Efficacy and Safety of East Asian Herbal Medicine for Brain Metastases in Non-small Cell Lung Cancer: A Systematic Review and Meta-analysis Protocol to Identify Specific Herbs

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Abstract

Introduction: Brain metastasis (BM) is a significant risk factor for survival and prognosis in non-small cell lung cancer (NSCLC). While surgical resection and radiotherapy are the primary treatment modalities, the overall prognosis in NSCLC patients with BM remains poor, and all therapies lead to adverse events. East Asian herbal medicine (EAHM) has broad prospects as an adjuvant treatment, but its efficacy and safety remain controversial. We propose to conduct a systematic review and meta-analysis to summarize the clinical efficacy and safety of EAHM for the treatment of NSCLC with BMs and to identify specific herbs that can improve the prognosis. **Methods:** The PubMed, EMBASE, CENTRAL, Web of Science, CBM, CNKI, Wanfang, VIP, Evidence Reports on Kampo Treatment, ICHUSHI, and Oriental Medicine Advanced Searching Integrated System databases will be searched from their inception to October 2022. Randomized controlled trials will be included. Two authors will evaluate the eligibility and quality of the included trials. The methodological quality will be assessed using the RoB 2 tool, and Stata 16 will be used for data synthesis. Publication bias will be assessed using funnel plots and Egger tests. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system will evaluate the quality of the synthesized evidence. Further sensitivity analyses will be performed to determine the efficacies of specific herbs in EAHM. **Discussion:** Given there are currently no systematic reviews and meta-analyses of the efficacy of EAHM as a treatment for NSCLC with BMs, a compilation and analysis of the available high-quality clinical research evidence are essential. The results will help establish guidelines for the application of specific herbs as a complementary alternative therapy for BMs in NSCLC. The findings will be published in a peer-reviewed journal.
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Keywords

East Asian herbal medicine, brain metastases, non-small-cell lung cancer, randomized controlled trials, systematic review, meta-analysis

Introduction

Lung cancer has become a significant public health issue and an enormous burden, with the second-highest incidence and highest mortality rate among all cancers worldwide.[1] Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer,[2] commonly leading to brain metastasis (BM). While approximately a quarter of NSCLC patients present BMs at diagnosis, nearly half develop BMs during disease progression, which is the leading cause of death in

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these patients.[3-5] Generally, the brain is regarded as a sanctuary site for metastatic tumor cells because the blood-brain barrier protects them from immune surveillance and chemotherapy.[6]

Surgery, stereotactic radiosurgery (SRS), and whole-brain radiation therapy (WBRT) have been regarded as primary treatment modalities for NSCLC. Over the past decades, insights into the biology of this disease have led to the development of novel systemic therapies, including combined chemotherapy, anti-angiogenic therapy, targeted therapy, and immunotherapy.[7] However, the prognosis of NSCLC patients with BMs remains poor, and some patients with multiple brain lesions or diffuse BMs may lose the opportunity to undergo surgical treatment.[8] Moreover, treatment-related adverse events (AEs) following radiotherapy and systemic therapy are common and seriously affect the quality of life (QoL) and treatment compliance in NSCLC patients. Therefore, it is important to seek safe and effective complementary alternative therapies, such as East Asian herbal medicine (EAHM), which can provide effective adjuvant treatment for NSCLC with BMs.

EAHM refers to natural materials used as medicines to treat diseases in East Asia, based on theories of syndrome differentiation and treatment, which include traditional Chinese herbal medicine (CHM), Korean herbal medicine (KHM) and Japanese Kampo medicine (KM).[9] EAHM provide comprehensive approaches to NSCLC therapies,[10] and have gradually become a huge resource base for developing anticancer drugs.[11-13] EAHM have the unique advantages of synergism, attenuation of cancer treatment, comprehensive palliative treatment,[14] alleviation of treatment-related symptoms, and improvement in the overall well-being.[15,16] Previous clinical trials and meta-analyses have already demonstrated that EAHM could prolong the survival time, improve survival rate, reduce recurrence and metastasis, and improve clinical symptoms and QoL in NSCLC.[17,18] In addition, the use of EAHM also could delay acquired resistance and reduce the occurrence of treatment-related AEs in NSCLC.[19-21]

Meanwhile, EAHM could benefit NSCLC patients with BMs. The brain microenvironment, with its unique cell types, anatomical structures, metabolic constraints, and immune environment, differs drastically from the microenvironments of extracranial lesions, imposing a distinct and profound selective pressure on tumor cells and affecting the therapeutic effect of drugs on BMs.[22] Thus, immunotherapy, which targets the cancer-immune microenvironment, may provide a breakthrough in the treatment of BMs.[23,24] Moreover, EAHM plays a positive role in cancer immune regulation by regulating both the innate (macrophages, dendritic cells, natural killer cells, and myeloid-derived suppressor cells) and adaptive (CD4+/CD8+ T lymphocytes, Treg cells, and B cells) immunity.[25] Dendritic cells (DCs) are key antigen-presenting cells (APCs) that orchestrate T-cell immunity and play an important role in antitumor

programs.[26] Through this mechanism, EAHM, such as ginseng polysaccharides, may have immune-stimulatory or immune-suppressive properties.[27,28] Peripheral T lymphocytes are mainly divided into 2 subgroups: CD4+ and CD8+ T cells, which play a crucial role in anti-tumor immunity.[29] An animal study showed that Astragalus polysaccharides and polysaccharopeptide could improve the CD4+/CD8+ T lymphocytes ratio. The results suggest that the herbal formula can enhance the immunological function by increasing helper T cells.[30] In addition, several randomized controlled trials (RCTs) have demonstrated the significant advantages of combined EAHM over chemoradiotherapy or targeted therapy alone in the improvement of QoL, clinical manifestations, and disease control rate (DCR).[31,32]

To date, no systematic reviews or meta-analyses have focused on EAHM for NSCLC with BMs. Therefore, we believe that a comprehensive evaluation of the available high-quality evidence on the efficacy and safety of EAHM in NSCLC patients with BMs is essential. This systematic review aims to assess the efficacy and safety of EAHM for the treatment of BMs in NSCLC patients to provide credible evidence for its clinical application and identify herbs associated with improved prognosis for further research.

Methods

This protocol and systematic review will be guided by the PRISMA Protocols (PRISMA-P) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, respectively.[33,34] This study was registered with the PROSPERO (No. CRD42022300527). The proposed start date of this study was October 1, 2022. The PRISMA-P checklist is available in Additional File 1.

Eligibility Criteria

Participants. This study will review RCTs including NSCLC patients with BMs diagnosed using pathological and radiographic tests.

Interventions and controls. The treatments administered to the control group will include chemotherapy, radiotherapy, targeted therapy, immunotherapy, and usual care, while the intervention group will receive EAHM alone or in combination with treatments given to the control group. EAHM treatments include EAHM formulas and patented CHM, KHM, and KM drugs.

Outcomes. This study will include RCTs reporting the clinical efficacy of EAHM. Studies reporting only the outcomes of laboratory tests would be excluded.

Study type. Only RCTs with or without a blinded method were included in this systematic review. Observational

and animal studies and those with incomplete data were excluded.

Outcomes of Interest

The outcomes evaluated in this study will include those related to clinical efficacy and safety. The primary outcomes will include overall response rate (ORR) and overall survival (OS). Response rates calculated using the Response Evaluation Criteria in Solid Tumors (RECIST)[35] or WHO criteria[36] will be included. Given the strong correlation between these 2 antitumor treatment response evaluation criteria, the outcomes reported by them were considered homogeneous and pooled together.[37] Secondary outcomes included progression-free survival (PFS), central nervous system progression-free survival (CNS-PFS), DCR, central nervous system remission rate (CNS-RR), 1-year-survival rate, mortality rate, and QoL. Safety outcomes will focus on the incidence of AEs, including neurological AEs such as tremors, vertigo, and dizziness, based on the WHO criteria[36] or the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).[38]

Search Strategy

For the systematic review, we will search English [PubMed, Excerpt Medica Database (EMBASE), and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, Web of Science], Chinese [Chinese Biomedical Literature (CBM), China National Knowledge Infrastructure (CNKI), Wanfang and Chinese Scientific Journals Database (VIP database)], Japanese [Evidence Reports of Kampo Treatment (EKAT) and ICHUSHI], and Korean [Oriental Medicine Advanced Searching Integrated System (OASIS)] databases for RCTs reported from the database initiation to October 2022. Studies published in English, Chinese, Japanese, and Korean will be included. Furthermore, ongoing trials reported on ClinicalTrials and the Chinese Clinical Trial Registry (ChiCTR) will be included.

The search strategy will be developed using a combination of controlled vocabulary (MeSH terms and Emtree terms) and free-text terms. The MeSH terms will include "Carcinoma, Non-Small-Cell Lung," "Brain metastasis," "Herbal Medicine," "Drugs, Chinese Herbal," "Medicine, Kampo," "Medicine, Chinese Traditional," "Medicine, Korean Traditional," and "Ethnopharmacology." Additional File 2 shows the relevant entry terms to construct the Pubmed search strategy. Modifications to this search strategy will be applied to other databases.

Screening and Selection

Figure 1 presents a flow chart of the screening and selection process. The retrieved results will be imported to EndNote 20. After removing duplicates, 2 authors (BX and YG) will go through the titles and abstracts. Subsequently, the full texts will be reviewed and assessed for eligibility. Two reviewers (BX and YG) will carry out the screening and selection independently and in duplicate. Any disagreements will be resolved by discussion or by interposition with another reviewer (HW). RCTs that meet the eligibility criteria will be included in this study. The screening and selection process has been summarized in a full report using a PRISMA flow diagram.[33]

Data Extraction

Data extraction will be performed in duplicate independently by 2 reviewers (BX and YG). Microsoft Excel will be used to extract data. If necessary, we will contact researchers of the original studies for missing or incomplete data. The following data will be extracted from the included studies.

(1) Identification information: first author and year of publication.
(2) General information: study location, study setting (single-center or multi-center; blinded or unblinded), number of centers, sample size, duration of the study, and funding source.
(3) Participant details: age, sex, race, tumor site, and number of BMs.
(4) Interventions and comparison details: type of EAHM used (CHM, KM, or KHM), composition, dose, and duration of intervention; type of comparison (chemotherapy, radiotherapy, targeted therapy, immunotherapy, and usual care); regimen, dose, and duration of the comparison.
(5) Outcomes details: clinical outcomes and their results.

Quality Assessment

The Cochrane Collaboration's Risk of Bias 2 (RoB 2) tool will be used to assess the methodological quality of the included studies.[39] We will evaluate each study for the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcomes, and selection of the reported results. The risk of bias in individual studies will be graded as low, with some concerns, and high.

Evidence Synthesis for RCTs

The meta-analysis will be carried out if adequate data on primary or secondary outcomes are obtainable and the studies' results are homogeneous. The results will be presented as forest plots. The risk ratio (RR) for dichotomous data and mean difference (MD) for continuous data with
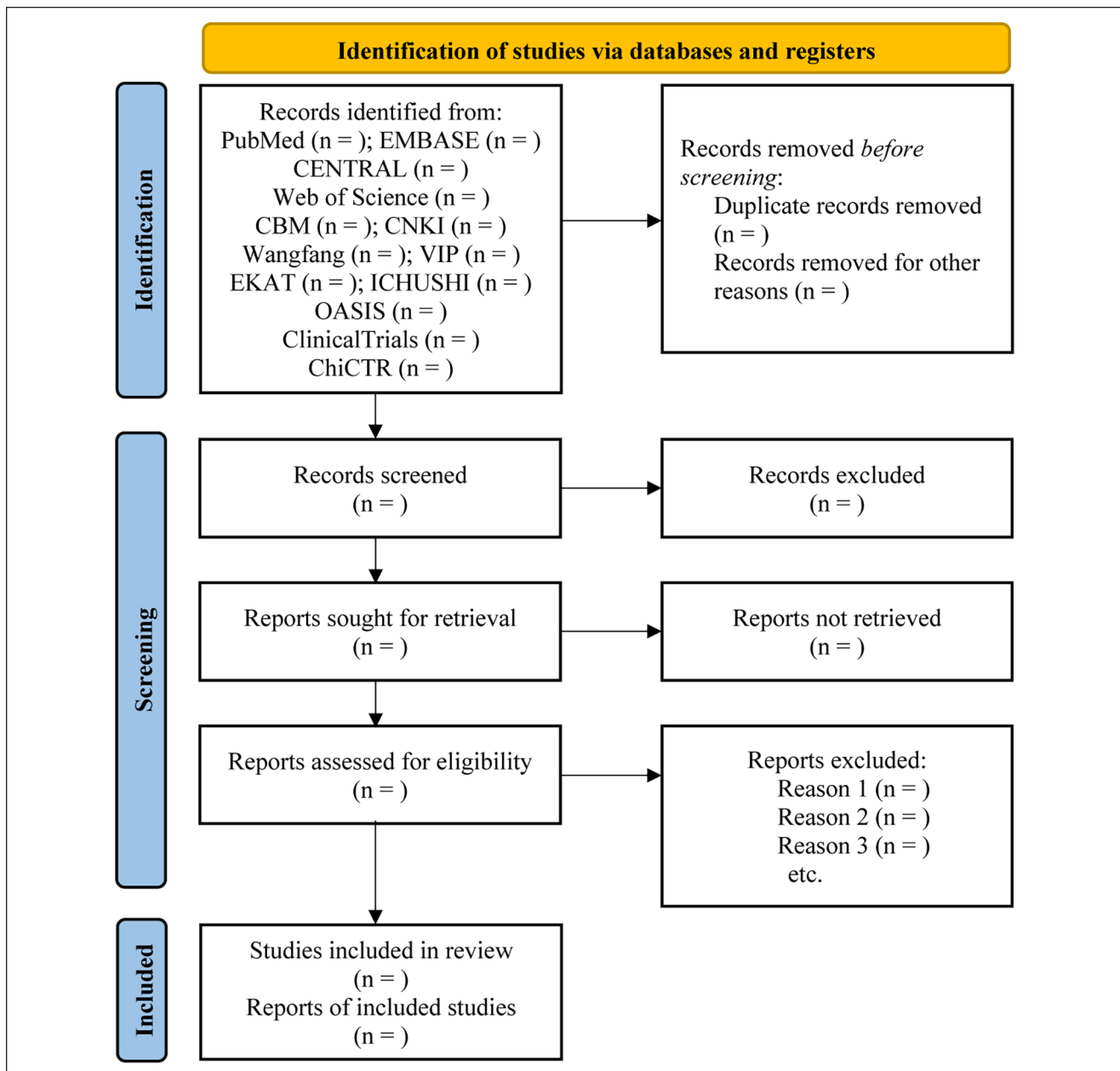
Figure 1. Flowchart of study selection.

95% confidence intervals (CIs) will be evaluated. A random-effects model will be used for data synthesis. Statistical inconsistency will be quantified using the I^2 statistic; $I^2 > 50\%$ and $>75\%$ will indicate substantial and considerable heterogeneity, respectively.[40] Subgroup and sensitivity analysis will be performed if substantial or considerable heterogeneity exists. Stata 16 will be used for data synthesis.

Meta-analyses will not be performed under conditions of considerable heterogeneity that remains resolved, limited evidence for comparison, incompletely reported outcomes, different effect measures, and considerable statistical heterogeneity. In these cases, a descriptive analysis will be performed.[40]

Subgroup Analysis

When conducting a meta-analysis, subgroup analysis will be performed according to (1) type of comparison (chemotherapy, radiotherapy, targeted therapy, immunotherapy, and usual care), (2) type of EAHM (CHM, KM, or KHM), (3) BM characteristics (tumor site and numbers), and (4) first-line treatment or backline treatment.

Publication Bias

Publication bias in the synthesized evidence will be assessed using funnel plots and the Egger et al test.[41]

Quality of Evidence

The quality of the cumulative evidence will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[42] The risk of bias, inconsistency, indirectness, imprecision, and reporting bias in the included studies will be assessed to determine whether the certainty of evidence should be downgraded. The quality of evidence will be classified as high, moderate, low, or very low.[42]

Selection of Herbs for Further Research

Previous studies proposed that if a particular herb in EAHM possessed antitumor effects, they would be reflected in the pooled effect estimates of the studies that used EAHM interventions containing this herb.[43,44] Sensitivity analysis of ORR will be performed for studies on multi-herbs used in NSCLC with BMs, herbs, or combinations of herbs presented in 2 or more studies, and the following principles will be applied:

(1) All studies will be grouped into several categories according to the differentiation of comparison; (2) studies containing the same herb or combination of herbs will be treated as one, and the pooled RR (95% CI) and I^2 will be calculated; (3) herbs or combinations of herbs will be excluded if there is no significant effect in the pooled results (95% CIs of RR overlap 1.0) and/or significant heterogeneity exists between studies ($I^2 \geq 40\%$); (4) the RR results will be listed in ascending order with 95% CI, the number of studies and I^2 values; (5) the combination of 3 or more herbs will be considered in turns until no possible combinations show significant effects; and (6) when herb combinations have higher RRs than herbs alone, they will be identified as potential examples of synergistic effects.

When evaluating herb combinations, only actual combinations will be included. For example, although the pairing of Herb 1 with Herb 2 appears possible, all the herb interventions that contain Herb 1 + Herb 2 may also include Herb 3. Thus, the RR in this group was actually from the combination of the 3 herbs, with no independent contribution from Herb 1 + Herb 2. Therefore, only Herb 1 + Herb 2 + Herb 3 are included in the RR results matrix.

Discussion

BM is a significant risk factor affecting the survival and prognosis of NSCLC patients. However, given the current existing clinical research and the ongoing prospective clinical trials, we believe that EAHM could be a new therapeutic strategy for NSCLC with BMs. The novelty of our proposed study is that it will be the first systematic review and meta-analysis to evaluate the efficacy and safety of EAHM for BMs in NSCLC. Our study will present valuable evidence supporting the use of EAHM either alone or in combination with other therapies for NSCLC with BMs, thereby providing a reference for subsequent treatment options.

In addition, the interventions included in this review will not be limited to CHM, but will also include other traditional herbal treatments, such as KHM and KM. It should be emphasized that research team of Professor Lee, starting from the properties of these traditional herbal medicine, defined them as EAHM for the first time and carried out evaluation studies of related diseases.[18] The researchers also conducted some SRs and meta-analyses to evaluate the efficacy and safety of EAHM for primary cancer pain, autism spectrum disorder, rheumatoid arthritis, and psoriasis.[9,45,46] At the same time, this team applied the association rule mining to identify core herb combination based on the collected data, to provide a methodological reference for our study. Interestingly, our study will use sensitivity analysis to mine herbal combinations. We will verify the similarities and differences of the results obtained by these 2 methods in formal work to demonstrate the advantages of EAHM.

This study will compare the efficacy (OS, PFS, CNS-PFS, ORR, CNS-RR, DCR, 1-year-survival rate, mortality rate, and QoL) and safety (grade 3 or higher AEs) of EAHM in NSCLC with BMs. We will also compare the efficacy of EAHM in combination with various therapies (radiotherapy, chemotherapy, targeted therapy, and immunotherapy) to explore its benefits more precisely. We will pool herb (s) with similar effects using a sensitivity analysis and assess the relative clinical efficacy of different herb combinations. The correlation between the type of intervention, sites of BMs, number of BMs, initial treatment status, and pathological staging will also be displayed by subgroup analysis. Any other outcomes reported in the eligible studies, such as cognitive function, will also be extracted and reported.

This study will provide valuable guidance for treatment regimens for NSCLC patients with BMs. One of the study limitations is that some potential literature (such as gray literature) may not be included because of the restrictions in the literature search strategy, which could impact the strength of our findings. However, we hope to use data from upcoming studies to update the existing evidence. More rigorously designed, large-sample, multi-center clinical trials or in vivo and in vitro experiments are needed in the future to better validate the synergistic effects of EAHM and its potential herbal combinations.

Author Contributions

BX, YG and HW conceived and registered this systematic review. BX, YG and HW drafted the first versions of this manuscript. XZ, JW, and JL provided critical revisions to the design of the study and edited the manuscript. JL revised the manuscript. All authors read and approved the final manuscript for submission.

Data Availability

All datasets presented in this study are included in the article/ Supplemental Files.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics and Dissemination

Given the nature of the study, approval from an Ethics Committee is not required. However, all the included trials will comply with the current ethical standards and the Declaration of Helsinki. We will evaluate the available evidence and provide precise advice on the use of EAHM in NSCLC patients with BMs. The findings will be published in a peer-reviewed journal or presented at a relevant conference.

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Supplemental Material

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