Efficacy, Mechanism, and Safety of Herbal Medicine for Respiratory Disease Induced by Particulate Matter: a Protocol for a Scoping Review

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Protocol

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Abstract

Background:

Particulate matter (PM) is an important environmental risk factor in the initiation and exacerbation of respiratory disease. Various herbal medicines have exhibited a reduction in symptoms of respiratory diseases induced by PM in animal models; however, their efficacy, mechanism, and safety have not been reviewed. This review will evaluate the efficacy, safety, and mechanism of action of herbal medicines in respiratory diseases caused by PM.

Methods:

We will follow the scoping review framework developed by Arksey and O'Malley. MEDLINE (via PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials will be searched for relevant English-language publications, and only peer-reviewed, controlled comparative *in-vivo/in-vitro* studies examining the effects of herbs in animal models of respiratory disease induced by PM will be included. The basic characteristics, research method, possible mechanism, and results will be extracted. The primary outcome will be pulmonary function; secondary outcomes will be inflammatory markers, reactive oxygen species, histology and mechanisms, and adverse events. Two researchers will independently perform the study selection, data extraction, and quality assessment. RevMan software (version 5.3) will be used for the quantitative data synthesis. When appropriate, data will be pooled for meta-analysis using fixed or random effects models; otherwise, evidence will be summarized qualitatively.

Ethics and Dissemination:

Ethical approval is not required because individual patient data will not be included. The findings will be disseminated through peer-reviewed publications or conference presentations.

Registration number:

This review protocol has been registered with the Open Science Framework on February 12, 2021 (https://osf.io/s7uvk/)

Background

Particulate matter (PM) is a form of air pollution that can be inhaled, and consists of microscopic particles of varying size, composition, and origins. The fraction of particles suspended in the air that are of less than 10 μm in diameter is defined as 'coarse PM' (PM10), that of particles less than 2.5 μm in diameter as 'fine PM' (PM2.5), and that of particles less than 0.1 μm in diameter as 'ultrafine PM' (PM0.1) [1]. In recent years, global interest in PM has rapidly increased, and many studies on the health effects of PM exposure have been conducted, revealing adverse effects on the respiratory and cardiac systems [2–4]. PM is known to induce or exacerbate respiratory diseases because of its direct effects on the respiratory system. Larger-sized particles affect the upper respiratory tract, while particles less than 2.5

μm in diameter reach further down into the respiratory system affecting the lung interstitium and alveoli [5, 6]. Epidemiological reports have shown that PM10 can exacerbate asthma or chronic obstructive pulmonary disease (COPD) and induce inflammation of the respiratory system [7–10]. PM2.5 also has adverse health effects, and the increment in PM2.5 is associated with an increased mortality rate of the respiratory disease [11], and long-term exposure to PM2.5 can increase the COPD incidence [12]. Substantial medical costs are derived from air pollution and PM that increase the economic burden [13].

With increase in environmental pollution and the aging global population, the incidence and exacerbation of asthma and COPD owing to air pollution are bound to increase. Therefore, it is important to seek strategies for the prevention and alleviation of respiratory diseases caused by PM. However, currently no drugs specifically developed for the prevention or management of the damage caused by PM.

To overcome the limitations and lack of evidence of conventional medicines available for the prevention and/or management of respiratory symptoms caused by PM, complementary and alternative medicine (CAM) and herbal medicine treatment strategies have garnered increased interest. Several systematic reviews on the effects of herbal medicines for respiratory diseases such as COPD, asthma, and lung cancer have been published [14–16]. However, there are few studies on lung disease induced by PM. Although some animal model experimental studies conducted sporadically for respiratory diseases induced by PM have demonstrated the mechanisms and effectiveness of herbal medicine [17–20]; however, we did not reach a conclusion on the herbal medicine, mechanism, regimen, and outcome appropriate for research on lung disease induced by PM. Therefore, there is an increasing need to review and verify the mechanisms and effectiveness of various herbal medicines for the treatment of respiratory symptoms. An agreement on the research methods and protocols were not met between researchers. In general, much of the evidence available is traced back to studies on experimental animals since ethical concerns are associated with clinical trial designs in which patients are directly exposed to PM.

In this scoping review, we will summarize and chart the experimental models used for respiratory diseases caused by PM, as well as the efficacy evaluation methods and the evaluation tools available for the use of herbal formulas or single herbs in respiratory diseases. In addition, the mechanism of action of herbal treatments and the markers used in the experimental models will also be reviewed. This summary of currently available research will facilitate the design of further experimental studies, and will provide information on the effectiveness of herbal medicine and the mechanisms by which PM induces or worsens respiratory diseases. These data will also be used as fundamental information for further clinical research and clinical practice.

Methods

Study design and Registration

We will follow the scoping review methodology developed by Arksey and O'Malley [21] and other authors [22,23]. This scoping review protocol complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extensions for Scoping reviews, (PRISMA-Scr) guidelines [23]. This review

protocol has been registered with the Open Science Framework on February 12, 2021 (https://osf.io/s7uvk/).

Stage 1: Identifying the Study questions

This stage was archived with a preliminary literature search on previous research and agreement of research team members for better scoping of research objectives. The research team comprised one respiratory disease specialist (KK), a specialist in clinical research on traditional East Asian medicine (JL), and a researcher on literature review (YK). Suggestions and revision of the research question were requested from other related experimental research experts. The following questions will be addressed in our scoping review following the consensus of the research team.

1. What is the popular herbal medicine prescribed for lung disease induced by PM and which herbal medicine is better for each indication?
2. What is the primary and secondary outcome reported in the studies on lung disease induced by PM?
3. What types of mechanisms were explored regarding the effect of herbal medicine for lung disease induced by PM?
4. What are the known adverse events of herbal medicine for lung disease induced by PM?
5. How long should the herbal medicine be prescribed?
6. What types of animal models are frequently used in experimental research and what are the strengths and limitations of each model?

Stage 2: Identifying relevant studies

2.1 Information source

We will restrict our research to peer-reviewed; English-language studies examining the efficacy of herbs in respiratory disease induced by PM will be included. The literature search will be conducted from the inception to the present (March 2021). The following databases will be searched: MEDLINE (via PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials. The reference lists of the retrieved articles and the relevant systematic reviews will be searched manually. Efforts will be made to get in touch with the authors of the published articles of which electronic files could not be obtained. The search strategy was consulted with the librarian, an expert on scoping review, and a specialist on lung disease. We will use search terms related to PM and intervention. Related medical subject heading (MeSH) terms and synonyms in various combinations will be used in the search strategy. The terms to be used in relation to PM include “fine dust,” “PM,” and “coarse particle.” The terms to be used in relation to intervention include “herbal medicine” and “herb.” The search strategies are presented in supplementary digital content (Appendix 1).

2.2 Eligibility criteria: Types of Studies

Only controlled comparative *in-vivo/in-vitro* studies examining the effects of herbs in animal models of respiratory disease induced by PM will be included.

2.3 Eligibility criteria: Types of Animal model

All types of animal models will be included; there will be no restrictions on species, sex, and age.

2.4 Eligibility criteria: Types of Interventions

Multiple or single medicinal herb preparations and fractions of medicinal herb preparations will be considered eligible as interventions. We will include herbal preparations of any type, such as liquids, gels, tablets, and extracts, but only those that are orally administered. Any type of comparative intervention will be included. The duration of the treatment period will not be restricted.

2.5 Eligibility criteria: Types of Outcome Measurements

The last time-point acquired value will be extracted. The primary outcome will be respiratory function. The secondary outcomes will be as follows: 1) inflammatory markers, 2) reactive oxygen species (ROS), and 3) histology and mechanisms. In terms of safety issues, we will also investigate adverse events and dropout rates.

Stage 3: Study selection

Two reviewers (YK and JL) will independently conduct the entire study selection process. After performing database searches and eliminating duplicate publications, the titles and abstracts of the searched studies will be screened for inclusion. For the articles identified as potentially relevant, the full text will be checked to determine whether the study will be included. All articles will be included or excluded based on predetermined criteria, and the reviewers will record the reasons for exclusion. Any discrepancies will be resolved through discussion with another researcher. The details of the study selection procedure are presented in Figure 1.

Stage 4: Charting the data

A preliminary data extraction sheet was developed with agreement on the pilot testing by the research team. After several revisions, a standardized data extraction form was developed.

4.1 Data extraction

The following items will be extracted from the included studies: general information, such as the last name of the first author and publication year; characteristics of the animals, such as species, sex, age, and weight; the respiratory models employed; methods for inducing respiratory disease; type of respiratory disease induced; details regarding the PM, such as type, origin, characteristics, and method by which it was obtained; herbal medicines characteristics, such as route of administration, composition,

dosage, and treatment period; and details of the control intervention. Data regarding research results (effect and safety), research findings, and proposed mechanisms will be extracted.

The data extraction process will be performed independently by two reviewers (YK, JL); these reviewers will crosscheck data from all of the included studies. Any disagreement between the two reviewers will be resolved through discussion with another researcher (KIK).

4.2 Assessment of the methodological quality and risk of bias of included studies

The inclusion of quality assessment in scoping reviews is controversial [24]. After discussion and consultation, we decided to include quality assessment for a better understanding of the methodological and reporting quality of the research community. The methodological quality of all included studies will be evaluated using the systematic review center for laboratory animal experimentation (SYRCLE's) risk of bias tool for animal studies [25]. This tool consists of 10 items and reflects the six aspects of the risk of bias: (1) selection bias (sequence generation, baseline characteristics, and allocation concealment), (2) performance bias (random housing and blinding), (3) detection bias (random outcome assessment and blinding), (4) attrition bias (incomplete outcome data), (5) reporting bias (selective outcome reporting), and (6) other sources of bias. For the consistency of critical appraisal, a pilot quality assessment will be conducted. Each reviewer will conduct a separate quality assessment. For each item, "yes" indicates a low risk of bias, "no" indicates a high risk of bias, and "unclear" indicates insufficient details to determine the risk of bias.

Stage 5: Collating, Summarizing and reporting the results

Extracted data will be utilized to develop an analytical framework for collating, synthesizing, and summarizing the extracted data. In the qualitative analysis stage, we will provide a table named 'Characteristics of included studies,' including the author, published year, country, animal model, number of analyzed participants, treatment group intervention (herbal medicine and composition) and dosage, control group intervention and dosage, and reported outcomes. We will also provide another table named 'Effect, mechanism, and safety herbal medicine for lung disease induced by PM. The results of the experiment are presented according to each intervention and dosage, possible mechanism suggested by the original research author, and the number of each adverse event. We will also gather research implications for further research from original articles that can be helpful for the research community. We will also provide a figure named 'Research map,' which will visualize possible mechanisms and candidate herbal preparation/medicinal plants. All of the processes for qualitative analysis will be conducted using Microsoft Excel.

If possible, we will conduct a quantitative synthesis of the extracted data. We will import the quantitative data into Review Manager software (version 5.3). For continuous variables, outcome measures will be represented as mean differences (MDs) with 95% confidence intervals (CIs). For binary variables, outcome measures will be represented by frequency and ratio. We will use random effects models for pooled-effect estimates; these models consider the variation between studies and assign weights for

each study accordingly. Between-study heterogeneity will be measured using the Chi-square test (using a significance threshold of $p < 0.1$) and quantified using the I^2 statistic. I^2 values < 25%, < 50%, and ≥ 50% indicate low, moderate, and high heterogeneity, respectively. If applicable, we will conduct subgroup analysis based on the herbal medicine classification and treatment duration.

Discussion

This is the first scoping review on herbal medicine for lung diseases included by PM. Throughout the scoping review, we were able to identify the effects, mechanism, safety, and preferred experimental protocol of herbal medicine. We adopted the scoping review methodology for several reasons. As we are focusing on the current research status on experimental research of herbal medicine for lung disease induced by PM, we are able to identify any type of available evidence in our field of interest by scoping review methodology [26]. We are also able to find knowledge gaps on the topic using a research map [26]. We are able to provide a comprehensive, detailed, and intuitive understanding of the topic's research status via our scoping review.

The deterioration of respiratory function due to PM is a global concern. The onset or exacerbation of respiratory disease due to PM is a major challenge to human health.

Therefore, in this scoping review of experimental studies, we aim to provide an objective and accurate assessment of the efficacy and safety of herbal medicines for treating respiratory diseases induced or worsened by PM. The search strategy has been established, and a conservative approach to data collection will be followed to avoid bias. For a rigorous review process, we will not consider gray literature or non-peer-reviewed articles to enhance the quality of the review. Moreover, predefined contributions and methods will enhance the robustness of our scoping review. If it is indicated, we will also consult experts in the field to increase the quality of the review.

This study has several limitations. We had not plan the optional sixth step (consultation) in our review. Since we focused on *in-vivo/in-vitro* research, we could not identify clinical trials in this field. Only restricted other types of clinical research are possible, such as case-control studies or retrospective cohort studies. Therefore, a scoping review of the candidate mechanisms of herbal medicine will enhance the quality of clinical research design. It will also be helpful for a better understanding of clinical data acquired from various clinical research designs. This scoping review may guide researchers to plan their experiments more effectively, thus reducing the resource burden for future research. It could also alleviate the advanced understanding of the mechanisms and target biomarkers of respiratory inflammation caused by PM exposure, ultimately assisting in overcoming the challenges involved in treating respiratory diseases induced by PM.

This research does not require ethical consideration and informed consent, as we will not use personal medical information but only information from previously published articles. For more dissemination, the research findings will be submitted to a scientific journal. This will also be presented at academic

conferences. Moreover, we will also develop an e-leaflet to provide key findings of our review to disseminate via social network services to the research community.

Abbreviations

CAM, complementary and alternative medicine; CENTRAL, Cochrane Central Register of Controlled Trials; CI, confidence interval; COPD, chronic obstructive pulmonary disease; MD, mean difference; MeSH, Medical Subject Heading; Particulate Matter, PM; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRISMA-Scr, PRISMA Extensions for Scoping reviews; ROS, reactive oxygen species; SYRCLE, Systematic Review Center for Laboratory Animal Experimentation.

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of data and materials:

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests:

The authors have no conflicts of interest to declare.

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Authors' contributions:

This study was conceptualized by KIK. JL and YK developed the search strategy. JL and YK drafted the protocol. KIK revised the manuscript and submitted the manuscript for publication. All authors have read and approved the final manuscript.

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