INPLASY PROTOCOL

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Corresponding author:
Guo Ying

837404672@qq.com

Author Affiliation:
Chengdu University of Traditional Chinese Medicine

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Conflicts of interest:
None.

Salvia miltiorrhiza improves Alzheimer's disease: a protocol for systematic review and meta analysis

Guo, Y[1]; Dong, X[2]; Zhang, RY[3]; Zhong, YM[4]; Yang, P[5]; Zhang, SY[6].

Review question / Objective: **Are Salvia miltiorrhiza effective and safety in the treatment of Alzheimer's disease?**
Condition being studied: **Alzheimer's disease (AD) is an age-related neurodegenerative disease characterized by progressive cognitive and memory disorders, senile plaques, neurofibrillary tangles, and neuronal cell death 127. According to Alzheimer's Disease International, there are approximately 46.8 million patients with dementia syndrome worldwide, which is expected to double every 20 years, or rises to approximately 131.5 million by 2050. Salvia miltiorrhiza, as an important lipophilic component of SM, has been one of the research priorities. Many clinical trials have found that Salvia miltiorrhiza has a significant improvement effect on Alzheimer's disease. However its quality and efficacy have not been systematically evaluated, which affects the reliability of the research conclusion. This brings confusion to the clinical application for clinicians.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 July 2020 and was last updated on 15 July 2020 (registration number INPLASY202070066).

INTRODUCTION

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an important lipophilic component of SM, has been one of the research priorities. Many clinical trials have found that Salvia miltiorrhiza has a significant improvement effect on Alzheimer's disease. However its quality and efficacy have not been systematically evaluated, which affects the reliability of the research conclusion. This brings confusion to the clinical application for clinicians.

METHODS

Search strategy: Two reviews will search the literature independently with cross-check. Any inconsistency will be solved by a third reviewer. Manual search will be performed if relevant literature are found in the included studies. The electronic search will be conducted using a combination of following keywords: AD, Alzheimer's disease, dementia, senile dementia, cognitive impairment, neurocognitive disorder, cognitive decline, Salvia miltiorrhiza, randomized controlled trial, controlled clinical trial, randomized, randomly.

Participant or population: Patients diagnosed with AD (using any recognized diagnostic criteria, such as Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), or Recommendations from the National Institute on Aging-Alzheimer's Association work groups on diagnostic guidelines for AD (NIA-AA), or Chinese Guidelines for the Diagnosis and Treatment of Alzheimer's Disease or Other Dementia. There is no restriction on the age, gender, nationality and nation of the patient and the duration and severity of the disease. Include: (1) vascular dementia, frontotemporal, or any other forms of dementia, (2) other disorders such as Parkinson disease, traumatic brain injury, stroke, and cancer that may impact cognitive function will be excluded.

Intervention: Analyzed interventions included Salvia miltiorrhiza used as monotherapies、Chinese herbal compound prescription and related injections. Studies are excluded, if no Salvia miltiorrhiza is involved in medical interventions.

Comparator: Patients diagnosed with Alzheimer's disease but who have not received it or who have only received non-pharmacological treatment.

Study designs to be included: Randomized controlled trial with no limitations on blinding or publication types will be included.

Eligibility criteria: Only randomized controlled trials of Salvia miltiorrhiza for the treatment of Alzheimer's disease will be includes. Collect only experiments recorded in Chinese and English. Non-randomized trials, case reports, observational studies, and reviews will be excluded.

Information sources: We search the following databases from January 2010 to July 1, 2020: China National Knowledge Infrastructure, China Biological Medicine, Chinese Scientific Journals Data base, Wanfang database, PubMed, EMBASE. We search English and Chinese articles for review, and collect additional references from review references and original research articles.

Main outcome(s): The primary outcomes include changes in the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog), and Activities of Daily Living (ADL) scale. Additional outcomes are clinical effective rate and adverse event rate.

Quality assessment / Risk of bias analysis: Two reviews will assess the risk of publication bias for every included RCT with the Cochrane Risk of Bias Tool independently in terms of seven items, including random sequence generation, allocation con- cealment, blinding of participants and researchers, incomplete outcome data, selective reporting bias, and other bias. Each item will be graded as high, unclear, or low risk of bias.

Inconsistency will be solved by consultation with a third reviewer.The Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines will be utilized to grade the quality of evidence as very low, low, moderate, or high.

Strategy of data synthesis: In line with the Cochrane guideline, a fixed-effect model will be utilized to pool and analyze the outcome data if I2< 50, and a random-effect model will be employed if I2≥ 50. Subgroup analysis or meta-regression will be performed to assess the potential sources and present reasonable explanations for the heterogeneity.

Subgroup analysis: (1) vascular dementia, frontotemporal, or any other forms of dementia, (2) other disorders such as Parkinson disease, traumatic brain injury, stroke, and cancer that may impact cognitive function will be excluded.

Sensibility analysis: Sensitivity analysis will be applied to evaluate the stability of the pooled results of included RCTs according to the methodological quality, sample size and missing data.

Country(ies) involved: China.

Keywords: Alzheimer's disease, Salvia miltiorrhiza, meta-analysis, protocol, randomized controlled trials, systematic review.

Contributions of each author:
Author 1 - Ying Guo.
Author 2 - Xing Dong.
Author 3 - Ren yan Zhang.
Author 4 - Yan mei Zhong.
Author 5 - Pneg Yang.
Author 6 - San yin Zhang.