. glomerata or M. laevigata), Pelargonium sidoides D.C., Petasites hybridus L., Pimpinella anisum L., Polygala senega L., Psychotria ipecacuanha* (Brot.) *Stokes, Sambucus nigra L.*

Outcomes of interest will include time to resolution of clinical symptoms and/or signs (where clinical symptoms and signs include cough, sputum production or activity limitations). Also of interest will be severity of symptoms prior to resolution. Other important outcomes will include hospitalization rates and duration of hospital stay, and days receiving antibiotics

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This will be the first systematic review to assess specifically the Brazilian medicinal plants approved in Brazilian Health Surveillance Agency (ANVISA) to treat the common cold, lower and upper respiratory tract infection and bronchial illness associated with cough and sputum.
- The results of this systematic review will help clinicians in making decisions in clinical practice and help patients with cough and sputum seeking effective and safe treatment options.
- The methods of the review are state-of-art, including explicit eligibility criteria, a comprehensive search, independent duplicate assessment of eligibility, and use of the GRADE approach to assessingassess confidence in estimates of effect

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including independent ~~duplicate~~ assessment of risk of bias, precision, consistency, directness and publication bias. We will make separate ratings for bodies of evidence from randomized trials and bodies of evidence from observational studies.

~~Our results~~ Because primary studies are likely to be limited ~~by limitations in the primary studies include~~to non-randomized studies and randomized 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.

~~BACKGROUND:~~

~~*Respiratory illness is common and important*~~

~~Respiratory illness, including the common cold and upper respiratory tract infection (URTI), and~~ The exact constituents of the plants being tested are likely to be associated ~~cough, are frequent[1] and a major cause of morbidity, especially in children and the elderly [2]. Although in most cases benign, respiratory illness results in many consultations to primary care [3-4].~~

- ~~Acute URTIs are the most common reason for people to seek medical care in the United States [5] and at least one billion colds occur there per year, with a frequency of two to six colds per person [6]. Symptoms of the common cold typically include a runny nose, congestion, sneezing, weakened sense of taste and smell, scratchy throat and cough. These start developing in the first three days following infection. Infants and young children are more likely than adults and teens to also develop fever. Symptoms usually abate within seven to 10 days but some colds last longer, especially in children, the elderly and those with generally poor health [7]. The most common symptom of respiratory tract infection, cough, is also the most common symptom presenting to general practitioners [5-8].~~ uncertainty.

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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 main stream of traditional Western medical practice~~Cough may arise from at least three mechanisms. One is virus induced postnasal drip. Alternatively, it has been proposed that a viral upper respiratory tract infection produces inflammatory mediators that result in an increase in the sensitivity of the afferent sensory nerves in the upper airway[9]. Third, the infection may spread from the upper to the lower respiratory tract with a resulting bronchitis. This third mechanism is often associated with sputum production.~~

~~Cough can be characterized based on time frame (ie, duration of cough), quality (eg, dry or wet, brassy, or staccato), or suggested etiology (ie, specific and nonspecific)[10]. Cough can be designated as acute (<3 weeks in duration), prolonged acute cough (3 to 8 weeks in duration) or chronic (> 8 weeks in duration) [11 12].~~

~~In adults, although there is no prospective study of the causes of acute cough, it has long been considered that the common cold is the single most common cause of acute cough (ie, cough < 3 weeks in duration)[9].~~

~~In most children acute coughing is usually due to a viral upper respiratory tract infection such as a simple head cold with bronchitis or croup. Less often, but still common, pathogens can involve the lower respiratory tract system causing bronchiolitis, whooping cough, or pneumonia. Symptomatic URTI with cough in school children typically occurs around 7–10 times per year[13].~~

~~**Non-herbal medication use to treat respiratory infection is common**~~

~~Worldwide, the desire to reduce the symptom of cough is reflected in the billions of dollars spent on over the counter (OTC) products, mostly cough and cold medications (CCMs) [1]. The preparations are usually a combination of several medications including antitussives, expectorants, antibiotic, antihistamines, decongestants and antipyretics [14].~~

~~Current systematic reviews addressing the use of CCMs show insufficient evidence to decide whether OTC medications for cough beneficial[14]. It has been suggested that zinc can inhibit viral growth[15]. As such, the treatment of cough and cold with zinc~~

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~~was tested in several studies[16]. While some of them showed benefits, especially if used within 24 h of the onset of common cold symptoms [17][18], others failed to show the same effect[18]. At the present time, the use of zinc in children with cough and cold is not recommended[1]. The available evidence does not support the use of high doses of vitamin C for treating the common cold [19]. Likewise, there is insufficient evidence to support the treatment of upper respiratory tract infections with antibiotics, and an increased adverse effects associated with antibiotic use in adult patients [20].~~

~~Antihistamines in monotherapy – in children as well as in adults – do not alleviate nasal congestion, rhinorrhea and sneezing, or produce subjective improvement of the common cold[21]. First generation antihistamines also cause more side effects than placebo, in particular they increase sedation in cold sufferers. Combinations of antihistamines with decongestives are not effective in small children. In older children and adults most trials show a beneficial effect on general recovery as well as on nasal symptoms. However, the extent to which improvement is important to patients remains unclear [22].~~

~~There are no effective licensed antiviral drugs for the common cold. Of the mucolytic drugs available to treat acute upper and lower URTI, the cysteine derivatives (that is, acetylcysteine and carbocysteine) are the most commonly prescribed in many European [23 24] and African countries[25] and in Brazil~~ [1 2]. Complementary and alternative medicine (CAM) has grown rapidly over the last two decades[1]. In the United States, approximately 38 percent of adults and approximately 12 percent of children are using some form of CAM[3]. In Brazil, of 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 subsidized 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 total of $ 1.147 billion dollars[5].

The license approval process for herbal medicines vary across countries, including wide variation in evidence of effectiveness required for licensing .[6 7]. Some countries, including Brazil, demand for licensing 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 (ie 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 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 over-the-counter 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 an 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, are 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 [8 26][20 21]. ~~and seem to have a limited efficacy and also appear to be safe in children older than two years.~~

~~**Herbal medicines represent an alternative for treatment of respiratory illness**~~

~~The synonyms of herbal medicines include herbal remedies, herbal medications, herbal products, herbal preparations, medicinal herbs and phytopharmaceuticals. Patients and physicians may be unaware that products with the same label differ appreciably in their composition, mainly due to the use of variable plant material, extraction methods and the addition of other components.~~ [22 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 did not address the plants that are the topic of the current review suggests 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 an URTI. Of these, Public Health System (SUS) funding is available for two. There are no systematic reviews available addressing 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 to management cough from an upper respiratory tract and bronchial illness.

In high-income countries there is increasing public interest in, and use of, a wide range of therapies that lie outside the main stream of traditional Western medical practice[27 28]. Complementary and alternative medicine (CAM) has grown rapidly over the last two decades[27]. The Cochrane Collaboration defines complementary and alternative medicine as a broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health systems of a particular society or culture in a given historical period. In the United States, approximately 38 percent of adults (about 4 in 10) and approximately 12 percent of children (about 1 in 9) are using some form of CAM.

In Brazil, up to 25% of the $ 8 billion of revenues of the pharmaceutical industry, in 1996, may come from sales of drugs derived from plants [29]. United States and Germany are among the largest consumers of Brazilian natural products. Between 1994 and 1998, imported, respectively, 1,521 and 1,466 tons plants that follow for these countries under the generic label "Plant material of Brazil," according to Brazilian Institute of Environment and Renewable Natural Resources[30].

Herbal medicines have been widely used in cough[31]. Antitussives act either centrally on the cough center of the brain or peripherally on the cough receptors in the respiratory passages. The putative antitussive effect of many herbs may result from the content of mucilage, which exerts protective and demulcent activity[31].

Expectorant herbs containing saponins may reduce the surface tension of the secretions, facilitating their separation from the mucous membranes. This induces reflex stimulation which leads to an increase in the secretion of bronchial glands. Volatile oil type expectorant herbs exert a direct stimulatory effect on the bronchial glands by means of local irritation. They may also have antibacterial activity. In colds and influenza, herbs containing volatile oil can be used; also, volatile oils are ingredients of syrups and liquids as well as external phytomedicines in the form of liniments, ointments, and inhalations[32].

Both limited research into possible mechanisms of action, and widespread use with many testimonials to success, suggest that treatment with herbal medicines may have great potential to treat respiratory diseases. The effectiveness of such treatment,

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~~however, needs to be reviewed systematically and appraised critically to inform current practice and direct future research.~~

~~In 2008, the Ministry of Health of Brazil has built a list (Renisus), with 71 species, pre-selected by regions that alluded to its use for indications of use and according to the categories of the International Classification of Diseases (ICD-10), with the potential to advance the productive chain and generate products of interest to the public health system in Brazil[33]. Moreover, in this same year, 36 species were recorded as herbal medicines simplified registration (IN05) ie not need to prove through clinical trials the effectiveness or safety record of its clinical indications only considered data from tradition of popular use[34].~~

~~A search in the database of the Brazilian Health Surveillance Agency, for herbal medicines registered for commercialization indicated for the treatment of respiratory diseases resulted in 15 species currently registered for this indication. Of these, six belong to Renisus and nine to IN05.~~

~~Therefore, this study will investigate the effects of all marketed Brazilian medicinal plants indicated to use in respiratory disease: *Ananas comosus, Echinacea purpurea Moench, Eucalyptus globules, Glycyrrhiza glabra L., Hedera helix L., Malva sylvestris L., Mentha spp* (M. piperita or M. villosa), Mikania spp* (M. glomerata or M. laevigata), Pelargonium sidoides D.C., Petasites hybridus L., Pimpinella anisum L., Polygala senega L., Psychotria ipecacuanha (Brot.) Stokes, Sambucus nigra L.*~~

OBJECTIVES

The primary objective is to address the safety and efficacy of 15 Brazilian ~~medicinal plants to treat the common cold and~~ herbal medicines approved by ANVISA for acute cough from upper respiratory tract ~~infection~~ and ~~associated cough~~bronchial illness.

METHODS~~/DESIGN~~ 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].

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Protocol and registration

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

~~Our review will conform to the PRISMA guidelines for reporting systematic reviews.~~

Eligibility criteria for considering studies for review

Inclusion criteria

~~Our eligibility criteria are as follows:~~

Patients: Studies must include patients with adult (>18 years old) or pediatric (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 - e.g. post-nasal drip - or to acute bronchitis~~,~~ or bronchiolitis).

Interventions: ~~study~~Studies must include an arm in which patient are taking one of Brazilian herbal medicine from any of the following plant preparation (whole, powder, extract, standardized mixture) with one of select plants ~~(*Ananas comosus, Echinacea purpurea Moench, Eucalyptus globules, Glycyrrhiza glabra L., Hedera helix L., Malva sylvestris L., Mentha spp* (M. piperita or M. villosa), Mikania spp* (M. glomerata or M. laevigata), Pelargonium sidoides D.C., Petasites hybridus L., Pimpinella anisum L., Polygala senega L., Psychotria ipecacuanha (Brot.) Stokes, Sambucus nigra L.)~~ :

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.)

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~~**Type of study and design:**~~ Stokes or *Cephaelis ipecacuanha* (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 (e.g. 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
- hospitalization 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 Cough-Specific Quality-of-Life Questionnaire [24] , Leicester Cough Questionnaire [35] or other validated questionnaires.

Study Design

We will include (1) any comparison (randomized controlled trials or observational study) including in an arm in which patients are taking one of the herbal ~~medicine~~medicines listed above via any route of administration compared to an arm in which patients receive with an inert (placebo) or no treatment or an active non-herbal medicine control ~~and open label, via any route of administration~~, or case-control studies comparing the frequency of use of herbal medicine in patients with better versus poorer outcomes of their respiratory illness.

~~*Exclusion criteria*~~

~~Trials that included~~We will exclude studies in which more than 20% of participating patients ~~with any~~suffered from one or more of the following conditions ~~will exclude~~in

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which results from the eligible population were not separately reported: chronic obstructive pulmonary disease~~–~~ (COPD), pneumonia, bronchiectasis, cystic fibrosis, bronco-pulmonary dysplasia, asthma or tuberculosis; underlying immunodeficiency or respiratory tract anatomical defect; acute respiratory distress requiring mechanical ventilation~~, and in which results from the clearly eligible population were not separately reported.~~. Also~~ if the population~~, we will exclude studies that investigate the simultaneous use of ~~study uses two of~~more than one the eligible plants~~ we will exclude~~.

Search methods for primary studies:

~~We will search the CENTRAL MEDLINE, EMBASE, CINAHL, AMED, Web of Science, Ovid Healthstar, Pubmed, Scielo and The Cochrane Central Register of Controlled Trials (CENTRAL), which includes the Cochrane Airways Group Specialized Trials Register.~~

~~We will restrict the search to human subjects but we will not restrict the searches or inclusion criteria to any specific languages.~~

Electronic searches

We will search the following electronic databases irrespective of language or publication status: 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, WHO Trial Register[36] and Brazilian thesis database (CAPES).

Searching other resources

For every eligible study we identify and for studies such as ~~other~~ review articles that ~~we identify that~~ may have citations including eligible studies, one reviewer will examine the reference list. ~~We will obtain and evaluate the full text of any potentially eligible studies thus identified and determine their eligibility as described below.~~

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 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 subjects but we will not restrict the searches or inclusion criteria to any specific languages. We stated the search strategy in in Appendix section to search MEDLINE and CENTRAL. We will not combine the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE[37] because we think 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 using individually for each plant. The following terms will be used to: 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 **Appendix 1.**

~~**Outcome Measures**~~

~~***Outcomes***~~

~~Outcomes of interest will include time to resolution of clinical symptoms and/or signs (where clinical symptoms and signs include cough, sputum production or activity limitations). Also of interest will be severity of symptoms prior to resolution. Other important outcomes will include hospitalization rates and duration of hospital stay, and days receiving antibiotics. Finally, we will summarize data addressing quality of life or functional status (including number of days of disability that may be defined as days in~~

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~~bed, days off work or days where patients were unable to undertake normal activities during the illness), and adverse events.~~

Eligibility determination

~~We will also record minor and serious adverse effects of the intervention and the proportion of patients requiring discontinuation of the herbal medicine.~~ Four reviewers ~~authors~~, working in pairs ~~(MC/MW; AM/LL)~~, 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 ~~(MC/CB)~~ will independently assess the eligibility of each full-text article and resolve disagreements by consensus.

To exclude duplicate articles, one ~~member (MCS)~~reviewer will ~~look through~~examine all eligible articles and identify those ~~in which~~that have one or more authors ~~are~~in common. For such articles, detailed review will determine if there is duplicate publication and, if there is, ~~MCS~~we will ~~decide which has~~use the article with the more complete data ~~and. We will record the less complete as a duplicate and abstract data only for the more complete.~~ .

Data extraction

The reviewers, working in pairs ~~(MCS-MW and MCS-LL)~~, will independently extract the data, recording information regarding patients, methods, interventions, outcomes, missing outcome data, and results using standardized, 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 2 articles and then check agreement with one another. This process will continue every 2 articles until reviewers are confident they can achieve very high rates of agreement. Disagreements will be resolved through discussion with any unresolved issues referred to another reviewer ~~(GG).~~.

Risk of bias in individual studies

For randomized trials, two reviewers will independently ~~will~~ assess the risk of bias, including sequence generation, allocation concealment, blinding, number of patients

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with missing outcome data, selective outcome reporting, and other sources of bias using a modified version of the Cochrane collaboration risk of bias tool~~[35]~~.[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 ~~stratification~~characteristics, accuracy of outcomes assessment, and missing data~~[36]~~.[39]

Confidence in pooled estimates of effect

We will also independently ~~rated~~rate the ~~overall~~ quality of evidence (confidence in effect estimates) for each of the outcomes by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach ~~[37-40]~~ [40-43]. We will make separate ratings for bodies of evidence from randomized trials and bodies of evidence from observational studies. In the GRADE approach, randomized trials begin as high~~-~~ quality evidence but may be rated down by 1 or more of 5 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 ~~a~~ dose-response gradient observational studies, or for consideration of all plausible confounding.

Documentation of agreement

We will document chance-corrected agreement for i) eligibility and ii) risk of bias of individual studies~~ and iii. all GRADE rating (precision, consistency, directness, and publication bias).~~ To measures of agreement we will use Kappa statistical. Values of kappa between 0.40 and 0.59 have been considered to reflect fair agreement, between 0.60 and 0.~~74 to reflect good agreement and 0.75 or more to reflect excellent agreement [41].~~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~~. We will conduct an analysis~~ for each outcome of interest.~~ For~~ For interventions and outcomes for which there are both randomized trials and observational studies available we will determine the confidence

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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, NJ, USA). ~~We will use random effects meta-analyses[42].~~We will use random effects meta-analyses[45], which are conservative in that they consider both within 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% confidence intervals. 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 odds ratios 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 ~~and represents the average difference between groups~~, with studies weighted by the inverse of their variance. Once the WMD has been calculated, we will contextualize 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 standardized mean difference (SMD). The SMD expresses the intervention effect in SD units, rather than the original units of measurement, with the value of a SMD depending on both 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 odds ratio (OR~~). 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[43]. If an estimated of the MID is not available we will use a statistical approach developed by Suissa [44]to provide a summary estimate of the proportion of patients who benefit from treatment across all studies. The statistical approaches to enhancing the interpretability of results of continuous outcomes outlined in this paragraph will use methods cited as well as those described by Thorlund et. al.[45]~~) and risk difference. We will complement this presentation by either converting the SMD into natural units of a widely accepted

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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. The statistical approaches to enhancing 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.~~

Funnel plots will be created to explore possible publication bias. ~~We will use recently developed approaches to address missing participant data for dichotomous outcomes[46] and continuous outcomes[47]. 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 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 hypothesize the following possible explanations for heterogeneity: (1) Doses (higher vs lower) with expected larger effect with higher ~~than lower~~ 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 larger effect in viral illnesses than bacterial; (4) Age (adult versus pediatric) with postulated larger effect in pediatric patients. The presence of heterogeneity will be investigated with the use of ~~likelihood~~

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~~ratio~~chi-squared test statistic~~. Any~~ and the I^2 statistic – the percentage of variability that is due to true differences between studies (heterogeneity ~~between the study results would have been described and tested to determine if it reached statistical significance using a chi-squared test.~~) rather than sampling error (chance).[51 52]

Summarizing evidence

We will present results in Evidence Profiles (EP) as recommended by the GRADE Working Group~~[48 49]~~[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 ~~called,~~ GRADEpro (http://ims.cochrane.org/gradepro) to include the following 7 elements: 1. A list of all important outcomes, both desirable and undesirable; 2. a measure of the typical burden of these outcomes (e.g. control group, estimated risk); 3. a measure of the difference between the 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~~

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 ~~[[50 52].~~[55-57]. We will prioritize patient important outcomes. The results of our systematic review will be of interest to of interest to public health and primary care practitioners in Brazil. Our review will inform these practitioners about best estimates of effect and confidence in those estimates for both effectiveness and safety of herbal medicines for URTI and identify key areas for future research.

List of abbreviations

CAM = Complementary and alternative medicine

~~CCMs = Cough and cold medications~~

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COPD = Chronic obstructive pulmonary disease

EP = Evidence Profiles

GRADE = Assessment, Development and Evaluation

~~IN05 = Herbal medicines simplified registration~~

MID = Minimally important difference

OR = Odds ratio

OTC =Over-the-counter

~~RENISUS = Ministry of Health of Brazil has built a list~~

SMD = Standardized mean difference

URTI = Upper respiratory tract ~~infection~~and bronchial illness

WMD = Weighted mean difference

~~Competing interests~~

~~The authors declare that they have no competing interests.~~

Authors' contributions

LCL is Principal Investigator and led the writing of the manuscript. GG is project manager and co-investigator and contributed to the writing and revision of the manuscript. MCOS, MW, CBM~~, JCO~~ and AMQ are co-investigators and contributed to the writing and revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

~~Supplementary Material~~

~~**Additional file 1:** Search Strategy.~~

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Appendix A: Search Strategy

We will acquire eligible studies through a systematic search of Cochrane Central Register of Controlled Trials (CENTRAL) which contains the Cochrane Acute Respiratory Illness Group's Specialized Register; MEDLINE, EMBASE; CINAHL; Web of Science; AMED; LILACS, CAB abstracts, clinical trial.gov, WHO Trial Register and Brazilian thesis database (CAPES)
Searches were conducted individually for each plant. Following the logic used to perform the search in databases.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

---

1 common cold.mp. or exp Common Cold/ (4703)
2 exp Respiratory Tract Infections/ (289046)
3 upper respiratory infection*.mp. (1993)
4 upper respiratory tract infection*.mp. (4109)
5 tonsillitis.mp. or exp Tonsillitis/ (8491)
6 exp Sinusitis/ or sinusitis.mp. (20370)
7 otitis media.mp. or exp Otitis Media/ (25752)
8 pharyngitis.mp. or exp Pharyngitis/ (15017)
9 laryngitis.mp. or exp Laryngitis/ (4279)
10 acute bronchitis.mp. (1138)
11 acute bronchiolitis.mp. (582)
12 exp Bronchiolitis/ and exp Acute Disease/ (706)
13 exp Acute Disease/ and exp Bronchitis/ (2044)
14 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 (321961)

This part of the research is performed individually by type of plants (the terms used are described in Table 1), as the following example:

15. ("Echinacea"[Mesh]) OR "Rudbeckia"[Mesh]
16. Echinaceas OR Echinacea purpúrea OR Echinacea purpúreas OR purpurea, Echinacea OR purpureas, Echinacea OR Coneflower, Purple OR Coneflowers, Purple OR Purple Coneflower OR Purple Coneflowers OR Rudbeckia purpúrea OR Rudbeckia purpúreas OR purpurea, Rudbeckia OR purpureas, Rudbeckia OR Echinacea angustifólia OR Echinacea angustifólias OR angustifolia, Echinacea OR angustifolias, Echinacea
17. ("Eucalyptus"[Mesh]) AND "Eucalyptus terpene oil" [Supplementary Concept]

18. Eucalyptus globules OR Eucalyptus OR Eucalipto

19. 15 or 16 or 17 or 18

From here the same for all plants, terms to search for the types of study design to be included (typically a 'filter' for randomized trials).

20 randomized controlled trial.pt. (376556)

21 controlled clinical trial.pt. (88568)

22 randomized.mp. (568931)

23 20 or 21 or 22 (651127)

24 14 and 19 and 23 (8)

****

Table 1. Descriptors by plants

Plants	Mesh terms	Others terms
A. comosus	"Ananas"[Mesh]	Ananas comosus OR Anana OR Pineapple OR Pineapples
E. purpurea	("Echinacea"[Mesh]) OR "Rudbeckia"[Mesh]	Echinaceas OR Echinacea purpúrea OR Echinacea purpúreas OR purpurea, Echinacea OR purpureas, Echinacea OR Coneflower, Purple OR Coneflowers, Purple OR Purple Coneflower OR Purple Coneflowers OR Rudbeckia purpúrea OR Rudbeckia purpúreas OR purpurea, Rudbeckia OR purpureas, Rudbeckia OR Echinacea angustifólia OR Echinacea angustifólias OR angustifolia, Echinacea OR angustifolias, Echinacea
E. globules	("Eucalyptus"[Mesh]) OR "Eucalyptus terpene oil" [Supplementary Concept]	Eucalyptus globules OR Eucalyptus OR Eucalipto
G. glabra	"Glycyrrhiza"[Mesh] OR "Glycyrrhiza uralensis"[Mesh] OR "licorice-saponin L3" [Supplementary Concept]	Glycyrrhizas OR Licorice OR Licorices OR Liquorice OR Liquorices OR Glycyrrhiza uralenses OR uralenses, Glycyrrhiza OR uralensis, Glycyrrhiza OR Gan zao OR Gan zaos OR zao, Gan OR zaos, Gan
H. helix	("Hedera"[Mesh]) OR ("hederacoside C" [Supplementary Concept] OR "didehydrofalcarinol" [Supplementary Concept])	Hederas OR Hedera helix OR Hedera hélices OR helices, Hedera OR helix, Hedera OR Ivy, English OR English Ivy
M. sylvestris	"Malva"[Mesh]	Malva sylvestris OR Malva OR Malvas OR Malva silvestre
M. piperita and M. villosa	"Mentha"[Mesh] OR "Mentha piperita"[Mesh]	Mentha piperita OR Mentha villosa OR Menthas OR Mint OR Mints OR Mentha piperitas OR piperita, Mentha OR piperitas, Mentha OR Peppermint OR Peppermints OR Menta
M. glomerata and M. laevigata	"Mikania"[Mesh]	Mikania glomerata OR Mikania laevigata OR Cipó-caatinga OR Cipó-catinga OR Guaco OR Guacos OR Mikanias
P. sidoides	"Pelargonium"[Mesh]	Pelargonium sidoides OR Pelargoniums OR Umckaloabo
P. hybridus	"Petasites"[Mesh]	Petasite OR Butterbur OR Butterburs OR Coltsfoot, Sweet OR Coltsfoots, Sweet OR Sweet Coltsfoot OR Sweet Coltsfoots
P. anisum	"Pimpinella"[Mesh] OR "Foeniculum"[Mesh]	Pimpinellas OR Pimpinella anisum OR Pimpinella anisums OR anisum, Pimpinella OR anisums, Pimpinella OR Anise OR Anises OR Erva-doce OR Anis OR Fennel OR Fennels
P. senega	"Polygala"[Mesh]	Polygalas OR Snakeroot, Seneca OR Seneca Snakeroot OR Seneca Snakeroots OR Snakeroots, Seneca OR Senegaroot OR rattlesnake root OR mountain flax
P. ipecacuanha	"Cephaelis"[Mesh]	Cephaeli OR Uragoga OR Uragogas OR Cephaelis ipecacuanha OR Cephaelis ipecacuanhas OR ipecacuanha, Cephaelis OR ipecacuanhas, Cephaelis OR Psychotria ipecacuanha OR Psychotria ipecacuanhas OR ipecacuanha, Psychotria OR ipecacuanhas, Psychotria OR Cagosanga OR Raiz-do-Brasil
S.nigra	"Sambucus nigra"[Mesh] OR "Sambucus nigra lectins" [Supplementary Concept]	Sambucus nigras OR nigra, Sambucus OR nigras, Sambucus OR Elder, Black OR Elder, European OR Elders, European OR European Elder OR European Elders OR Black Elder OR Black Elders OR Elders, Black

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A 9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10-11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12-13
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	12-13

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	NA
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	NA
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

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