AYUSHDHARA
ISSN: 2393-9583 (P)/ 2393-9591 (O)
An International Journal of Research in AYUSH and Allied Systems

Review Article

EFFECT OF *BRAHMI* (*BACOPA MONNIERI*) IN THE TREATMENT OF ALZHEIMER'S DISEASE FROM AYURVEDIC PERSPECTIVE - A SYSTEMATIC REVIEW

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Article info

Article History:
Received: 16-05-2023
Revised: 01-06-2023
Accepted: 28-06-2023

KEYWORDS:
Bacopa monnieri, Alzheimer disease, Ayurveda, *Brahmi (Bacopa Monnieri)*, systematic review, randomized controlled trial.

ABSTRACT

Objectives: Treatment of Alzheimer's disease is the worldwide problem as it is having major impact on the memory. Ayurveda science describes *Brahmi (Bacopa Monnieri)* as memory enhancing drug which can improve the memory power in the Alzheimer's disease. **Data Sources:** Classical textbooks and published research studies were searched in the context of use of *Brahmi (Bacopa Monnieri)* in the Alzheimer's disease. Online search engines namely J gate, Google scholar, PubMed, DHARA online and AYUSH research portal were used for data mining of published research works. **Review Methods:** References and studies including the effect of *Brahmi (Bacopa Monnieri)* in the treatment of Alzheimer's disease were reviewed and reported according to the PRISMA guidelines. We include randomized controlled trials with mild cognitive impairment in Alzheimer's disease which involves *Bacopa Monnieri*, its extract or its active ingredients. **Results and Discussion:** 5 studies found eligible for the search. Two studies used extracts of *Bacopa Monnieri* extracts while three studies used other drugs in combination with the *Bacopa Monnieri* extract. The cognitive subscale scores of the Alzheimer's disease Assessment scale found in one study, mini mental state examination scores were found in three studies. All the studies found a significant difference in statistics. Hence, *Brahmi* (*Bacopa Monnieri*) may find to be effective in Alzheimer's disease and its equivalent disease in Ayurveda. **Conclusion:** The evidence obtained from the present systematic review is of very low certainty. The evidence from 5 trials suggests that there is a very little difference between *Bacopa Monnieri* and a placebo or donepezil in the treatment of Alzheimer disease or mild cognitive impairment which needs to find in further future studies No major safety issues were reported in the trials included in this review.

INTRODUCTION

Treatment of Alzheimer's disease is the worldwide problem as it is having major impact on the memory. 65 years or above aged persons suffered with the mild cognitive impairment up to 20% and dementia approximately 1% to 25%.[1] A chronic condition called dementia causes a progressive deterioration in intelligence, behavior, and personality.[2]

It is slowly progressive neurodegenerative disease.[3] Certain conditions such as Alzheimer's disease, multi infarct dementia, uremia, chronic hepatic encephalopathy, thyroid/adrenal dysfunction, pernicious anemia, pellagra, brain tumors, subdural hematoma and head injury may cause dementia. [4]

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https://doi.org/10.47070/ayushdhara.v10iSuppl3.1266

Phases of Alzheimer's disease

This disease can be classified into four stages [5]

1. **Preclinical phase:** This last for several years or more. This is characterized by mild memory loss, early pathological changes in the cortex, hippocampus with no functional impairment in daily activities and absence of clinical signs and symptoms of classical Alzheimer's disease.
2. **The mild or early phase:** Trouble in the daily life of the patient with a loss of concentration and memory, disorientation of place and time, a change in the mood, and a development of depression.
3. **Moderate phase:** The disease has progressed to parts of the cerebral cortex and has caused memory loss, difficulty identifying relatives and friends, lack of impulse control, and difficulties with reading, writing, and speaking.
4. **Severe AD or late phase:** It involves the spread of the disease to the entire cortex area with a severe accumulation of neuritic plaques and neurofibrillary tangles, resulting in a progressive functional and cognitive impairment where the patients cannot recognize their family at all and may become bedridden with difficulties in swallowing and urination, and eventually leading to the patient's death due to these complications. [6] Treatment of Alzheimer's disease includes inhibiting acetylcholinesterase (AChE) that increases cognitive and neural cell function.[7] N-methyl d-aspartate (NMDA) Antagonists causes for synaptic neurotransmission, plasticity, and memory formation. It is used to treat moderate to severe AD. [8]

Ayurveda mentioned *Smritinasha* (loss of memory) among the prodromal symptom of *Jara* (ageing).[9] *Smritinasha* can be correlated with the AD. In *Jaravastha* (old age), which starts from 60 years of age as per *Caraka*, *Smriti* and other mental faculties gradually deteriorate naturally. As per *Vagbhata* (*As.Sam.Sha* 8/25) and *Sharangadhara* (*Prathama Khanda* 6/20), the functions of mind and *Buddhi* decline start declining from the 9th decade of life. Mental function declines at 11th decade of life as per *Sharangadhara*. Further, *Smritibramsha* (disturbed memory) is described as a symptom where *Smriti* (memory) is vitiated by *Rajas* (passion) and *Tamas* (obscurity).[10] Thus, senile dementia can be interpreted as *Jarajanya Smritibhramsha* according to Ayurvedic principles. [11]

Drug named *Brahmi (Bacopa Monnieri)* is described in the Ayurveda text as memory enhancer.[12] Considerable number of studies (animal experiments and clinical trials) have been done to evaluate its efficacy in learning and memory. It was concluded that *Brahmi (Bacopa Monnieri)* has a positive effect on learning and both short-term and long-term memory.[13]

In different phases of life, different *Doshas* predominate: In the early part of life, *Kaphaja dosha* (those arising out of biological humor which maintains structural integrity) predominates in the body; in the middle age, *Pitta* (biological humor which resembles enzymatic and endocrinal functions) related diseases predominate and *Vata* (biological humor representing nervous system functions) dominance leads to degenerative changes during old age. *Rasayana* drugs by their specific activity subdue the vitiated *Vata* and help in preserving the bodily physiological functions by restoring the feeling of well-being.[14] *Vagbhata* considers *Brahmi (Bacopa Monnieri)* as a prime drug from *Apasmara* which is characterized by loss of *Smriti* (memory) and *Samjnya* (consciousness).[15]

Considering the potential of Bacopa Monnieri as a neuroprotective agent and the gap in the existing literature connecting Bacopa Monnieri and dementia, we aimed to perform a systematic review to determine whether it has beneficial effects on cognitive impairment due to Alzheimer disease and identify gaps in the literature.

MATERIALS AND METHODS

Implication of comprehensive search strategy was done to identify all relevant studies. Classical textbooks and published research studies were searched in the context of use of *Brahmi (Bacopa Monnieri)* in the Alzheimer's disease. Online search engines namely J gate, Google Scholar, PubMed, DHARA online and AYUSH research portal, Cochrane Library, clinical trial registries (World Health Organization, Australia-New Zealand, United States, and South Africa, the MetaRegister of Controlled Trials, and CINAHL were searched from 2010 to December 2022. Strategic search terms used were '*Brahmi*', 'Alzheimer's disease', 'Ayurveda', 'Randomized controlled trial'. We searched for the studies in the reference lists of all studies included in the light of retrieved papers. We contacted authors to obtain the full published papers. The study has been reported according to the PRISMA statement.

There was no restriction in the type of study to be included, but randomized controlled trials were preferred. The focus of review was to obtain information about the *Brahmi (Bacopa Monnieri)* as memory enhancing drug which can improve the memory power in the Alzheimer's disease. This extensive review would help in proposing possible intervention of *Brahmi (Bacopa Monnieri)* for Alzheimer's disease based on the basic principles of

Ayurveda and already available evidences in the research area.

Initially titles and abstracts were screened followed by the review of articles. Duplicate articles were removed, after manual screening for duplicity of titles and authors.

Inclusion Criteria

1. Randomized controlled trials
2. Males and females
3. Cognitive function (determined by the change from baseline in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), Mini-Mental State Examination, Postgraduate Institute Memory Scale, or any culturally adapted or validated tools to assess cognition), activities of daily living using scores such as the Alzheimer Disease Cooperative Study, clinician-rated global impression tests, behavioral symptoms, and safety as measured by incidence of adverse effects, dependency, or death.

Exclusion criteria

1. Letter to editor, commentaries, call for paper, conference reports, situation reports, people and company reports, articles in other languages.
2. Trials that were confounded by treatment or a control group receiving another active treatment that has not been factored into the randomization.

The data were recorded following PRISMA guidelines. Points as per Critical appraisal checklist appropriate to the study design was applied.

Systematic review

A total of 179 articles were obtained during the search with the keywords 'Bacopa monnieri', 'Alzheimer's disease', 'Dementia and Bacopa monnieri' (from January 2010 to December 2022). Studies including randomized controlled trials all age groups including both male and females were taken into consideration. Articles containing mild cases were included. Duplication removal was done manually, 23 articles with same title and authors, 2 protocols and 2 abstracts appeared with different keywords were removed. Further 164 full articles were read. Among them 144 articles excluded containing 49 animal studies, 32 narrative studies, 22 preclinical studies, 13 systematic reviews, 3 informatics, 1 editorial, 1 case report, 1 online promotion, 1 book chapter and 1 adverse events reporting. Total 20 randomized studies assessed for the eligibility. Among them 15 were excluded containing 12 healthy adult subjects, 1 healthy school children, 1 child with attention deficit hyperactivity disorder and 1 healthy medical student. So, finally 5 studies included for the qualitative synthesis and analysis as mentioned in the fig.no.1.

RESULTS

Overall, 164 studies were identified by the search. The abstracts of all studies were screened, and 5 were found to be eligible.[16,17,18,19,20] The primary objective of the study conducted by Prabhakar et al was to determine if Bacopa Monnieri improved the memory of patients with Alzheimer disease and MCI-AD (Mild Cognitive Impairment- Alzheimer disease) compared with donepezil.[21] The diagnosis of Alzheimer disease and MCI-AD was aided by magnetic resonance imaging of the brain, fluorodeoxyglucose-positron emission tomography of the brain, and cerebrospinal fluid biomarkers (beta amyloid and total tau). *Bacopa Monnieri* was administered once daily at a dose of 300mg, while 10mg of donepezil was given once daily for 12 months. Although a sample size of 48 patients (24 in each arm) was planned, only 34 patients (17 in each arm) could be recruited after 45 months, due to which the study was terminated. The primary outcome was the difference in change of the ADAS-Cog score and Postgraduate Institute Memory Scale score from baseline after 12 months of treatment between the 2 treatment groups. However, patients were followed up for changes in scores at 3, 6, and 9 months of treatment. Change from baseline of neuropsychological tests such as the verbal fluency-controlled oral word test and animal names test, quality of life-Alzheimer disease, activities of daily living inventory, adherence to treatment, and adverse events were secondary outcomes. The authors reported attempts to follow up on all patients with whom contact was lost during the study period, and an intention-to-treat analysis was used. Missing data were handled by multiple imputations due to loss of follow-up. A total of 4 and 9 patients were lost to follow-up in the donepezil and Bacopa Monnieri arms, respectively, at the end of 12 months. There were differences in baseline characteristics (more patients with Alzheimer disease in the donepezil arm and more patients with MCI-AD in the Bacopa Monnieri arm), which were adjusted for during analyses.

Cicero et al compared the effect of a combination of agents (Bacopa Monnieri, L-theanine, Crocus sativus, copper, folate, vitamin B complex, and vitamin D) over 2 months and those of a placebo in improving cognitive functions in older adult patients. They included 30 participants with Mini-Mental State Examination scores between 20 and 27 or self-perceived cognitive impairment (whether the impairment was dementia or mild cognitive impairment was not reported). The primary outcome was change in Mini-Mental State Examination score from baseline at 2 months. The Perceived Stress Questionnaire and Self-Rating Depression Scale scores were other outcomes. [22]

Sadhu et al investigated the efficacy of a polyherbal test formulation composed of extracts of *Bacopa Monnieri*, *Hippophae rhamnoides*, and *Dioscorea bulbifera* (total dose of 500mg) on cognitive functions. The test formulation was compared with a placebo in healthy adults without dementia and the test formulation was compared with donepezil (10mg twice a day) in older adult patients (aged 60-75 years) with Alzheimer disease (n=123; deterioration of memory in at least 3 of the following: poor orientation, poor judgment and problem-solving, difficulty in community affairs, inability to function independently at home, or difficulties in personal care) for 12 months. Subsequently, the participants underwent a clinical screening using the Dementia Rating Scale-2 before being randomized to test formulation or donepezil. The primary outcome was cognitive function assessed by a composite of mental status (Mini-Mental State Examination), verbal memory, complex psychomotor tests, and attention or executive functions at 12 months. [23]

Raghav et al studied the efficacy of Bacopa Monnieri extracts in patients with age-associated memory impairment and no evidence of dementia or psychiatric illness.[24,25] Participants were adults older than 55 years of age with memory loss in daily activities and a logical subset score 24 were excluded. Eligible patients (N=40; Bacopa Monnieri group: n=20; placebo group: n=20) were randomized to receive 125 mg of Bacopa Monnieri extract or a placebo twice a day for 12 weeks followed by the placebo for both groups for another 4 weeks. The outcomes were the Mini-Mental State Examination and the Wechsler Memory Scale (subsets Logical Memory, Visual Reproduction, and Paired Associated Learning).

Barbhaiya et al studied the effects of Bacomind (an enriched phytochemical combination containing 450 mg of standardized Bacopa Monnieri extract) on 65 individuals aged 50 to 75 years with self-reported memory impairment (Mini-Mental State Examination score >24) for at least 1 year. The study duration was 24 weeks (drug administered for 12 weeks, then no drugs for 12 weeks). Neuropsychological assessment was performed at baseline, week 12, and week 24. Outcomes were analyzed for attention, memory, and speed of information processing. Three patients were lost to follow-up for the second visit, and 15 patients were removed as outliers. The final analysis was completed for 44 patients (Bacomind: n=23; placebo: n=21). Further, 3 patients were lost to follow-up during the study.[26] All 5 studies were deemed to have a high risk of bias.

Effects of Intervention

None of the studies described the effects of Bacopa Monnieri in patients with different classes of disease severity (mild, moderate, severe Alzheimer disease and MCI-AD). Effects of different dosages of Bacopa Monnieri were not tested in any eligible studies. Hence, the primary and secondary objectives of the review remain unanswered.

Cognitive Functions

Only Prabhakar et al reported effects on cognition using ADAS-Cog and Postgraduate Institute Memory Scale. Prabhakar et al, Sadhu et al, and Cicero et al reported changes in Mini-Mental Status Examination; although Raghav et al mentioned that Mini-Mental State Examination was performed at baseline in all participants, we could not extract data about the change in scores. Barbhaiya et al used Mini-Mental State Examination only for screening. Prabhakar et al performed an intention-to-treat analysis; after adjustment for confounders, no difference in the rate of change in the ADAS-Cog score was noted between the Bacopa Monnieri arm and donepezil arm at any of the prespecified time points (3, 6, 9, and 12 months) from baseline. At 12 months, the mean ADAS-Cog score was 2.27 (SD 5.65) in the donepezil arm and 0.51 (SD 5.65) in the Bacopa Monnieri arm (mean difference −1.76; P=.39). There was a significant difference in the change in overall Postgraduate Institute Memory Scale score between the 2 arms at 12 months (donepezil: mean 0.46; SD 10.96; Bacopa Monnieri: mean 7.94, SD 10.96); mean difference −8.40; P=.04]. The donepezil arm had reduced progression of symptoms (measured by ADAS-Cog scores) in individuals with MCI-AD or mild-to-moderate AD, compared to those in the Bacopa Monnieri arm. However, analysis of individual components of the Postgraduate Institute Memory Scale revealed no differences.

Changes in Mini-Mental State Examination scores from baseline were reported by Sadhu et al, Cicero et al, and Prabhakar et al. At 3 months, a significant difference in the mean change from baseline was noted between the donepezil arm (mean 0.72, SD 3.13) and the Bacopa Monnieri arm (mean −2.02, SD 3.13) by Prabhakar et al (mean difference 2.74; P=.02); however, there were no differences between the arms at any further time points (6, 9, and 12 months). Sadhu et al also found no difference between the donepezil arm (mean 7.882, SD 1.956) and the Bacopa Monnieri formulation arm (mean 7.914, SD 2.106) at 12 months in terms of change in Mini-Mental State Examination scores from baseline (P=.9375). Cicero et al found significant improvements in the Mini-Mental State Examination score and the Perceived Stress

Questionnaire index in the Bacopa Monnieri formulation arm compared to the placebo. Both were reported as mean scores before and after treatment. Raghav et al used the Wechsler Memory Scale to report outcomes. They reported scores of individual subsets of the scale at baseline, 4, 8, 12, and 16 weeks as means and standard deviations. The total memory score of the Bacopa Monnieri arm showed a significant difference from the placebo arm in terms of change from baseline at 4, 8, and 12 weeks but not at 16 weeks. Raghav et al also reported that 55% of participants in the Bacopa Monnieri arm showed more than 20% improvement in memory parameters compared with 44.4% of participants in the placebo arm (P<0.1).

Barbhaiya et al used various tests for attention (digit span, digit cancellation, serial subtraction), memory (Rey Auditory Verbal Learning Test, Wechsler Memory Scale-1, paired associates, and visual retention), speed of information processing (digital symbols). There was a significant improvement in the digit span backward task (P=.008) and digit cancellation time test (P<0.001) between baseline and week 12. A significant improvement in list learning delayed recall (P=.014), paired associates dissimilar delayed recall (P=.047), and visual retention test (P=.035) were also reported.

Functional Outcomes

Different tools were used in the studies to determine functional outcomes. Prabhakar et al found no significant difference in the change in activities of daily living scores such as Alzheimer Disease Cooperative Study activities of daily living at any time during follow-up between the donepezil and *Bacopa Monnieri* arms. Similarly, no changes were noted in quality of life measured using Quality of Life Patient and Informant questionnaires. Sadhu et al used the Functional Activity Questionnaire and reported a significant difference in change at 12 months between the donepezil arm (mean 9.801, SD 1.458) and the *Bacopa Monnieri* formulation arm (mean 11.873, SD 2.751; P<0.001). Raghav et al did not report any functional or quality of life–related outcomes. Cicero et al reported significant improvement in Self-Rating Depression Scale scores in the *Bacopa Monnieri* formulation arm. Barbhaiya et al did not report any functional outcomes.

Safety

Prabhakar et al reported no significant differences in the number of patients who experienced one or more adverse events. No major adverse events were reported either. There were 3 deaths (2 in donepezil arm and one in *Bacopa Monnieri* arm) reported due to myocardial infarction. Raghav et al reported diarrhea in 1 patient and headache in 2 patients in the placebo arm. One participant of the *Bacopa Monnieri* arm was reported to have experienced rashes. Sadhu et al reported nausea, constipation, and drowsiness; however, no data on the number of participants with these events were reported. In the study conducted by Cicero et al, 1 participant was reported to have an aftertaste following ingestion of the *Bacopa Monnieri* formulation. Barbhaiya et al did not report any adverse events.

Quality of the Evidence

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to assess the certainty of the evidence in the included studies, using the criteria outlined in the Cochrane Handbook. The certainty of the evidence for the reported outcomes was very low. We assessed the quality of evidence for 4 major clinically relevant outcomes (ADAS-Cog, Postgraduate Institute Memory Scale, Mini-Mental State Examination, and Wechsler Memory Scale). We judged that all 5 included studies had a high risk of bias, downgrading the evidence by 2 levels. Hence, the overall certainty of evidence was very low.

DISCUSSION

There was very little high-quality evidence which needs to be evaluate in further studies for the benefits of *Bacopa Monnieri* compared with a placebo or donepezil for cognitive function, functional outcomes, or adverse events. All 5 studies were heterogeneous with respect to doses of *Bacopa Monnieri*, as part of a polyherbal combination, use of a placebo or donepezil as the control group, duration of treatment (2 months to 12 months), cognitive tests to assess primary outcomes, and the diagnostic criteria for Alzheimer disease and mild cognitive impairment.

Lack of Neuroimaging for the Diagnosis

Prabhakar et al was able to demonstrate a statistically better outcome in the donepezil group compared to the *Bacopa Monnieri* group, even though there was no difference at 3, 6, and 9 months. Any statistical significance in this study was limited by a small sample size (34 patients) due to poor recruitment (the trial was stopped prematurely because of this issue).

Raghav et al, Sadhu et al, and Cicero et al were able to demonstrate improvements in one or more facets of cognition using *Bacopa Monnieri* compared to the placebo or donepezil. All 3 studies had small sample sizes. Furthermore, duration of treatment and follow-up were also short. Since Sadhu et al and Cicero et al used a polyherbal preparation and combined nutraceuticals (with *Bacopa Monnieri* as one component), improvements noted cannot be attributed

to *Bacopa Monnieri* alone. These 2 studies did not use brain imaging; hence, the accuracy of Alzheimer disease diagnosis cannot be ascertained.

Although Barbhaiya et al reported significant improvements in several tests of cognition, removal of 15 participants after randomization as outliers without giving any reasonable explanation and the absence of 33% of participants from the final analysis are major issues.

Comparison with Other Studies or Reviews

A previous meta-analysis that evaluated the efficacy of *Bacopa Monnieri* for cognitive performance included studies with both healthy participants and individuals with memory impairment (518 participants from 9 studies); however, there were only 2 trials with cognitively impaired patients. Similar to our observation, Barbhaiya et al described an overall dropout of around 33%. However, there is no mention of the exclusion of 15 participants as outliers. A meta-analysis performed on data from 437 participants showed a shortened duration taken to complete the Trail B test (−17.9 ms, 95% CI −24.6 to −11.2; P <0.001) and decreased choice reaction time (10.6 ms, 95% CI −12.1 to −9.2; P<0.001**)**. However, the Trail B test results were based on a single study with 46 healthy volunteers while the decreased choice reaction time was based on a subgroup analysis of 2 studies on healthy volunteers (46 and 62 participants) using 300 mg of *Bacopa Monnieri*. Hence, it cannot be truly considered as pooled estimates of efficacy in those with dementia. We did not perform a meta-analysis since the heterogeneity of data from the studies on people with dementia precluded meaningful pooling.

Another systematic review on the effectiveness of *Bacopa Monnieri* as a nootropic, neuroprotective, or antidepressant supplement included studies involving healthy volunteers and those with dementia and depression. Three studies evaluated *Bacopa Monnieri* in Alzheimer disease or mild cognitive impairment, of which Goswami et al was a nonrandomized study. A meta-analysis was not performed in this review.

In a systematic review by Cicero et al, the meta-analysis by Kongkeaw et al was cited, and no new studies were included apart from those included by Kongkeaw and colleagues. Brioschi Guevara et al had included 2 studies (Raghav et al and Barbhaiya et al) in their systematic review and described these studies as follows: "two old small studies on *Bacopa Monnieri* in individuals with memory complaints suggest a potential effect on some aspect of memory function or on attention tests that still need to be confirmed." No data or study characteristics were mentioned in the review.

Though previous systematic reviews had included most of the studies that this review also found eligible, they had not specifically addressed the question of the efficacy of *Bacopa Monnieri* in persons with Alzheimer disease. Inclusion of healthy volunteer studies and nonrandomized studies in these reviews makes it difficult to draw conclusions about similarities, and although significant improvements in specific tests had been noted in pooled analyses, they were mostly based on data from subgroups or single studies**.**

Strengths

We have thoroughly searched for and analyzed all the available evidence critically. Only 5 eligible trials were identified due to the use of stringent inclusion criteria. Due to severe heterogeneity in the included studies in terms of criteria for diagnosis, cognitive tests used, *Bacopa Monnieri* formulations (including polyherbal), duration of treatment, and lack of confidence in the diagnosis of dementia in the included patients, we did not conduct a meta-analysis.

Limitations

First, the use of very stringent inclusion criteria led to few eligible trials. However, this also means that the review question has been addressed specifically without any dilution of intent. Second, 1 author (VVY) was involved in a trial included in this review (i.e., Prabhakar et al). This potential source of bias was addressed because author VVY did not participate in the risk-of-bias assessment of trials (performed independently by authors AB and BM). Third, as with any systematic review, it is possible that some studies might have been missed. We ensured the inclusion of all potential studies by searching multiple databases. Moreover, independent screening of search output by 2 authors ensured that bias was minimized in assessing eligibility. We followed the guidance provided in the Cochrane Handbook to minimize potential biases in the review process[34]. Fourth, because only 5 trials were included in this review, we could not use funnel plots to assess the risk of publication bias.

Future Directions As discussed above, this review found that there was no high-quality evidence for the benefits of *Bacopa Monnieri* compared with a placebo or donepezil for cognitive function, functional outcomes, or adverse events. All 5 studies had heterogeneity with respect to the *Bacopa Monnieri* dosage used in the trials, *Bacopa Monnieri* used as part of a polyherbal combination, use of a placebo or donepezil as the control group, duration of treatment (2 months to 12 months), cognitive tests used to assess primary outcomes, and diagnostic criteria used for Alzheimer disease and mild cognitive impairment.

These hindered the generation of high-quality evidence for the use of *Bacopa Monnieri* in Alzheimer disease and MCI-AD. Based on these results, we opine the following design changes for future trials of *Bacopa Monnieri* in patients with Alzheimer disease.

Outcome Measures

Primary outcomes for Alzheimer disease trials should include cognitive and functional endpoints or a single cognition-function composite endpoint, and the tools selected to capture these outcomes should have cultural validity and international harmony. Prodromal Alzheimer disease assessment requires newer, sensitive measures, such as tests of metacognition, social cognition, and prospective memory, rather than traditional neuropsychological tests. The detection of functional impairment in the early stages will also require instruments that are sensitive to subtle functional changes such as tests for financial capacity, performance-based skill assessments, and computerized assessments based on virtual reality and video technology. Other options are time to onset of dementia or the proportion of patients who develop Alzheimer disease dementia; however, Alzheimer disease prevention trials that use time to event as an outcome require extended observation periods to accurately assess disease progression.

CONCLUSION

The evidence obtained from the present systematic review is of very low certainty. The evidence from 5 trials suggests that there is no difference between *Bacopa Monnieri* and a placebo or donepezil in the treatment of Alzheimer disease or mild cognitive impairment. No major safety issues were reported in the trials included in this review.

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Cite this article as:
Raut Disha Anil, Meena Jaikishan, Arti, Anshul. Effect of Brahmi (Bacopa Monnieri) (Bacopa Monnieri) in the treatment of Alzheimer's disease from Ayurvedic perspective - A Systematic Review. AYUSHDHARA, 2023;10(Suppl 3):74-82.
https://doi.org/10.47070/ayushdhara.v10iSuppl3.1266
Source of support: Nil, Conflict of interest: None Declared

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Fig. No.1: PRISMA Chart showing the identification, screening and inclusion of trials for this systematic review