INPLASY PROTOCOL

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**Conflicts of interest:**
**None declared.**

# Efficacy and safety of Chinese Herbal Medicine for Vascular dementia: A protocol of systematic review and meta-analysis

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**Review question / Objective:** **As a common type of clinical dementia, the prevalence rate of vascular dementia(VaD) increased rapidly in recent years, damaging both patients' health and social-economic prospect. There is currently no effective treatment for VaD, though western medicines can slightly improve patients' cognitive function, but not brought a significant improvement in daily life ability. Chinese herbal medicine(CHM) has been widely employed to treat dementia for more than 2000 years in China. Despite the proliferation of relevant literature, there is still a lack of evidence to prove the effectiveness and safety of such therapy. Therefore, this systematic review and meta-analysis protocol is aimed to assess the efficacy and safety of CHM forVaD.**
**Information sources:** **6 English databases (PubMed, Web of Science, Embase, Springer, CENTRAL and WHO International Clinical Trials Registry Platform) and 4 Chinese databases (Wan fang Database, Chinese Scientific Journals Database, China National Knowledge Infrastructure Database and Chinese Biomedical Literature Database).**

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 January 2022 and was last updated on 18 January 2022 (registration number INPLASY202210098).

## INTRODUCTION

**Review question / Objective:** **As a common type of clinical dementia, the prevalence rate of vascular dementia(VaD) increased rapidly in recent years, damaging both patients' health and social-economic prospect. There is currently no effective treatment for VaD, though western medicines can slightly improve patients' cognitive function, but not brought a significant improvement in daily life ability. Chinese herbal medicine(CHM) has been widely employed to treat dementia for more than 2000 years in China. Despite the proliferation of relevant literature, there is still a lack of evidence to prove the effectiveness and safety of such therapy.**

Therefore, this systematic review and meta-analysis protocol is aimed to assess the efficacy and safety of CHM forVaD.

**Condition being studied:** Vascular dementia(VaD) is a clinical syndrome of acquired intellectual impairment, which caused by clinical stroke or subclinical vascular brain injury, involving at least one cognitive impairment. Being the most common type of dementia after Alzheimer's disease(AD), VaD accounts for more than 20% of dementia worldwide. The prevalence of cerebrovascular diseases and dementia are also rising with the increase of the aging population, bringing a heavy burden to patients and society. In developed countries, approximately 5%-10% of elderly people over the age of 65 suffer from dementia, while the incidence of VaD doubles every 5.3 years. The prevalence of dementia in China is slightly lower than that in the richer countries. There are about 5% of dementia patients in the elderly over 65 years old, of which the prevalence of VaD is 1.50%. The incidence of VaD increases dramatically with age. The incidence of VaD is as high as 15% among the elderly aged 80 and above, while the rate is about 1.5% in 70-year-old. Cognitive damage caused by VaD may involve multiple cognitive domains such as attention/executive function, memory, emotion, audio-visual, language, etc. It may also be accompanied by mental, behavioral, and personality abnormalities, which seriously disturb the daily living ability or socially occupational function. Clinical pathological studies suggest that vascular risk factors and cerebrovascular disease will increase the risk of AD. In clinical dementia patients, the prevalence of vascular form and Alzheimer's type is similar. Vascular lesions and neurodegenerative pathological processes may have an additive effect on cognitive impairment and increase the risk of clinical dementia. VaD has caused critical social and economic implications in terms of direct medical, social care costs, and the costs of informal care. Currently, there is no effective treatment for VaD. The standard treatment plan mainly focuses on preventive intervention and symptom management.Preventive interventions include improving lifestyle, controlling vascular risk factors, and treating primary diseases. Symptom management medicine mainly include Cholinesterase inhibitor and NMDA receptor antagonists. Besides, some other medicines can be employed to prevent further brain damage, such as Butylphthalide, Cerebrolysin, deproteinized calf blood extract, and Nimodipine. Even though the drugs can slightly improve the cognitive function of VaD patients, these effects have not brought a significant improvement in daily life ability. Also, the safety and long-term efficacy of these VAD treatment interventions have not been fully validated. Chinese herbal medicine(CHM) has been widely used as the treatment of dementia for more than 2000 years in China. Several meta-analyse suggested that CHM may be effective treatment option for VaD and is generally safer. However, most of the data included in the previous studies was only derived from the Chinese medical database, and the methodological quality of some studies was low. There is non-sufficient evidence to recommend the routine use of CHM for VaD. This systematic review intends to evaluate the efficacy and safety of CHM in the treatment of VaD by employing objective result measurements and indices on the inclusion of newly released Randomized controlled trials(RCTs).

## METHODS

**Search strategy:** Searching strategy: 1. Data sources - The two researchers will independently collect data through computer retrieval. All RCTs of CHM for the treatment of VaD will be included from 6 English databases (PubMed, Web of Science, Embase, Springer, CENTRAL and WHO International Clinical Trials Registry Platform) and 4 Chinese databases (Wan fang Database, Chinese Scientific Journals Database, China National Knowledge Infrastructure Database and Chinese Biomedical Literature Database). Trials will be collected from the establishment of the database to July 1, 2020. 2. Searching strategy - The search strategy will be created based on the Cochrane handbook

for systematic reviews of interventions. The two researchers will strictly follow the tactics for data collection. The search strategy for PubMed is given as an example . Other electronic databases will also be searched according to similar search strategies. Meanwhile, some related documents will also be supplemented by manual searches.

**Participant or population:** This article is a protocol that does not involve patients and personal information collectionThis study does not involve a population or participant

**Intervention:** Not applicable.

**Comparator:** Not applicable.

**Study designs to be included:** Systematic review and meta-analysis.

**Eligibility criteria:** 2.3. Inclusion criteria for study selection2.3.1. Types of studies. The type of RCT that utilize CHM or combine CHM with conventional western medicine treatment will be eligible. Non-randomized controlled studies, quasi-randomized controlled studies, observational studies, retrospective studies, cross-sectional studies, prospective studies numbered by medical records will be excluded. The language will be limited to English and Chinese.2.3.2. Types of participants. Patients diagnosed with VaD will be included in this study and the following eligibility diagnostic criteria were accepted: American Stroke Association/American Heart Association (ASA/AHA) 2011 standard, American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM) 2013 standard, vascular behavioral and cognitive disorders (Vas-Cog) 2014 standard, and vascular injury recognition jointly developed by global experts Guidelines from the vascular impairment of cognition classification consensus study (VICCCS) 2018 standard, Chinese vascular cognitive impairment 2019 standard. All patients who meet the diagnostic criteria will be included in this study, regardless of gender, age, race, nationality, education, and economic status. Patients diagnosed with mild cognitive impairment, dementia but no cerebrovascular disease, evidence of other neuropathy causing dementia, drug abuse, alcoholism, drug dependence, and other clinical trials are excluded from this study.2.3.3. Types of interventions.Studies reporting all sorts ofNot applicable.

**Information sources:** 6 English databases (PubMed, Web of Science, Embase, Springer, CENTRAL and WHO International Clinical Trials Registry Platform) and 4 Chinese databases (Wan fang Database, Chinese Scientific Journals Database, China National Knowledge Infrastructure Database and Chinese Biomedical Literature Database)

**Main outcome(s):** 2.4. Outcome measures evaluation - The outcome measures of this review evaluated efficacy through cognitive function, daily and social life abilities, and mental symptoms. Assess safety through safety indicators. 2.4.1. Primary outcome measures. The primary outcome indicators will be selected: Mini-mental state examination(MMSE), Montreal Cognitive Assessment(MoCA), Hasegawa Dementia Scale(HDS), Alzheimer disease assessment scale-cog(ADAS-cog), Vascular dementia assessment scale-cog(VaDAS-cog), Alzheimer disease cooperative Study-Activities of Daily Living(ADCS-ADL), Functional activities questionnaire(FAQ), Instrumental Activities of Daily Living scale of Lawton (LADL), Neuropsychiatric Inventory (NPI). 2.4.2. Secondary outcome measures. The secondary outcome measures will be chosen: clinical dmentia rating Scale(CDR), Wechsler Memory Scale 4th Edition(WMS-IV), Rey Auditory Verbal Learning Test(RAVLT), Hopkins Verbal Learning Test-Revised(HVLT), Boston Naming Test-Second Edition (BNT-2), Trail Making Test-Part A(TMT-A), Trail Making Test-Part B(TMT-B), Clock drawing test(CDT), Progressive Deterioration scale(PDS), (disability assessment for dementia(DAD), Alzheimer's disease cooperative study-Activities of Daily Living-severe(ADCS-ADL-severe), Center for Epidemiologic Studies Depression Scale(CESD). 2.4.3. Security Index. 1.

Treatment Emergent Symptom Scale (TESS). 2. General physical examination (temperature, pulse, respiration, blood pressure). 3. Routine examination of blood, urine and stool. 4. Electrocardiogram. 5. Liver and kidney function examination.

**Quality assessment / Risk of bias analysis:** 2.5.3. Assessment of risk of bias. The Cochrane bias risk assessment tool (RevMan5.3) will be employed to evaluate the literature's quality by the risk of bias. The judgment of the risk of bias includes seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. According to the scores of bias assessment, every literature will be divided into high-grade, low-grade, and not clear. The two researchers will independently conduct the risk evaluation of bias, and the third reviewer will give a final decision if the researchers have any disagreement.

**Strategy of data synthesis:** 2.5.4.Statistical Analysis Methods and Data synthesis - The process of statistical analysis and data synthesis will be conducted by Review Manager 5.3 software provided by the Cochrane Collaboration. Dichotomous data will be analyzed by using the risk ratio (RR) with 95% confidence interval (CI). In comparison, continuous data will be analyzed by using the mean difference (MD) or standard mean difference (SMD) with 95% CI. Statistical heterogeneity will be assessed by the chi-square test and I2 index. If the outcome of heterogeneity analysis shows that P>0.10, I2<50%, which means no statistical heterogeneity among trials, a fixed-effect model will be utilized. If there is statistical heterogeneity among studies (P≤0.10,.I2≥50%), the heterogeneity sources will be analyzed by meta-regression or sensitivity analysis, and subgroup analysis might be undertaken. If statistical heterogeneity exists among comprised studies, the subgroup analysis will be performed to detect the source of statistical heterogeneity. The sensitivity analysis for this research will be based on heterogeneity. When heterogeneity occurs, sensitivity analysis will be operated by changing the effect model and statistical methods. Certain low-quality studies or unblinded trials may be excluded, for instance. Publication bias would be evaluated only if the subgroup included more than ten studies. Asymmetric funnel arising from publication bias will be identified and corrected by the trim and fill method if necessary.

**Subgroup analysis:** Not applicable.

**Sensitivity analysis:** Not applicable.

**Country(ies) involved:** China.

**Keywords:** vascular dementia, Chinese herbal medicine, protocol, systematic review.

**Contributions of each author:**

Author 1 - Aihua Tan - Aihua Tan conceived and designed the protocol, and rafted the protocol manuscript,planned the data extraction,critically revised the manuscript for methodological and intellectual content.
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Author 6 - Simiao Ran - Simiao Ran conceived and designed the protocol, and rafted the protocol manuscript, critically revised the manuscript for methodological and intellectual content.
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