Chinese Herbal Medicine for Mild Cognitive Impairment Using Mini-Mental State Examination: A Systematic Review and Meta-Analysis

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Abstracts: BACKGROUND: The prevalence of mild cognitive impairment (MCI) in the elderly population aged 60-84 years ranges from 6.7% to 25.2%, and the effective prevention and reversal of MCI progression to AD is crucial. MMSE is the most commonly used screening tool in Chinese outpatient clinics, with sufficient sensitivity and specificity to allow useful stratification from average to abnormal with adequate consideration of age and education. OBJECTIVE: To investigate the clinical significance of Chinese herbs on Mini-Mental State Examination (MMSE) scores in MCI patients and discuss the effectiveness of Chinese herbs through pharmacology. METHODS: Three English databases and four Chinese databases we have searched, and the risk of bias was assessed according to the Cochrane tool. Statistics will be used for heterogeneity assessment, sensitivity analysis, data synthesis, funnel plot generation and subgroup analysis. If sufficiently homogeneous studies are found, a Meta-analysis will be performed, with subgroups describing any differences. RESULTS: A total of 21 studies were included, 4 studies were placebo-controlled, 14 Chinese Herbal Medicines (CHMs) were compared with other cognitive improvements, 3 CHMs were combined with other medications, and the results of 17 studies favored the herbal group. CONCLUSION: The results indicate that herbal medicine can improve MMSE scores, and herbal medicine combined with other drugs that can improve cognition can significantly improve MMSE scores, but there are methodological flaws in the study. Experimental studies have found a basis for the ability of herbs to improve cognition and memory impairment, and herbal medicine has great potential to improve MCI cognition. PROSPERO international prospective register of systematic reviews protocol registration number: 42020202368

Keywords: mild cognitive impairment, herbal medicine, MMSE, systematic evaluation, meta-analysis

1. Background

Mild cognitive impairment (MCI) is a complex clinical entity that manifests significant deficits in attention, learning, memory, processing speed, and semantic language ¹, and it is a transitional state between normal aging and Alzheimer's disease (AD) ². This state can progress to dementia, primarily in Alzheimer's disease ³. The prevalence of MCI ranges from approximately 6.7% to 25.2% in the 60-84-year-old population ⁴. In Asia, on average, 10.5 out of 100 people aged 60 years or older will progress to MCI each year ⁵. Alzheimer's disease (AD) is the most common form of dementia, accounting for almost 60-70% of dementia cases ⁶, and the prevalence of dementia worldwide is expected to double every 20 years, from 46.8 million in 2015 to 131.5 million in 2050, with most of the increase occurring in low- and middle-income countries ⁷. China currently has more than 10 million people with dementia and already has the highest number of patients in the world ⁸. Each year, 16% of MCI patients develop dementia ⁹, and the progression of MCI to dementia is associated with poor treatment outcomes and a heavy financial burden on families and society. Therefore, it is crucial to prevent and reverse the progression of MCI to AD effectively. Slowing or even reversing the progression of MCI may facilitate early intervention and ultimately prevent AD. The US Federal Drug Administration approves
cholinesterase inhibitors (e.g., donepezil, rivastigmine, galantamine) for the treatment of mild to moderate Alzheimer's disease. These drugs have also been used clinically to treat MCI; unfortunately, they are ineffective in MCI, and they do not delay the onset of dementia 10. Studies have shown improved semantic memory in aMCI patients treated with ionotropic glutamate receptor antagonists (memantine) 11, but more evidence is still needed to support this, and the pros and cons of pharmacological treatment of MCI are open to debate 12,13. Based on the favorable efficacy and safety profile of EGB761®, an extract of Ginkgo biloba, the Asian Clinical Expert Group on Neurocognitive Disorders agreed to include it as part of the treatment of MCI 14. EGB761VR has been approved in several EU countries and is the only pharmacological treatment recommended in the existing guidelines for the symptomatic treatment of MCI 15. In recent years, Chinese herbs have shown great potential in the prevention and treatment of cognitive decline 16-19. Studies have shown that diet and dietary supplements have a positive additive role in preventing cognitive decline 20-22, and exercise may slow down the rate of cognitive decline in MCI 23-25. In addition to common drugs such as cholinesterase inhibitors and ionotropic glutamate receptor antagonists, herbal medicines have been commonly used in clinical practice in China. In contrast, the calcium channel blockers nimodipine, piracetam, aniracetam, and olanzapine are also used synergistically with the above drugs to improve cognitive function 26-27. A practical method for clinicians to grade cognitive status, called the MiniMental State Examination (MMSE), was first proposed by Professor Marshal Folstein in 1975 28 and includes temporal orienting force, place Orientation, immediate memory, attention and computation, delayed memory, language, visual-spatial. Another question is a short test that takes 7 to 10 minutes to complete and is still the most well-researched instrument today 29. The most commonly used screening tool on an outpatient basis, although Montreal Cognitive Assessment (MOCA) has been shown to be more sensitive in screening and diagnosing MCI compared to MMSE30-31, both tests are accurate in the detection of AD 32. By observing how the MMSE changes over time, rather than a single measurement, the transition from the MCI stage to dementia can be better predicted 33, although most of the time, it is used in combination with other outcome measures to improve the accuracy of the diagnosis of MCI 34.

2. Methods

Data retrieval MCI clinical trials were searched using Chinese and English databases from inception to July 31, 2020: Cochrane Library, EMBase, PubMed, China Biomedical Literature Database (CBM), China National Knowledge Infrastructure Project (CNKI), Wanfang Medical Database (WANFANG.DATA), and Vip Database (VIP). Search terms were grouped into four groups: (i) intervention (including herbal medicine, herbal medicine, a combination of Chinese and Western medicine, etc.), (ii) clinical status (including cognitive impairment, memory impairment, memory loss, etc.), (iii) study design (including a clinical trial, placebo, randomized, double-blind, controlled, etc.), and (iv) outcome measure: MMSE. Searches were performed in accordance with the Cochrane Collaboration Network requirements .See appendix (Search strategy).

2.1 Incorporation criteria

2.1.1 Types of participants.

Participants diagnosed with MCI or mild neurocognitive impairment based on valid criteria: patient or informed report, or a validated clinician finding of cognitive impairment, presence of objective evidence of impairment in one or more cognitive domains (from cognitive tests), complex instrumental daily abilities can be mildly impaired, but maintain independent daily living skills, and have not yet reached the diagnosis of dementia. Diagnostic criteria for inclusion of subjects in this study with no restrictions on age or sex included the Mayo diagnostic criteria 35, Petersen diagnostic criteria 36 and 2018 guideline update 37, diagnostic criteria for MCI due to Alzheimer's disease developed by the National Institute on Aging (NIA) and Alzheimer's Association (ADA) group in 2011 38, 2013 the annual Diagnostic and Statistical Manual of Mental Disorders in the United States (DSM-VI), among others 39.

2.1.2 Interventions

The intervention group consists of: any form of single herbal medicine, herbal preparation, or combination of herbal and non-herbal medicine, excluding ginkgo biloba extracts and purified compounds of plant origin as the primary test intervention in the study, such as stilbene A and purified extract EGb 761 present in the test group must be used in combination with herbal medicine, with no
restrictions on the dose, dosage form, frequency of use, or duration of treatment. The control group could be placebo or drug treatment, with no restrictions on the mode of administration or dose.

2.1.3 Outcome indicators

There are many outcome indicators for MCI, including neuropsychological assessment, biomarkers, and neuroimaging. Although biomarker and neuroimaging methods are well consolidated in the medical community, they are expensive, invasive, and potentially dangerous for the diagnosis and observation of this disease; the most commonly used is the neuropsychological assessment, which has the advantage of being convenient, quick and cost-effective, and is the preferred observational indicator in large samples of MCI clinical trials, with the disadvantage that the results are subjective. The more commonly used MMSE neuropsychological assessment scale was chosen for this study to observe the change in scores before and after treatment.

2.1.4 Type of study design

All randomized controlled trials studying herbal medicine or a combination of traditional Chinese and Western medicine in patients with mild cognitive impairment, with or without blinding, had no restrictions on study duration, background, or publication language.

2.2 Exclusion criteria

Studies with mean baseline MMSE scores below 20 in either the experimental or control groups were excluded, as participants with scores below 20 are typically classified as having mild AD. There are also studies of repeated publication, non-clinical randomized controlled trials with other complementary therapies such as yoga, massage, tai chi, qi gong, acupuncture, etc. studies with AD, VaD, healthy young participants, or other Studies of people with dementia and missing data.

2.3 Screening and data extraction for inclusion

In the study The literature screening was carried out independently by two researchers, according to the literature screening flowchart stated by PRISMA. Apparent discrepancies were eliminated, and the screened out literature was further searched, read in full, and screened again according to the inclusion and ranking criteria, and evaluated in full for studies that met the main criteria. Data from trials that met the inclusion criteria were extracted into a preconstructed spreadsheet containing the necessary information for the study, including, among other things, first author, title, year of publication, trial site, diagnostic criteria, sample size, the mean age of participants, study duration, intervention (composition, dose), control (drug, dose), data information (baseline, end of treatment, follow-up)—outcome indicators, number of shedding, adverse effects, etc. When the data in the original document are deviated or incomplete, the original author should be contacted to obtain further relevant information and exclude the original document for which specific data cannot be obtained. The data were extracted in the original language. Chinese names were translated using Hanyu Pinyin and scientific names of herbs based on authoritative pharmacopeia.

2.4 Risk of bias assessment

According to the literature evaluation criteria provided in the Cochrane Handbook 5.1.0, the methodological quality of the included studies was evaluated based on random sequence generation, allocation concealment, blinding of researchers and subjects, blinding of outcome evaluators, completeness of outcome data, selective reporting, and other factors that may affect the validity of the results. The final results were divided into 3 levels: “low risk of bias,” “unclear,” “high risk of bias.” and the quality assessment was still cross-checked independently by 2 researchers. Any disagreements will be discussed and adjudicated with the third reviewer to reach a final agreement, and the assessment will be reported in a grade summary of the final findings table.

2.5 Data analysis

Statistical analysis was performed using RevMan 5.3 software provided by the Cochrane Collaboration. The relative risk (RR) and 95% CI were used for the bicategorical data; the weighted mean difference (WMD) was used for the continuous data. Suppose there was no significant heterogeneity (P>0.1, I² <50%), the combined effect volume was calculated by fixed-effects model; if there was heterogeneity (P<0.1, I² >50%), but the groups were judged to be clinically consistent and
needed to be combined, the combined effect volume was calculated by the random-effects model, and subgroup analysis was performed to find the heterogeneity between the studies. Heterogeneous sources; if heterogeneity was excessive, only descriptive analysis was performed. The large number of papers included in this study (more than 10) requires a funnel plot to detect publication bias. To determine the stability of the outcome measures, a sensitivity analysis was performed by comparing the differences between the combined effect measures using a literature-by-life exclusion method.

3. Results

3.1 Literature search process

According to the search strategy, an initial search of 7953 documents was conducted, all of which were obtained through electronic search, leaving 2142 documents after weight picking and 153 documents after reading the title, abstract, and keywords; after reading the full text of the literature, 118 did not find the full text, and 106 did not use MMSE as an outcome measure. Thirty-five pieces of literature were included in the quality evaluation, of which 7 high-quality papers described changes in MMSE using graphs and language, did not report specific changes in scores, did not receive a response after contacting the authors, 1 study used CHM as a control group, 6 were non-RCT studies, and finally 21 pieces of literature were included for data analysis. See FIG 1 (search and selection process).

Fig 1. Search and selection process. CHM: Chinese herbal medicine; AD, Alzheimer’s disease; MCI, mild cognitive impairment; VaD, vascular dementia; VCIND, vascular cognitive impairment with no dementia

3.2 General characteristics of the included studies

Of the 21 studies included, all conducted in China, 17 were published in Chinese journals, and 4 in English journals, including a total of 1560 patients (treatment group: 830 patients, control group: 730 patients). 4 studies used CHM vs. placebo in the treatment group; 14 studies used CHM vs. other drugs in the treatment group; 3 studies used CHM vs. Chinese medicine plus other drugs vs. other drugs. Only 1 study followed the subjects for 24 months, and 16 study pairs reported the number of years of education, of which reported the mean number of years of education of the patients. See Table 1.
## Table 1 General information of included studies

<table>
<thead>
<tr>
<th>Author; Published Date</th>
<th>Sample size; Duration (in weeks)</th>
<th>Intervention/Chinese herbal formulae/dosage</th>
<th>Control/dosage</th>
<th>AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Zhang 2016</td>
<td>30/30; 96</td>
<td>Bushen capsule; 4 capsules /day</td>
<td>Placebo capsule; 4 capsules /3day</td>
<td>Decreased appetite, constipation</td>
</tr>
<tr>
<td>2. Zhang 2014</td>
<td>16/12/13; 12</td>
<td>CCRC capsule; 4 grains for each time, 3/day</td>
<td>Placebo capsule; 4 capsules /3day</td>
<td>Decreased appetite, Mild nausea</td>
</tr>
<tr>
<td>3. Zhou 2007</td>
<td>42/38/37; 48</td>
<td>Shenyn Oral Liquid (10 mL/piece); 2/day</td>
<td>Placebo Oral Liquid (10 mL/piece); 2/day</td>
<td>Facial pimpls with itching</td>
</tr>
<tr>
<td>4. Wu 2016</td>
<td>62/16/12</td>
<td>Bushen Jiangi Huatan Pills, 9 g/time , 2 /day</td>
<td>Placebo Pills, 9 g/time , 2 /day</td>
<td>Swollen gums, constipation</td>
</tr>
<tr>
<td>5. Zhang 2018</td>
<td>30/30; 12</td>
<td>Qingmao Yizhi Granules; 10g/pack/time; 3/day</td>
<td>Nimodipine Tablets 30 mg/time, 3/day</td>
<td>None</td>
</tr>
<tr>
<td>6. Zhao 2009</td>
<td>30/30; 12</td>
<td>Jinkui Shenqi Pills Modified Pills 9 g, 2/day</td>
<td>Nimodipine Tablets 30 mg/time, 3/day</td>
<td>Not reported</td>
</tr>
<tr>
<td>7. Cui 2015</td>
<td>16/16/12</td>
<td>Naofucong: 150 ml/pack, 1pack /time, 2 /day</td>
<td>Nimodipine Tablets 30 mg/time, 3/day</td>
<td>None</td>
</tr>
<tr>
<td>8. Guo 2010</td>
<td>32/32/15; 12</td>
<td>Huanglian Wendan Decoction 200ml; 2/day</td>
<td>Nimodipine capsules (0.1g / capsule) /2 grains / 3 day, Mock decoction 200ml; 2/day</td>
<td>None</td>
</tr>
<tr>
<td>9. Zhong 2007</td>
<td>83/83; 12</td>
<td>Shenwu Capsule (5 capsules each time); 3/day</td>
<td>Nimodipine capsules (2 capsules /time) and Aniracetam Capsule Simulotor(3 capsules /time); 3/day</td>
<td>None</td>
</tr>
<tr>
<td>10. Gu 2015</td>
<td>50/50; 12</td>
<td>Dihuang Yizhi decoction: 1pack /time, 2 /day</td>
<td>Nimodipine capsules 200mg/time, 3/day</td>
<td>None</td>
</tr>
<tr>
<td>11. Chen 2016</td>
<td>43/43; 12</td>
<td>Kaixin Yizhi decoction 120ml /time, 2 /day</td>
<td>Nimodipine capsules 200mg/time, 3/day</td>
<td>None</td>
</tr>
<tr>
<td>12. Wang 2011</td>
<td>45/35; 12</td>
<td>Shouwu Yanshou pill, 6g /time, 3 / day</td>
<td>Nimodipine capsules 0.4g/time, 3/day</td>
<td>None</td>
</tr>
<tr>
<td>13. Zhu 2010</td>
<td>50/50; 12</td>
<td>Xuan yun ning tablets, 2 tablets /time, 3 / day</td>
<td>Piracetam Tablets 0.8g/time, 3/day</td>
<td>Insomnia, decreased appetite, palpitation</td>
</tr>
<tr>
<td>14. Li 2016</td>
<td>30/30; 12</td>
<td>Shenwu Granules, 1 pack /time, 3 / day, Naofukang tablets placebo 0.8 g/time, 3 / day</td>
<td>Piracetam Tablets 0.8g/time, 3/day</td>
<td>Nausea, dry mouth</td>
</tr>
<tr>
<td>15. Lin 2020</td>
<td>47/41; 12</td>
<td>Tiaobu Xinshen Recipe, 150ml/time; 2/day</td>
<td>Donepezil hydrochloride 5 mg/time 1/day</td>
<td>None</td>
</tr>
<tr>
<td>16. Miao 2012</td>
<td>48/24; 12</td>
<td>Bushen Huatan Quya granules, 1 pack / time, 2 / day</td>
<td>Donepezil Hydrochloride, 5mg/time, 1/day</td>
<td>Insomnia, Nausea, Diarrhea</td>
</tr>
<tr>
<td>17. Chen 2017</td>
<td>35/34; 24</td>
<td>Shenzhi oral liquid, 1 g /time, 2 / day</td>
<td>Huperzine A tablets: 50 µg / tablet; 2 tablets / time; 2/day</td>
<td>None</td>
</tr>
<tr>
<td>18. Sheng 2016</td>
<td>32/32; 24</td>
<td>Xintiaoxingfang granules, 1 pack /time, 2 / day</td>
<td>Huperzine A tablets: 50 µg / tablet; 2 tablets / time; 2/day</td>
<td>None</td>
</tr>
<tr>
<td>19. Wang 2012</td>
<td>26/26; 12</td>
<td>Donepezil Hydrochloride, 5mg/time, 1/day; nimodipine, 40mg /time, 3/day, Guipi Decoction 200ml daily, 2/day</td>
<td>Donepezil Hydrochloride, 5mg/time, 1/day; nimodipine, 40mg /time, 3/day</td>
<td>None</td>
</tr>
<tr>
<td>20. Xu 2013</td>
<td>30/30; 12</td>
<td>Nimodipine tablets 30 mg, 3 / day, Qingli zengzhiyin : 150 mL/time, 2/day</td>
<td>Nimodipine Tablets 30 mg/time, 3/day</td>
<td>Abdominal discomfort, Head swelling</td>
</tr>
<tr>
<td>21. Wu 2017</td>
<td>53/49; 8</td>
<td>Citicoline Sodium Tablets 0.2g, 3/day and Dream sweet oral liquid 20ml, 2/day</td>
<td>Citicoline Sodium Tablets 0.2g, 3/day</td>
<td>Mild constipation</td>
</tr>
</tbody>
</table>

**Control Group**

- **Sample size:**
- **Duration (in weeks):**
- **Intervention/Chinese herbal formulae/dosage:**
- **Control/dosage:**
- **AEs:**

**Experimental Group**

- **Sample size:**
- **Duration (in weeks):**
- **Intervention/Chinese herbal formulae/dosage:**
- **Control/dosage:**
- **AEs:**
3.3 Evaluation of the quality of the included studies

All 21 included studies that were described as RCTs, of which nine specified an appropriate method of sequence generation and six referred to assignment concealment. All studies mentioned blinding, but only six specifically described blinding; all studies had complete outcome data, counted and described dropouts and lost patients, and did not selectively report results; four studies declared no conflicts of interest, and 17 did not declare conflicts of interest. See FIG 2.

Fig 2. Risk of bias

4. Comparative results

The collation revealed that the control groups included in the study were different, according to which they could be divided into three main groups: (1) herbal and placebo groups; (2) herbal and other drug groups; (3) herbal combined with other drugs and other drugs groups; the changes in MMSE scores in the experimental and control groups after the end of treatment were compared between the groups collated and analyzed.; because the Chinese herbal formulae (CHFs) in the experimental group were all compound drugs, each with many individual herbal medicines (single Chinese herbal medicines (CHMs)) in the mix, these studies emerged as Many duplicate herbs, and therefore the individual herbs that appeared were categorized and summarized, and (4) the 10 drugs with the highest frequency of occurrence in the 21 studies were organized and summarized for a systematic evaluation concerning current herbal pharmacology studies.

4.1 CHM vs. Placebo

There were four studies in this group, with a treatment duration of 12-96 weeks, 245 participants at baseline, and three studies using randomized numbers and table-blinded double simulations, which were assessed as high-quality studies. The other study only mentioned randomization and blinding without specifying the method, and the risk was unclear. After a heterogeneity test, I² =37%<50% and P=0.19>0.1 for the Q-test, suggesting no heterogeneity between groups. A fixed-effects model could be selected for meta-analysis, which showed that the MD=0.95, 95% confidence interval [0.39, 1.52], Z=3.33, and P=0.0009<0.05 for the four literature summaries were statistically significant, and the results were significantly biased towards the CHM group. In one of the two 12-week studies, Bushen Jianpi Huatan Pills had a significantly higher MMSE score (MD=2.53 [0.92, 4.14]), whereas the change in Compound congongyizhi capsule was not very significant (MD=[-0.67,2.03]). In the remaining two studies, Bushen capsule treatment for 96 weeks (MD=1.33 [-0.34,3.00]) and Senin Oral Liquid treatment for 48 weeks (MD=-0.64 [-0.09, 1.52]) there was no
significant pattern in the length of treatment cycle or change in MMSE score can be followed. All changes in scores in the placebo group were not significant. See Fig 3.

![Fig 3. Chinese Herbal Medicines VS Placebo meta analysis](image)

### 4.2 CHM vs. Other treatments

There were 14 studies in this group, treatment duration was 12-24 weeks, there were 1101 participants at baseline, and 3 studies were assessed as high-quality studies using randomized numerical and tabular double-blind, double simulations. After heterogeneity test, I²=34%, Q test P=0.12, indicating that there is no heterogeneity between the groups, and the overall result is biased towards the CHM group, indicating that the CHM group is better than other drug intervention groups. The research found that the intervention can be based on Divided into 5 subgroups. See Fig 4.

![Fig 4. Chinese Herbal Medicines VS other treatments meta analysis](image)
the heterogeneity between the groups is very low. One study Kaixin Yizhi decoction MD 0.24 [-0.41,0.89] [55] The results were significantly more focused on the CHM group. The results of the remaining two studies Shenwu Capsule MD=-0.06[-0.61,0.49][53] and Dihuang Yizhi decoction MD=-0.39[-1.04,0.26][54] are slightly more important than the aniracetam group, 3 items The overall MD of the study was -0.07, 95% confidence interval [-0.42, 0.28], Z=0.39, P=0.70. The third group of traditional Chinese medicine vs. Piracetam (CHM vs. Piracetam) There were two studies, the treatment time was 12 weeks, F=61%>50%, P=0.11>0.1 of the Q-test suggested that the difference between the groups was not significant, which may be related to the sample size and results. The MMSE scores of the two studies were higher than piracetam, and the more participants Xuan yun ning tablets MD=0.90 [0.37, 1.43] 57 scored higher than Shenwu Granules MD=0.29 [-0.23,0.81] 58, which had fewer participants. The MD=0.59, 95% confidence interval [-0.01,1.19], Z=1.94, P=0.05 for both studies was not statistically significant and needed to be supported by more evidence. The fourth group of CHM vs. Donepezil (CHM vs. Donepezil) had two studies with a treatment duration of 12 weeks, F=0%<50%, P=0.94>0.1 in Q-test suggesting no difference between the groups, two studies Tiaobu Xinshen RecipeMD=0.21[-0.95,0.53]65 and The results of Bushen Huatan Quyu granule -0.17 [-0.80,0.46] 60 were biased towards the donepezil group MD=0.19, 95% confidence interval [-0.67,0.29], Z=0.76, P=0.45, which was not statistically significant. The fifth group of traditional Chinese medicine vs. Huperzine A (CHM vs. Huperzine) had a total treatment duration of 24 weeks, F=0%<50%, P=0.35>0.1 of Q-test suggested no difference between the groups; Shenzhi oral liquid MD=0.54[-049, 1.57] 61 had significantly higher MMSE scores. The two groups' scores were not significantly different MD=0.06, 95% confidence interval [-0.19,0.30], Z=0.47, P=0.64, and were not statistically significant.

4.3 CHM plus Other treatments vs. Other treatments

This group consisted of two studies 63–65, with a treatment duration of 8-12 weeks and 154 participants at baseline, two studies only mentioned randomization and blinding without specifying methods, and the risk is unclear. After heterogeneity testing, I² =0% and P=0.33 for the Q-test, There is no heterogeneity between groups. The fixed-effect model was selected for meta-analysis, and the results showed that MD=3.90, 95% confidence interval [3.49, 4.32] Z=2.28, and P= <0.00001, which were statistically significant. The results were significantly more focused on traditional Chinese medicine combined with other Drug group. See FIG 5.

![Fig 5.Chinese Herbal Medicines plus other treatment VS others](image)

5. Adverse event

In 21 studies no serious adverse events were reported, 10 reported mild adverse events, and 6 studies in the CHM group reported adverse events, mainly insomnia, swollen gums, nausea, decreased appetite, constipation, diarrhea, and several other mild adverse events, none of which were suspended after the adverse events and no pharmacological interventions were performed, and the participants improved spontaneously. In one study, 11 participants in the piracetam group had mildly elevated glutamyltransferase [(46-49) μg/L], and 2 participants had panic attacks 57. Three studies had no adverse events, and eight studies did not report adverse events, with insufficient safety data for statistical analysis.

6. Discussions

This study conducted a comprehensive search of English and Chinese databases and retrieved a total of 35 RCTs on herbal medicine for MCI using MMSE as an outcome measure. only 21 studies containing MMSE outcome data were meta-analyzed. MMSE scores increased at the end of treatment in all herbal groups, with 18 studies in the experimental group (n=721) using herbs alone increasing their scores by an average of 1.76 points; 17 studies in the control group (n=635) using other cognitive-
improving drugs, increasing their scores by an average of 1.34 points; and 3 studies in the experimental group (n=109) using herbs plus other cognitive-improving drugs scoring The mean increase was 4.74 points; in the herbal and placebo groups the mean MMSE score for one 96-week study increased by only 0.68 points 45 the mean scores for two 12-week studies increased by 1.50 and 1.35 points, respectively 46, 48. The score for one 48-week study increased by 2.22 points, considering that herbal medicine’s efficacy may peak at one year of treatment, exceeding the efficacy of the treatment tapers off after one year. In the herbal and other cognitive improvement drugs group, the results of three 12-week studies comparing with nimodipine were skewed in favor of the herbal group, with the herbal group scoring significantly ahead of nimodipine by 3.15 points in one study 49 and not significantly in the other two 50,51. In a 12-week comparison with anisiracetam, MMSE scores in 2 of the studies significantly favored the herbal group. However, the change in scores was not significant in the other 3 studies. The results in the 12-weeks comparison of the piracetam group were heavily weighted towards the CHM, with significant changes in both the CHM and aniracetam groups in one of the more heavily attended studies (n=100) and a decrease in the aniracetam score of -0.9 in the other study (n=60), rather than an increase. The two 12-week studies' scores comparing the donepezil group were both heavily weighted towards donepezil, but the change in scores was not significant. The two studies' scores comparing the stigmata A's were heavily weighted toward the CHM group, and the change in scores was not significant. One 8-week (n=100) study in the CHM combined with other drugs group improved the mean score by 8.15 points, the largest change in this study. The changes in the other two 12-week studies were also significant. These studies showed that herbal medicine was significantly better than placebo in improving MMSE scores; although most of the results were in favor of the CHM group, the evidence was insufficient to show that the herbal medicine group possessed a better ability to improve cognition compared to other drugs. The combination of herbal medicine with other cognition-improving medications was able to improve MMSE scores substantially. There was little correlation between the number of participants and final MMSE scores in this study, with greater variation in shorter studies scores. It is noteworthy that some studies have shown that the level of education, age, and gender can make a difference in MMSE score results. A mean MMSE score change of 3.7 is an important threshold for AD, but how much the MMSE of MCI changes to be clinically meaningful needs further validation. The MMSE sensitivity to MCI has been much debated in recent years, and although it is less sensitive in screening, it is still a good tool for detection Future studies would be more meaningful if the participants were observed in different stages according to their age and if a protocol for use that is consistent with Chinese conditions was used.

7. Limitations of this study

These studies varied widely in the number of participants and duration of treatment, with only 4 studies with more than 100 participants, many with low numbers of participants, 1 study in the comparative placebo group lasted 96 weeks, and another lasted 48 weeks. Two studies in the comparative stigmata A group lasted 24 weeks, and the remaining studies were observed for shorter periods. Only 6 studies specifically elaborated on blinding, there was significant heterogeneity between groups when performing the meta-analysis, and many studies were methodologically flawed. Many subjective factors can confound MMSE scores in addition to the patient's education, age, and gender, and these weaknesses limit the strength of the evidence. More high-quality, large-sample clinical studies with clear objective outcome measures (e.g., biomarkers, imaging tests, etc.) are needed to further delve into whether herbs can improve cognition of MCI.

8. Conclusion

The results show that herbal medicine can improve MMSE scores, and herbal medicine combined with other drugs that can improve cognition can significantly improve MMSE scores, but there are methodological flaws in the study. Experimental studies have found a basis for herbs' ability to improve cognition and memory impairment, and herbal medicine has great potential to improve MCI cognition.

References

[25] Biazus-Sehn LF, Schuch FB, Firth J, Stigler FS. Effects of physical exercise on cognitive function


