

INPLASY PROTOCOL

To cite: Liu et al. Effects of Different Chinese Herbals on Animal Models of Vascular Dementia: a Protocol for Systematic Review and Network Meta-analysis of preclinical studies. Inplasy protocol 202090066. doi: 10.37766/inplasy2020.9.0066

Received: 15 September 2020

Published: 15 September 2020

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Support: Chengdu Science Bureau.

Review Stage at time of this submission: Preliminary searches.

Conflicts of interest:
There are no conflicts of interest to disclose.

Effects of Different Chinese Herbals on Animal Models of Vascular Dementia: a Protocol for Systematic Review and Network Meta-analysis of preclinical studies

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Review question / Objective: Which Chinese herb is more effective on improving memory in animal models of Vascular Dementia? **P:** All animal models with Vascular Dementia **I:** Traditional Chinese herbs and their effective extracts or derivatives **C:** Placebo, no treatment, or sham-treated **O:** the escape latency and frequency of crossing former platform in Morris water maze test **S:** Controlled studies with at least one comparative group.

Condition being studied: Traditional Chinese herbs, which have been applied in the treatment of dementia in Asian countries for more than 2000 years, have drew growing concerns from clinical researchers around the world. A number of traditional Chinese herbs and their effective extracts or derivatives have been proven effective in animal models of VaD, which are potential to become novel therapeutic agents of VaD. However, the comparative effectiveness of these herbs has not been studied. Therefore, aiming to compare, rank and interpret the effectiveness of traditional Chinese herbs in treating animal models of VaD, we attempt to perform a systematic review and network meta-analysis to provide further evidence for explore novel potential drugs.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 September 2020 and was last updated on 15 September 2020 (registration number INPLASY202090066).

INTRODUCTION

Review question / Objective: Which Chinese herb is more effective on improving memory in animal models of Vascular Dementia? **P:** All animal models

with Vascular Dementia **I:** Traditional Chinese herbs and their effective extracts or derivatives **C:** Placebo, no treatment, or sham-treated **O:** the escape latency and frequency of crossing former platform in Morris water maze test **S:** Controlled

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Rationale: Vascular dementia (VaD), accounting for approximately 20% of all dementia cases, is the second most common type of dementia following Alzheimer disease. VaD is mainly caused by aging of the cerebrovascular structure. With growth of age, the incidence of VaD increases steeply, rising from 1.5% at the age of 70–75 to 15% at the age of 80- years old. The VaD patients always have suffered from stroke, obesity, hypertension or hyperlipidemia. Thus, the incident of VaD is much higher in developing countries due to the uncontrolled cerebrovascular risk factors. Although some anti-AD pharmaceuticals, such as cholinesterase inhibitors and excitatory glutamate receptor antagonists, have been applied in treatment of VaD, the effectiveness remains unsatisfactory. Therefore, it is crucial to develop novel therapeutic agents for VaD.

Condition being studied: Traditional Chinese herbs, which have been applied in the treatment of dementia in Asian countries for more than 2000 years, have drew growing concerns from clinical researchers around the world. A number of traditional Chinese herbs and their effective extracts or derivatives have been proven effective in animal models of VaD, which are potential to become novel therapeutic agents of VaD. However, the comparative effectiveness of these herbs has not been studied. Therefore, aiming to compare, rank and interpret the effectiveness of traditional Chinese herbs in treating animal models of VaD, we attempt to perform a systematic review and network meta-analysis to provide further evidence for explore novel potential drugs.

METHODS

Search strategy: Search strategy in PubMed #1 "Models, Animal"[Mesh] #2 "animal model"[All Fields] OR "animal disease model"[All Fields] OR "feline model"[All Fields] OR "cat model"[All Fields] OR "porcine model"[All Fields] OR "pig model"[All Fields] OR "swine

model"[All Fields] OR "rodent model"[All Fields] OR "murine model"[All Fields] OR "mouse model"[All Fields] OR "rat model"[All Fields] OR "canine model"[All Fields] OR "dog model"[All Fields] OR "ovine model"[All Fields] OR "sheep model"[All Fields] OR "primate model"[All Fields] OR "monkey model"[All Fields] OR "simian model"[All Fields] OR "macaque model"[All Fields] OR "rabbit model"[All Fields] OR "leporine model"[All Fields] #3 #1 OR #2 #4 "drugs, Chinese herbal"[Mesh] OR "medicine, Chinese traditional"[Mesh] OR "medicine, oriental tradition"[Mesh] OR "phytotherapy"[Mesh] #5 "Chinese herb"[All Fields] OR ("Chinese"[All Fields] AND "herb"[All Fields]) OR "Chinese herbs"[All Fields] OR ("Chinese"[All Fields] AND "herbs"[All Fields]) OR "Chinese herbal"[All Fields] OR ("Chinese"[All Fields] AND "herbal"[All Fields]) #6 #4 OR #5 #7 "dementia, multi-infarct"[MeSH Terms] or "dementia, vascular"[MeSH Terms] #8 ("dementia"[All Fields] AND "multi-infarct"[All Fields]) OR "multi-infarct dementia"[All Fields] OR ("multi"[All Fields] AND "infarct"[All Fields] AND "dementia"[All Fields]) OR "multi infarct dementia"[All Fields] OR ("dementia"[All Fields] AND "vascular"[All Fields]) OR "vascular dementia"[All Fields] OR ("vascular"[All Fields] AND "dementia"[All Fields]) #9 #7 OR #8 #10 #3 AND #6 AND #9.

Participant or population: All animal models with Vascular Dementia.

Intervention: Experimental group were treated with traditional Chinese herbs and their effective extracts or derivatives.

Comparator: Comparative group were handled with placebo, no treatment, or sham-treated.

Study designs to be included: Controlled studies with at least one comparative group.

Eligibility criteria: The eligibility criteria for identifying studies is designed according to PICOS. Only the studies qualified with all inclusion criteria will be considered for inclusion. The studies meet with any of

exclusion criteria will be excluded. 1. Participants: 1.1. Inclusion criteria All animal models with Vascular Dementia, regardless of species, ages or sexes. 1.2 Exclusion criteria Animal models with comorbidities or in-vitro models will be excluded. 2. Interventions: 2.1. Inclusion criteria Experimental group were treated with traditional Chinese herbs and their effective extracts or derivatives. Dose or duration of administration is not limited. 2.2. Exclusion criteria We will exclude the studies combining with other therapies. Chinese herbal formula studies will also not be included. 3. Comparator: 3.1. Inclusion criteria Comparative group were handled with placebo, no treatment, or sham-treated will be included. 3.2. Exclusion criteria Other control conditions. 4. Outcome measure: 4.1. Inclusion criteria The outcome measures are the escape latency and frequency of crossing former platform in Morris water maze test. 4.2. Exclusion criteria Studies without the selected outcomes. 5. Study design: 5.1. Inclusion criteria Controlled studies with at least one comparative group. 5.2. Exclusion criteria Case-reports, cross-over studies will be excluded.

Information sources: Both Chinese and English database resources will be searched for the identification of valid data, including CNKI, EMBASE, PubMed, Scopus, Wanfang Database, VIP Database, Web of Science, and Chinese Biomedical Literature Database. We will search the databases from their inception to June 30, 2020. Potential literatures in reference lists of included studies will also be searched for supplement. After scanned with a pre-designed search strategy in mentioned databases, duplicate articles will be excluded. Afterward, two reviewers will review titles and abstracts of the rest papers independently to select qualified studies in line with the eligibility criteria. Finally, the two reviewers will download the full-text of selected literatures for further evaluation. Division of opinion between the two reviewers will be addressed through discussion or consultation with a third reviewer.

Main outcome(s): As a classic test for evaluation of memory, Morris water maze is widely accepted and used in animals' studies on VaD. The escape latency in Morris water maze is selected as our main outcome.

Additional outcome(s): As a classic test for evaluation of memory, Morris water maze is widely accepted and used in animals' studies on VaD. The frequency of crossing former platform in Morris water maze is selected as our secondary outcome.

Data management: Three initial studies will be used to pilot and refine to establish standard extraction table. Afterward, two independent reviewers will extract available data from the full-text of qualified studies. Numerical data will be extracted from tables, text or figures initially. If these data are not detailed, we will use digital ruler software to extract data from graphs. A third reviewer will be invited to be consulted with in case of divided opinions. If there is any missing data, the researchers will try to get touch with the authors to obtain complete data.

Quality assessment / Risk of bias analysis: SYRCLE's risk of bias tool will be applied by two independent reviewers to evaluate the risk of bias. Division of opinion between the two reviewers will be solved by discussion or consultation with a third one.

Strategy of data synthesis: To obtain further evidence of Chinese herbs on VaD, we will perform a narrative synthesis of the qualified studies based on basic characteristics. Then a network meta-analysis will be conducted due to the absence of direct comparisons between these herbs. Since all selected outcomes are continuous variables, we will computer the standardized mean difference and related 95% confidence intervals. A random effect model will be applied to data synthesis. The homogeneity across the included studies will be analyzed by I^2 statistic. We will use node splitting method to examine the inconsistency between direct and indirect results. If the inconsistency exists, we will apply

inconsistency model, otherwise the consistency model will be chosen. Ten or more qualified articles are needed in meta-analysis. If not enough studies, we will report descriptive summary.

Subgroup analysis: Possible subgroup analysis based on homogeneity analysis will be performed, if necessary. The potential variables for subgroup analysis are animal sex, species and methods of induction of VaD.

Sensibility analysis: We will perform global or local sensitivity analysis to evaluate the effect of each research on the random effects model, if necessary.

Language: Only articles written in English or Chinese will be considered for inclusion.

Country(ies) involved: China.

Other relevant information: We will perform Funnel plot and Begg's test or Egger's test for publication bias assessment.

Keywords: traditional Chinese herbs; vascular dementia; animal models; network meta-analysis; systematic review.

Dissemination plans: The findings of this research will be published on a recognized peer-review journal.

Contributions of each author:

Author 1 - Yunlu Liu - Conceptualization and original draft writing.

Author 2 - Xinshang Zhang - Data curation.

Author 3 - Ming Lan - Investigation.

Author 4 - Wenyan Jiang - Formal analysis.

Author 5 - Yong Li - Review & editing draft.

Author 6 - Juan Yang - Methodology.

Author 7 - Yang Wang - Supervision and funding acquisition.