

INPLASY PROTOCOL

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None declared.

Chinese Herbal Medicine for People with Multiple Sclerosis: a systematic review and meta-analysis

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Review question / Objective: To assess the benefits and adverse effects of Chinese herbal medicine (CHM) in people with multiple sclerosis.

Condition being studied: Multiple sclerosis (MS) is an unpredictable chronic disease of the central nervous system that interrupts the information flow within the brain, and between the brain and body. MS is a potentially disabling disease, which is characterized by inflammation, demyelination and degenerative changes. MS is becoming the major cause of chronic disability, especially in young adults. Estimates suggest that over 2 million people around the world have MS, corresponding to a prevalence of 30.1 cases per 100, 000 population. The prevalence and incidence of MS has increased almost globally over time. The female to male ratio in MS varies from 2:1 to 3:1, depending on geographic region, and has increased over the past decades. The precise pathogenesis and etiology of this complex disease are still a mystery. It is believed that a combination of environmental and genetic factors contributes to the risk of developing MS. Yet, low serum vitamin D levels, smoking, childhood obesity, and Epstein–Barr virus infection may play a role in disease development.

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INTRODUCTION

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characterized by inflammation, demyelination and degenerative changes. MS is becoming the major cause of chronic disability, especially in young adults. Estimates suggest that over 2 million people around the world have MS, corresponding to a prevalence of 30.1 cases per 100, 000 population. The prevalence and incidence of MS has increased almost globally over time. The female to male ratio in MS varies from 2:1 to 3:1, depending on geographic region, and has increased over the past decades. The precise pathogenesis and etiology of this complex disease are still a mystery. It is believed that a combination of environmental and genetic factors contributes to the risk of developing MS. Yet, low serum vitamin D levels, smoking, childhood obesity, and Epstein-Barr virus infection may play a role in disease development.

METHODS

Participant or population: We will include adults, males and females (18 years or older), diagnosed with MS, according to the Poser, or McDonald criteria and its revisions. We will consider participants with any form of MS, regardless of degree of disability, or duration of disease.

Intervention: All forms of CHM, including herb extracts, single herbs, Chinese patent medicines, or a mixture of herbs (herbal formula), used as monotherapy or as add-on treatment, irrespective of dose, route, frequency, or duration of use.

Comparator: Placebo, no intervention, or any other intervention.

Study designs to be included: All randomised controlled trials (RCTs) or cross-over trials reported as full-text. We will include related trials regardless of their publication status and language of publication. For cross-over trials, we would only include the first period of randomization to intervention or control to avoid a unit of analysis error.

Eligibility criteria: We will include adults, males and females (18 years or older), diagnosed with MS, according to the Poser, or McDonald criteria and its revisions. We will consider participants with any form of MS, regardless of degree of disability, or duration of disease. All forms of CHM, including herb extracts, single herbs, Chinese patent medicines, or a mixture of herbs (herbal formula), used as monotherapy or as add-on treatment, irrespective of dose, route, frequency, or duration of use. We will include placebo, no intervention, any other intervention as a comparison intervention. All randomised controlled trials (RCTs) or cross-over trials reported as full-text. We will include related trials regardless of their publication status and language of publication. For cross-over trials, we would only include the first period of randomization to intervention or control to avoid a unit of analysis error. The main outcome is the number of participants who experienced disability worsening measured by Expanded Disability Status Scale (EDSS). The additional outcomes including (1) The number of participants who experienced at least one new relapse during the treatment and follow-up periods; (2) Quality of life, measured by any validated health-related scales or MS-specific scales or any other scale used in the trials, measured at the end of follow-up; (3) The number of participants with magnetic resonance imaging (MRI) activity, for instance, new T2-hyperintense lesions or gadolinium-enhancing lesions in participants with MS during the trial period; (4) The number of participants with cognitive function, characterized by any validated tool, for instance Brief Paced Auditory Serial Addition Test (PASAT); or any other validated tool; (5) The change of fatigue, characterized by any validated instrument, for example the Modified Fatigue Impact Scale (MFIS); or any other validated tool; (6) The change in TCM Syndrome Differentiation Efficacy Scales (SDES) used to evaluate the efficacy of CHM intervention for MS; (7) The number of participants who withdrew due to any adverse event, lack of efficacy, lack of compliance or a combination of these causes at the end of the follow-up, from

the total number of participants randomly assigned to each treatment arm; (8) Safety: number of participants with at least one adverse event, including (but not limited to) complaints by participants, pain, sleep disturbance or any event considered as adverse by the participant.

Information sources: We will search the following electronic databases, including CENTRAL, MEDLINE, EMBASE, Web of Science, CNKI, CQVIP, Wanfang Data, SinoMed. We will conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) for ongoing or unpublished trials. We will also check the reference lists of all primary studies and review articles for additional references as the backward citation tracing; consider the publications that cite any primary study, directly or indirectly, as the forward citation tracing; search a number of grey literature sources: ISI Web of Knowledge Conference Proceedings, Conference Proceedings Citation Index-Science (Web of Science), and MS societies (www.nationalmssociety.org); search relevant manufacturers' websites for trial information; contact trial authors and experts if the reported information is incomplete or for unpublished data; and examine any relevant retraction statements and errata for included studies.

Main outcome(s): The number of participants who experienced disability worsening measured by Expanded Disability Status Scale (EDSS). The EDSS is a common measure of MS disability ranged from 0 (no neurologic abnormality) to 10 (death due to MS) and is used to measure disability worsening in clinical trials. Disability-worsening is defined as an increase in EDSS of ≥ 1.0 point from baseline, sustained on subsequent visits for at least 12 weeks if the baseline score ≤ 5.5 , and of ≥ 0.5 sustained for at least 12 weeks if the baseline score > 5.5 .

Additional outcome(s): 1. The number of participants who experienced at least one

new relapse during the treatment and follow-up periods.

2. Quality of life, measured by any validated health-related scales or MS-specific scales or any other scale used in the trials, measured at the end of follow-up.

3. The number of participants with magnetic resonance imaging (MRI) activity, for instance, new T2-hyperintense lesions or gadolinium-enhancing lesions in participants with MS during the trial period.

4. The number of participants with cognitive function, characterized by any validated tool, for instance Brief Paced Auditory Serial Addition Test (PASAT); or any other validated tool.

5. The change of fatigue, characterized by any validated instrument, for example the Modified Fatigue Impact Scale (MFIS); or any other validated tool.

6. The change in TCM Syndrome Differentiation Efficacy Scales (SDES) used to evaluate the efficacy of CHM intervention for MS.

7. The number of participants who withdrew due to any adverse event, lack of efficacy, lack of compliance or a combination of these causes at the end of the follow-up, from the total number of participants randomly assigned to each treatment arm.

8. Safety: number of participants with at least one adverse event, including (but not limited to) complaints by participants, pain, sleep disturbance or any event considered as adverse by the participant.

Quality assessment / Risk of bias analysis:

Three review authors will assess risk of bias for each trial using the Cochrane 'Risk of bias 2' (Rob 2) tool for both parallel and cross-over trials considering that we are going to include only the first phase. We will resolve any disagreements by discussion or by involving another author.

Strategy of data synthesis: We will pool data from parallel-group and cross-over trials. We will perform meta-analysis using a random-effects model due to anticipated heterogeneity both within and between studies. We will use a random-effects model because we assume that the studies are not all estimating the same intervention

effect, and are estimating intervention effects that follow a distribution across studies. We will calculate MD or SMD with 95% CIs in the meta-analysis for continuous outcomes, RR with 95% CIs for dichotomous outcomes. For rare events such as event rates below 1%, we will use the Peto odds ratio method, provided there is no substantial imbalance between intervention and control group sizes and intervention effects are not exceptionally large. We will report adverse event outcomes narratively if a quantitative analysis is not possible. We will perform analyses using the random-effects method following RevMan Web. If it is applicable, we will further conduct meta-regression to examine the impact of covariates on the effect estimate using R software. For outcomes that we could not perform quantitative analysis, we will present the results of individual studies in a narrative synthesis.

Subgroup analysis: We will perform subgroup analyses for efficacy outcomes if we can identify a sufficient number of studies by using the following effect modifiers as possible sources of heterogeneity:

1. Study design: parallel or cross-over;
2. Study duration: short-term (less than one month post- intervention), intermediate (one month to less than six months post-intervention), and long-term (\geq six months post-intervention);
3. Participants: types of MS; disability, spasticity, and pain score baseline; gender (male versus female), anticipating that men experience greater disability; age ($<$ 60years versus \geq 60years), anticipating that older individuals experience greater disability;
4. Intervention: different type of CHM; different dose, frequency, or duration of treatment.

We will interpret the results with caution. However, lack of data did not permit subgroup analysis.

Sensitivity analysis: We will perform sensitivity analyses to explore the influence of important factors on effect sizes, if a sufficient number of studies could be

included, for the critical and important outcomes, to assess the strength of the results by:

1. Excluding from the meta-analysis studies judged to be at high risk of bias through both RoB 2 tool.
2. Excluding studies with very long study duration or very large sample size (to explore the extent to which they dominate the results).
3. Additional factors may be considered: diagnostic criteria, language of publication (English versus other languages), country (depending on data).

We will also test the robustness of results by repeating analyses using different measures of effect size (i.e. RR, OR, etc.). The sensitivity analyses will inform the downgrading decisions relating to risk of bias.

Country(ies) involved: China.

Keywords: Chinese herbal medicine; multiple sclerosis; systematic review; meta-analysis.

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