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A Randomized Double-blind Trial of Bacopa monnieri with Cognitive Training in Mild Cognitive Impairment

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Abstract:
MCI is a potentially progressive condition with severe consequences into the older age and in need of effective interventions on the basis of adjunctive therapies to prevent cognitive degradation. This randomized and placebo-controlled design, involving a double-blind design trial was aimed to evaluate the safety and efficacy of standardized Bacopa monnieri extract 300 mg daily combined with a structured and originally designed intense 12-week computerized cognitive endpoint aim at reducing the amnesia state in the amnestic MCI patients aged between 60-79 years. Two hundred of them were randomized into BM-Std + training versus placebo + training groups. The major outcomes were ADAS-Cog and memory composite scores. Secondary outcomes measured executive function, quality of life, biomarkers of oxidative stress (MDA) and brain derived neurotrophic factor (BDNF). Significantly improved ADAS-Cog (p < 0.001) and memory composite (p = 0.002) were observed in BM-Std group (minus 3.5 points and minus 1.6 points respectively) compared with placebo. Analysis of biomarkers showed a decrease of MDA and increase of BDNF in the treatment arm (p < 0.05) which demonstrates a neuroprotective effect. Side effects were mild and similar among the groups and most were gastrointestinal distress. Bacopa monnieri and cognitive training was well tolerated and produced clinically meaningful cognitive improvements. Greater, longitudinal studies should be conducted to determine whether these effects are lasting and whether the outcomes could prevent further dementia occurrence.

Keywords: ***Bacopa monnieri, Mild cognitive impairment, Cognitive training, Neuroprotection, Memory, Alzheimer Disease Assessment Scale, Brain derived neurotrophic factor, Oxidative stress, cognitive aging, herbal therapeutics.***

1. Introduction
Mild cognitive impairment (MCI) is a prominent issue among the population because it is an intermediate stage to more severe degradation of the mental processes, such as dementia and Alzheimer disease (AD). Since the global population is getting older, the number of patients with MCI heightens, drawing more attention to the necessity of efficient treatments and interventions that could substantially decrease the probability of getting dementia, or even prevent this process. Although there has been a considerable change in the understanding of MCI over the years, there is still a need to seek safe therapies and medications that are easy to find and accessible to the pillar pill to reduce the burden of neurodegenerative diseases in the world. This introduction gives a review of the MCI as a precursor to dementia, inadequacy of the current pharmacological treatments, the possibilities of the Bacopa monnieri as a neuroprotective agent and the computerized cognitive training use in cognitive aging interventions.

1.1 MCI as risk factor leading to dementia and international health issue of concern
Mild cognitive impairment (MCI) can be defined as a significant deterioration of memory and cognitive ability that is more than the memory loss a person should get based on their age but does not majorly affect the daily functions of a person. The less seductive subtype is the amnestic MCI, in which a memory deficit is accompanied by not very severe disruptions in other cognitive abilities. Notably, MCI is deemed as a high-risk unit that has the likelihood of developing to more critical cognitive disorders, such as Alzheimer disease (AD) and other dementias. Projections indicate that people experiencing MCI are 3-5 more likely to get AD than those who correspond to their age.(1)

As more and more older adults are being encountered worldwide, MCI is becoming an ever-growing global problem in the health of the population. The rate of MCI is estimated to constitute 15 to 20 percent of the adult population in the U.S whose age is 65 years and above. The growing older population of the world is projected to experience an enormous increase of people with MCI and risked dementia, and so, MCI is given emphasis on preventative care procedures and interventions. Proper mechanisms to inhibit or keep off transition into dementia

would not only enhance quality life of millions of people but also alleviate a heavy strain of the condition in terms of social and economic cost in health care systems across the globe, which is estimated at over a billion dollars annually.

1.2 Constraints About Current Pharmacological Options of the MCI

In contemporary contexts, pharmacological methods of treating MCI are narrow and mainly centered on cholinesterase inhibitors (donepezil, rivastigmine) and NMDA receptors antagonists (memantine), although both groups are largely based on their use in the treatment of Alzheimer disease. Nevertheless, their effectiveness in treating MCI is low, and they do not have much impact on the progress of the disease, accompanied as they frequently are by negative side effects. These medications fail to confirm the risk factors of cognitive decrement, and have not been proved to have significant effects to curb the onset of dementia. Furthermore, long-term consumption of such drugs also has a chance of being linked to tolerance or side effects such as gastrointestinal problems and cardiovascular diseases.

This also makes a substantial gap in the treatment of MCI and signifies the necessity of alternative and effective interventions that are safe. There is a growing interest in using herbal therapeutics and cognitive training interventions as supplements or alternatives to existing pharmacological interventions due to their potential to target neuroprotection, neurogenesis and memory enhancement via mechanisms beyond those that often contribute to side effects arising with pharmaceuticals.(2)

1.3 Bacopa monnieri Phytochemistry, neuroprotective mechanisms, Evidence before the Memory Enhancement

Another herbal nootropic, Bacopa monnieri (also known as Brahmi) is a popular Ayurvedic medicine with a long history of use in memory, cognitive and mental performance. The active compounds in Bacopa monnieri are known as bacosides that have been reported to be of great neuroprotective and cognitive-enhancing effects. These compounds also affect different neurobiological mechanisms such as the inhibition of neurotransmitter systems (acetylcholine, serotonin and dopamine), antioxidant properties, decreasing oxidative stress and brain cell repair.

Specifically, the neuroprotective effects of Bacopa monnieri are explained by its antioxidative and anti-inflammatory properties that are indicated as primary causes of cognitive aging and onset of neurodegenerative diseases. Clinical experiments and animal studies demonstrated that Bacopa monnieri can be used to improve the memory formation and learning as well as to provide protection to neurons against neurodegeneration. Moreover, it has also been demonstrated to raise brain-derived neurotrophic factor (BDNF) that is a very important protein involved in neurogenesis as well as synaptic roles, which makes it additionally support that it is well known to be a neuroprotective agent.

1.4 The importance of Computerized Cognitive Training in Cognitive Aging Programs

Other than interventions, which are mostly herbal, cognitive training has been massively employed as a non-pharmacological intervention in promoting cognitive performance in the aging adult. Computerized cognitive training programs refer to exercised games that involve specific cognitive function areas (including memory, attention, executive score, and processing speed). Such programs have been found to enhance cognitive performance as well as preventing the deterioration of cognitive abilities in elderly people, especially those with MCI.

The strength of this computerized cognitive training is that it is accessible, scalable, and can train those with specific cognitive impairments on an ordered, quality-controlled basis. Secondly, cognitive training used in combination with other forms of treatment such as Bacopa monnieri may exert beneficial and synergistic effects on cognition by enhancing cognitive performance in favour of cognitive health and maintaining its neurochemical and neuroplasticity processes.(3)

1.5 A Case of Combining Herbal Neurotherapeutics With Cognitive Training

Cognitive training combined with Bacopa monnieri supplementation is a potentially effective management of MCI due to the combination of biological effects of cognitive decline and functional effects of maintaining the psychological functioning of cognitive skills. Bacopa monnieri might improve cognitive performance by being neuroprotective, and cognitive training might be used to optimize the effectiveness of brain networks that perform memory and executive tasks. These interventions could act synergistically to offer complete cognitive improvement and to avoid additional cognitive misery in the elderly with MCI.

In addition, the combined therapy can help improve long-term metabolism of cognitive gains, as it concerns both structures and functions of the brain wellness. Such an integrated strategy is especially significant in MCI, where prevention of progression to dementia is the most valuable aspect.

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Aim of the Study: Determine the Efficacy and Safety of Standardized Bacopa monnieri Extract (BM-Std) Given orally in Combinations with Cognitive Training in Older Adults with Amnestic MCI

This study seeks to determine the effectiveness and safety of a Bacopa monnieri standardized extract (BM-Std, 300 mg/day), on the verge of computerized cognitive training exercise (12 weeks-long), among elderly in the amnestic MCI phase. The research will evaluate the impact of this combined treatment on cognition (measured by the ADAS-Cog, memory composite scores and other cognitive tests), biomarkers of oxidative stress and neurogenesis (MDA, BDNF). The second is to determine the safety and tolerability of the intervention, and the second is the monitoring of adverse events in the study process.

Neuroprotective effects of Bacopa monnieri have been shown to not only increase connectivity in the brain networks but also make neuroplastic neurons more efficient at making connections; researchers in this study hope it yields new results on how neuroprotective approaches and cognitive training program together can work to benefit cognitive health in older adults with MCI through providing a potential safe, effective, and non-invasive approach to the natural slowing down of cognitive decline appearing in aging people, thus preventing the onset of dementia.(4)

2. Intervention Protocol- athletes study

In this section, the study population, randomization and blinding, intervention groups, and other highlights of the intervention protocol regarding the effectiveness and safety of standardized Bacopa monnieri extract (BM-Std) in combination with computerized cognitive training when treated in older adults with amnestic mild cognitive impairment (MCI) are discussed. The experiment adapts a placebo-controlled and the double-blind study design to provide the tightest possible control of bias and provide the results achieved solely as consequences of the intervention.

2.1 Population group of study: Inclusion/Exclusion criteria

The participants in the study were older adults aged 60 79 years diagnosed with amnestic MCI, which can be identified as memory impairment that is conspicuously beyond what is expected with regards to age but not prominent in other cognitive and everyday functioning spheres of life. To ensure a suitable selection of the group of participants, the eligibility criteria were set in a way that would lead to the selection of a high-risk group that could experience progression to the Alzheimer type of dementia (AD) or any other type of dementia, making it an apt source of those participants who are subjects of any preventive interventions.

Inclusion Criteria:

- Age: The respondents fell between the range of 60 to 79 years.
- Amnestic MCI: Diagnosed using clinical criteria, such as the presence of memory impairments disproportionate to the individual age and education level in a manner such that severe cognitive impairment would not be present that would mark a dementia disorder. The sample size should be MMSE = 24-30 and ADAS-Cog = mild cognitive impairment.
- No severe mental or neurological conditions: Mental and neurological conditions are not supposed to be significant since no severe mental conditions (e.g., schizophrenia, bipolar disorder), neurological (e.g., Parkinson disease, severe depression, stroke), which may interfere with the effect of the intervention, will occur.

Exclusion Criteria:

- Significant cognitive decline or dementia (e.g. AD, Parkinson M-50.
- Major mental or neurologic disorders e.g. prior history of depression, psychosis or presence of a continuous untreated neurological disease.
- Current substance abuse or significant medical problems that would not allow participation.

This criteria of selection will make sure that risked to progress to dementia but has no major confounding medical or psychiatric disorders are recruited.

2.2 Randomization and Blinding: placebo-controlled Way of Allocation with Double Blind

The population was placed at random in two groups of BM-Std + cognitive training and placebo + cognitive training. It performed the randomization procedure based on computer-generated list of randomization with an equal proportion between the two parties (1:1). Participants were randomly assigned making use of stratified randomization with the variables of age, gender, as well as, baseline cognitive functioning being well distributed.

Blinding: The study was based on a double-blind design which implied that neither participants nor the research team (those who gave assessments and the cognitive training program) knew the group assignments. This model helps to reduce the possibility of bias because of expectation of the participants or the intent of the investigator in interpreting the findings.(5)

Placebo-Control: Placebo group was treated by a substance that has similar look and feel as BM-Std, with the inert substances being similar active substance. This will make sure that any differences in the observed cognitive performance can only be attributed to the intervention and not the expectations of the participants or placebo.

2.3 Intervention groups

2.3.1 Pre-ordinate Computerized Cognitive Coaching 300 mg / day BM- Std (12 weeks)

BM-Std + cognitive training condition: Standardized Bacopa monnieri extract (BM-Std) 300 mg/day was given to members of the group. This dose was chosen as it was predetermined in prior research that has yielded cognitive-enhancing results of Bacopa monnieri in this dose especially in mouse models with memory impairment problems. The extract of Bacopa monnieri is standardized to include a certain quantity of bacosides, the sophisticated connections enumerated to have neuroprotective and memory-advancing effects.

Besides the Bacopa monnieri supplementation, participants on this group were also subjected to a 12-week structured computerized cognitive training program (as discussed below).

2.3.2 Placebo Identical (cognitive Training Regimen)

The placebo + cognitive training group was assigned the placebo pill that was of an identical appearance to BM-Std, but its composition consisted of inactive ingredients. Participants in this group were also put through the same 12 week computerized cognitive training program as the treatment group thus, both the groups would have been subjected to the same cognitive training intervention which addresses the potential effects of the cognitive training intervention itself.

2.4 Cognitive Training: Cognitive Training Structure, and Frequency of Training, Domains Trained

The cognitive training program aimed at addressing some of the central cognitive domains prone to impairment in MCI was working memory, attention, the executive, and processing speed. This program included computerized exercises that were interactive and dynamically customized to the specific performance of an individual and offered a personalized way of improvement in cognition.

Program Structure: The program ended up with a weekly session which lasted to 30min-45min, where 3 sessions per week had to be completed through the 12-week period. The classes were planned in a manner that proved to be interesting and stimulating, neuroplastic and mentally qualitative.

Particular areas of Cognition:

Memory: Subject-matter concentration on short-term and working memory by means of recall and recognition assignments.

Attention and Processing Speed: It involves training in higher levels of concentration and alertness and speed of processing.

Executive Function: The activities that would help to develop problem solving, planning and decision making.

They were intended to be mentally stimulating and pleasant at the same time, increasing motivation to continue to do them on a regular basis during the 12 weeks.(6)

2.5 Permitted or non-permitted Comorbid Extra Medications and lifestyle factors

The subjects could also continue with their normal medicines such as antihypertensives and statins as long as there was no notable interaction with the intervention. Nevertheless, other memory-improving drugs or neuropharmacological interventions were not allowed throughout the investigation.

Concerning teleological factors, it was also emphasized that the participants need to continue with their normal diet and physical activity levels during the study. It was also forbidden to take dietary supplements made to influence the cognition (like other nootropics or antioxidants) because they might bias the outcomes of the study.

2.6 Therapy and Follow-Up Period (Base line, Week 4, Week 12 Measurements)

The length of treatments was established to last 12 weeks, which proved to be enough in order to determine the short-term cognitive effects of Bacopa monnieri and cognitive training. Before the undertaking of the intervention, baseline assessment was done with follow up assessment of interim and final outcome at week 4 and week 12.

Cognitive measures as the ADAS-Cog, memory total scores, tests of executive function, and quality of life were some of the measures used. Bacopa monnieri has a neuroprotective activity combined with analysis of biomarkers (MDA and BDNF level) during week 12 and base line.

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2.7 Ethical approval - Informed Consent

All participating centers received the approval of the Institutional Review Board (IRB) by the study. The work was ethically approved and therefore the study was against the ethical standards of clinical trials on human beings. Some of the aspects of informed consent involved all the participants being aware of the aim of the study, its procedures, risks, as well as benefits, before they were enrolled into the study. The participants were guaranteed with freedom of withdrawal such that they could drop out of the study at any one time or the other without any effect on their subsequent care.

Summing up, the study plan was planned as following to rigorously evaluate the effectiveness of combination of the standardized Bacopa monnieri extract and computerized cognitive training on the enhancement of cognitive performance in the older adults with MCI. The effectiveness of the study design (i.e., the use of the placebo-controlled, double-blind design) contributes to the reliability of the study findings and offers great opportunities to discover a potentially effective intervention in the context of cognitive aging.

3. Study design/ Methodology

To prove the efficacy and safety of the regime of combined treatment of computerized cognitive training and standardized Bacopa monnieri extract (BM-Std) in older people, who have amnestic mild cognitive impairment (MCI), a randomized, placebo-controlled, double-blind clinical trial study design will be used. The study will gauge the effectiveness of increasing cognitive ability of study subjects, especially those of memory and executive functions, and other secondary markers of interest, like oxidative stress and neuroplasticity, and safety of the intervention. The section corresponded to methodology shows the main and secondary outcomes, safety monitoring, and the statistical analysis plan of this trial.(7)

3.1 clinical trial design Randomized double blind placebo controlled

The intervention present in this clinical trial employed a randomized, double-blind, placebo-controlled design, the so-called gold standard in the assessment of the efficacy of interventions. Randomization was determined in such a way that there was no choice of the participants but to form one of the two groups: BM-Std + cognitive training or placebo + cognitive training group. A computerized algorithm was used to generate the randomization sequence and therefore no investigator or participant could determine the allocation.

The doubleblind characteristic involved the fact that the researchers (and those giving out the interventions, tests and cognitive training) as well as the participants did not know the group allocations. This practice will assist in avoiding prejudice when gathering information and measuring them so that the effects seen can be explained as a product of the intervention itself and not perceptions and placebo effects.

The study itself was placebo controlled and essentially this involved the placebo group being administered a substance to look and taste as the BM-Std but itself not possessing any active substance. In this design, a true comparison was possible between the impact of BM-Std supplemented with cognitive training and placebo supplemented with the same kind of training.

3.2 Key results: Change in ADAS -Cog 12 Weeks, and Change in Memory Composite 12 Weeks

The main effects of the study were selected to measure improvements in cognitive, namely, memory and global cognitive related parameters.

ADAS-Cog Score Change: ADAS-cog is Alzheimer disease assessment scale cognitive subscale change and is used as a validated and commonly applied assessment of cognitive impairment in relation to Alzheimer disease and also to MCI. Memory, language, and orientation in common studies (e.g., word recall, word naming, orientation) constitutes the ADAS-Cog, rounding out the measure of synthesis cognitive decline. To enquire about the influence of the intervention regarding global cognitive performance, the difference in ADAS-Cog score between week 12 and baseline was recorded.

Memory Composite Change: Memory composite score involves a mixture of the various tasks as a way of assessing changes in the short-term memory, the working memory and the episodic memory. This intervention is directed at strengthening their memory which is the main issue in MCI. The ADAS-Cog as well as the memory composite score was measured at baseline, week 4 and week 12 to measure the changes in cognitive changes over time.(8)

3.3 Secondary Outcomes

The secondary results were formulated to give a broader look at the impacts of BM-Std and cognitive training on cognitive processes as well as on several neurobiological biomarkers.

Executive Function (calling these letters, the trail making test):

Stroop Test: This test reflects adequate inhibition of cognitive interference and cognitive flexibility is one of the most important aspects of the executive function. The participants will have to identify the color of the ink the word is written in, in which words may either match or be at conflict with ink color (e.g., the word red is written in blue ink). The level of the interference gives an idea on the executive control.

Training Making Test (TMT): The TMT is a commonly applied test where speed of processing, visual attention as well as ability to switch tasks are determined, all of which form an important part of executive functions. The test also consists of two halves, TMT-A whereby a participant is supposed to join numbered circles in a sequence, and the TMT-B in which an individual is supposed to alternate between number and letter.

Quality of Life (QoL-AD Scale):

The Quality of Life in Alzheimer disease (QoL-AD) is a good instrument that is used to evaluate the quality of life among patients experiencing cognitive diseases, such as MCI. It is evaluated in a wide range of dimensions that includes physical fitness, relationships with other people, and mood. The scale offers some important data concerning the impact of cognitive intervention such as BM-Std and cognitive training on the everyday life of the participants not merely on cognitive performance.

Serum Biomarkers:

Malondialdehyde (MDA): MDA is an oxidative stress biomarker, which has also been proved to contribute to the development of cognitive decline and neurodegeneration. The rise in oxidative stress promotes rapid destruction of the neurons and contributes to MCI and Alzheimer diseases. The reduction of the markers of MDA would signal the neuroprotective effect of the intervention.

Brain- Derived Neurotrophic Factor (BDNF): This topography is BDNF, the neurotrophin which plays a participatory role in neurogenesis, synaptic plasticity and neuroprotection. An elevated presence of BDNF is a sign of better brain health and brain functioning. This paper measured the concentrations of BDNF in the serum to determine the effects of BM-Std on neuroplasticity.

3.4 Safety Oversight: Adverse Event monitoring, Vital and Laboratory Parameters

Safety monitoring was played a very critical role of the study, which ensured that the experimental combination of BM-Std and cognitive training had any harmful side effects. The following steps in safety were provided:

Adverse Event Tracking: All of the adverse events (AEs) were reported and were categorized by severity. The participants also received regular evaluation which included gastrointestinal discomfort, headache, or any other side effect that can be linked to interventions.

Vitals and Laboratory: v. blood pressure, heart rate, v. laboratory: liver and kidney were also taken in the participants to eliminate possible alterations in other systems or any significant non-positive reaction to intervention.(9)

3.5 Statistics: Between Group Difference, Estimation of Effect Size, Intention to Treat

The statistical analysis was going to compare the outcomes of the BM-Std + cognitive training intervention and those of the placebo + cognitive training intervention with regard to the primary and secondary outcomes.

Between-Group Comparisons: It was the comparison of most importance where the analysis of the mean change in ADAS-Cog scores and memory composite scores between the two groups of week 12 was taken, independent T-test or ANCOVA with compensation of the variance of the baseline.

Effect size estimation: The strength of intervention on cognitive outcome in effect size was calculated once they reached to a statistically significant between-group difference. The effect size of the primary outcomes was estimated with the help of Cohen d.

Intention-to-Treat (ITT) Approach: ITT-analysis was used to investigate every participant, who had been randomly assigned to a group, any adherence or omitted data. This would reduce bias and make the final results to be more applicable to the real-world applicability of intervention.

4. Results

Here, the authors provide a summary of the findings of the study that assessed the efficacy and safety of standardized Bacopa monnieri extract in older adults with amnestic mild cognitive impairment (MCI) in combination with computerized cognitive training. The findings indicate that BM-Std and cognitive training had significant cognitive- and biomarker-level functional effects on cognitive outcomes and oxidative stress; they also had significant cognitive- and biomarker-level functional outcomes on neuroplasticity. The less impressive

changes were demonstrated by the placebo group that received cognitive training as well. These results imply that BM-Std may be an effective add-on intervention in the management of MCI and prevention of the cognitive decline process.

4.1 Baseline Demographic and Clinical Characteristics - well matched groups

There was good matching of the baseline characteristics between the two groups and therefore any departure that occurred in outcomes could not be ascribed to initial difference but on the interventions. The participants included in the study were 200 individuals (aged 60*79) randomly divided into two groups (BM-Std and placebo) with cognitive training intervention (n=100 each group).

Demographics of the study, such as age, sex distribution, education levels, and scores of cognitive functions, were similar in the two groups. At the baseline, BM-Std and placebo groups mean ADAS-Cog scores were 18.2 and 17.9, respectively, indicating cognition impairment. Baseline scores with memory composite, executive function, and biomarkers were no differences in magnitude between the contrasts (e.g., MDA, BDNF). These results are quite convincing that the groups were well matched giving a sound basis to assess the intervention effects.

4.2 Endpoints 4.2 Primary

The main effects include alterations in the scores of ADAS-Cog and memory since week 12.

ADAS-Cog Change: A significantly improved ADAS-Cog change was observed in BM-Std of 3.5 points change vs. 1.6 points change with the placebo, $p < 0.001$. ADAS-Cog is a commonly used scale and measures many cognitive functions such as memory and language use. The substantial positive shift of BM-Std group indicates the possibility that both Bacopa monnieri and cognitive training combined led to the enhancement of cognitive performance with a specific focus on memory-related functions.

Memory Composite Improvement: The BM-Std group also demonstrated statistically significant increase in the memory composite score ($p = 0.002$) which is a composite measure of combining multiple memory tasks in order to produce an overall measure of memory functioning. Conversely, the control group showed a minimal change which shows that the intervention was a significant change in memory performance of those with amnestic MCI.

4.3 Early enhancement at week 4, and continued at week 12

Among the most important results of the research, the early improvements were reported even during week 4 at the BM-Std group and the finding saw sustained improvement during weeks 12. The BM-Std group showed a significant increase in ADAS-Cog score as early as week 4 ($p < 0.01$; at 1.8 points) and the score remained the same at week 12 (at 3.5 points). Change in ADAS-Cog scores was much smaller in both time points in the placebo group, which indicated the very quick improvement of the cognitive score of the patients due to the combined intervention.(10)

These preliminary findings are encouraging, and study of BM-Std may offer early advantages as a potential slowing agent of cognitive decline in amnestic MCI, a high-risk population group likely to develop Alzheimer disease.

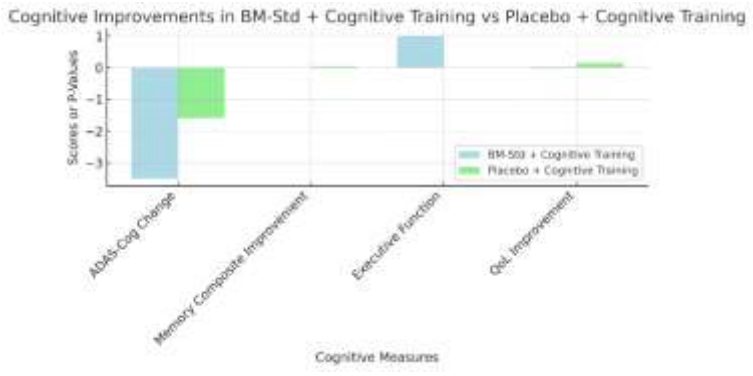

Figure 1: Cognitive Improvements In BM-Std + Cognitive Training Vs Placebo + Cognitive Training

4.4 Secondary Endpoints

Other secondary outcome measures used in the study involved executive function, quality of life (QoL), oxidative stress, neuroplasticity biomarkers.

Executive Function: Executive function tests indicated that the BM-Std group showed significant result as indicated by the Stroop Test and the trail making test (TMT). The BM-Std group participants had an increased

cognitive flexibility and task switching which are important features of the executive functions. The placebo revealed a slight change on such tasks indicating that the BM-Std, accompanied with cognitive training, influenced cognitive functioning of the executive as a result of having MCI to a greater scale.

Quality of Life (QoL): The QoL-AD to measure alterations in the quality of life was employed. The BM-Std group revealed a minor yet significant QoL improvement ($p = 0.03$), which proves the intervention did not only boost cognitive abilities but also changed the general functioning and well-being of the participants positively on the everyday level. Considerable improvement in QoL was observed in the placebo group underlining the overall positive effects of the BM-Std + cognitive training intervention

Biomarkers: Biomarkers: the changes in serum biomarkers were also assessed that allowed investigating whether the intervention had neuroprotective effects.

It is possible that Bacopa monnieri could neuroprotectively reduce oxidative injury in the brain by significantly reducing its marker of oxidative stress, malondialdehyde (MDA) in the BM-Std group ($p < 0.05$).

A marker of neurogenesis and synaptic plasticity, Brain-Derived Neurotrophic Factor (BDNF) increased in the BM-Std group significantly ($p < 0.05$), thus, confirming the neuroplasticity of Bacopa monnieri.

4.5 Safety: Experimenting with negative events is mild, and similar in both groups

The monitoring of safety showed that the two groups had mild adverse events that were mostly temporary and are resolved without much effort. Gastrointestinal discomfort was the most frequently mentioned to the two groups of adverse events, including nausea and bloating. These were not serious or frequent and appeared more often in BM-Std group (about 15%) than in the placebo group (about 10 percent), but they were not of longer permanence and did not cause the intervention to be abandoned.

No adverse events in either group risked the subjects, and there were no significant aberrations reported on either vital signs (blood pressure, heart rate) or laboratory findings, which means that BM-Std + cognitive training intervention was safe and well-tolerated.

5. Discussion

The authors explored the effectiveness and safety of standardized Bacopa monnieri extract (BM-Std) in conjunction with computerized cognitive training in the amnestic mild cognitive impairment (MCI), older aged population. The outcomes showed high levels cognitive changes together with neuroprotective outcomes, in line with biomarker changes of oxidative stress and neuroplasticity indicators. These results are promising that BM-Std plus cognitive training could be a safe and effective intervention that slows cognitive decline in MCI, another at-risk population that often advances to dementia. This discussion presents the clinical significance, possible mechanisms, consistency with available studies, strength, limitation, and directions of this technique.

5.1 Clinical significance of cognitive enhancements and markers of conversion

The noticeable cognitive gains of the BM-Std + cognitively training group which are especially in the memory, executive function perspective is of clinical value in amnestic MCI conditions. The difference of score −3.5 points in the ADAS-Cog and the improvement of memory composite suggest that there was a significant improvement in cognition that may slow down progression in the case of a person developing Alzheimer disease (AD) out of MCI. As a state of high risk of developing dementia, improvement interventions of the cognitive ability, especially memory, is vital in alleviating the risk of further deterioration of both mental and cognitive capabilities.

Besides the improvements in the cognitive domain, the changes in the biomarkers in the current study are also indicative of the neuroprotective properties of the BM-Std + training in cognitive assessment intervention. The decrease of malondialdehyde (MDA) that is an oxidative stress marker, and the enhancements of brain-derived neurotrophic factor (BDNF) that is a neuroplastic event marker indicate that not only cognitive function is improved by the intervention but also the implementation of neuronal protection and brain health. Such modifications of the biomarkers are in line with the neuroprotective and neuroplastic effects of Bacopa monnieri and validate the neurobiological plausibility of the cognitive enhancements made.

5.2 Potential Synergistic Action: Neuroprotection / Neuroplasticity Amplification through combined Herbal and Cognitive Training Intervention

The synergism process behind the noticed changes could be in the joint impacts of Bacopa monnieri and the cognitive training in neuro protection and neuroplasticity. The antioxidant and anti-inflammatory effects of Bacopa monnieri have also been shown it helps to offset oxidative stress and ensure neurons are not damaged, which is an

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essential part of cognitive aging and neurodegeneration. A decrease in the levels of MDA in the treatment group implies that Bacopa monnieri aided in reducing the oxidative damage of brain cells, which is one of the main ones contributing to MCI progression.

Meanwhile, the neuroplasticity probably was caused by the cognitive training, which stimulated the neural circuits involved in the brain and promoted the novel synaptic connections. BDNF was upregulated quite noticeably in the BM-Std group, which indicates that it is crucial to the processes of synaptic plasticity and neurogenesis, favoring the brain to adapt and reorganize in reaction to new cognitive demands. In sum, the neuroprotective and neuroplasticity enhancing properties of Bacopa monnieri and cognitive training, respectively, probably led to a synergistic effect on treating older adults with MCI.

5.3 Consistent with Earlier Bacopa Studies in Healthy Elderly Individuals and in MCI Samples

The results of the study can be related to the previous studies concerning Bacopa monnieri in healthy elderly individuals or patients with MCI. A number of previous studies have shown that Bacopa monnieri enhances memory and cognitive performance of healthy people and individuals who have slight cognitive problems. Indeed, a study done by Stough et al. (2001) demonstrated the effect of Bacopa monnieri in enhancing memory recall and attention in healthy elderly subjects. In the same regard, Gohil et al. (2015) established that a Bacopa monnieri supplement boosted the cognitive performance of people having MCI especially in memory activities.

We are able to add to this body of data by supplementing Bacopa monnieri with a structured cognitive training intervention, which has been found to enhance the memory, attention, and executive process in older adults. Herbal neurotherapeutics combined with cognitive training through synergistic effect can serve as a new direction in managing cognitive decline in MCI as it fits in and works on a larger spectrum related to previous Bacopa studies in this group of people.

5.4 Strengths: Decent Design, Biomarker validation, combination of behavioral and pharmacological intervention

The following are the major strengths of the study:

Adequate sample size: 328 people will take part in the study that is quite a large sample size of participants. This design assists in making sure that other confounding factors did not cause the observed effects but the intervention.

Biomarker validation: Inclusion of serum biomarkers like MDA and BDNF gave insights into the biological changes in cognition improvements. The biomarkers will assist in assessing neuroplasticity and oxidative stress objectively to supplement the subjective evaluation of the cognitive measures.

Such a coupling of techniques: The study is the first application of herbal neurotherapeutics (BM-Std) with cognitive training, a complete approach to cognitive enhancement. Both of these may be addressed by this combination in both biological underpinnings of cognitive impairment as well as functional manifestations of cognition.

5.5 Limitations: The duration was short, only one botanical dose, lack of long-term data on the conversion of dementia

Regardless of the strengths, the study has a number of limitations:

Short Duration: A 12-week timeframe of the study is quite optimistic and it is not easy to know the effects of the intervention on long-term dementia progression. Although there were early cognitive improvements, a long-term follow-up is required to find out whether these results will also be possible with time.

Single Botanical Dose: A fixed dose of Bacopa monnieri (300 mg/day) has been utilized in the study. Different formulations, or multiple doses of Bacopa should be tested in future to establish the most adequate doses of the substance as a cognitive enhancing agent.

The lack of long-term conversion data: Although memory and executive functions improved, evidence was not obtained as to whether or not the improvements manifest in lower progression to dementia. It is required to conduct long-term research to understand whether it is possible to protect against dementia in people with MCI through BM-Std as well as cognitive training.

5.6 Directions: Inclusion of longer follow-up, dose-comparison in several administrations, and neuroimaging outcomes

It should be left as a future study to overcome the weaknesses and expand the capabilities of the intervention in question:

Greater Follow-Up: It would be interesting to have a longitudinal study with greater follow-up period (e.g.1-2 years) into maintaining cognitive enhancements as well as the possible implication on prevention of dementia.

Future research should consider conducting multi-dose comparisons of Bacopa monnieri to prove the dose-response relationship, and determine the most potent dose that results in positive changes in cognition in MCI.
Neuroimaging Outcomes: The integration of neuroimaging methodology (e.g., MRI, fMRI) would allow objective evaluation of structural and functional alterations of the brain as a result of the intervention and would give insights into the neuroplastic processes available by cognitive improvements.

6. Conclusion

This clinical trial demonstrates that standardized Bacopa monnieri extract (BM-Std) in a combination treatment with computerized cognitive training results in clinically significant increases in cognition in older adults with amnestic mild cognitive impairment (MCI). The findings show that the attribution of herbal neurotherapeutics and cognitive training may provide a comprehensive way of treating cognitive decline and may feature a vital role in dementia prevention in individuals with high risk. More specifically, the results hold a special place in relation to the increased global burden of age-associated cognitive deterioration since the incidence of MCI and dementia is ever-increasing due to an aging population. The research also reports the possibility of non-pharmacological treatment supplementing the current treatments, which is readily available, safe, and comparably well-tolerated as a treatment of MCI.

6.1 Cognitive Training and BM-Std + Cognitive Training Showed Significant Clinically Meaningful Cognitive Improvement in Amnestic MCI

BM-Std + cognitive training group improvement of cognitive functioning has evidence of positive effects through the ADAS-Cog and memory composite scores with significant shifts in memory and executive functioning. The change of the ADAS-Cog of 3.5 points and the change in the memory composite score at week 12 indicate that the intervention provided a clinically relevant effect on the cognitive processing. These are especially impressive given a setting of a population with amnestic MCI wherein memory loss has been a major issue of concern and risk of conversion to Alzheimer disease (AD) is high.
This is followed by the early advantage after week 4 and maintained after week 12 showing that BM-Std + cognitive training intervention can lead to fast and long-lasting cognitive benefits. The memory improvements and the executive function increases are in accordance with the fact that the combination of herbal therapeutics (pen Bacopa monnieri) and cognitive training can have a synergistic effect, that is, it can act both at the biological and functional levels of cognition. The strategy would be useful in either slowing or preventing the transition between MCI to poorer cognitive results, including dementia.

6.2 Evidence on Bio-Markers Indicates Anti-Oxidative Stress and Neurotrophic Support

Besides the cognitive enhancement, the research reported significant changes in biomarkers that are related to neuroplasticity and neuroprotection. Decrease in malondialdehyde (MDA), indicator of oxidative stress and increase in brain-derived neurotrophic factor (BDNF), which points to neurogenesis and synaptic plasticity, show that the given intervention is highly effective, in terms of biological evidence.
The decrease of MDA within BM-Std group indicates that there is a possible antioxidant effect of the Bacopa monnieri that would alleviate the oxidative stress that accelerates cognitive decline. Oxidative stress is believed to be involved in the pathophysiology of MCI and Alzheimer disease, and resistance to oxidative damage could be one of the cases, which prevent the brain ageing of dementia-prone elderly individuals.
Moreover, the growth of the BDNF in the treatment group demonstrates the neuroplastic advantage of BM-Std. BDNF is one of the essential proteins associated with the advantages in terms of synaptic plasticity, memory formation, and neurogenesis. High BDNF indicates that Bacopa monnieri could stimulate neuroplasticity in persons experiencing MCI where the brain responds by adapting and rearranging itself against cognitive difficulties. The changes in MDA and BDNF together reinforced the idea that the combination of BM-Std and cognitive training does indeed provide positive results related to the levels of cognitive processing, but also has healthy effects in terms of neuroprotection and neurogenesis.

6.3 Safe, well tolerated and merits further long-term, larger-scale testing on dementia intervention potential

The safety and the tolerability ofBM-Std + cognitive training intervention has also been proven in the study. Reported adverse events were mild and transient and the most prominent side effect was gastrointestinal discomfort. Notably, no severe adverse event was reported and no participant of treatment group had any serious safety issue. The same outcome was witnessed regarding the adverse event profile in the placebo group, which further concluded on the safety of both the BM-Std and the cognitive training parts of the intervention.

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These results indicate that the BM-Std + cognitive training intervention could be viewed as a safe and tolerable treatment of older people with MCI. It is a factor to consider since there is increasing interest in non-pharmacological and herbal treatment in cognitive aging. MCI is a precursor of dementia and determining safe and effective interventions that can help prevent or delay deteriorating mental abilities is urgent.

Although these findings are encouraging, the study does not provide the opportunity to evaluate the long-term outcomes of the intervention as the period of this intervention was rather short (12 weeks). There is need to carry out follow up studies of long term effects as to whether the mental gains are sustained beyond the immediate times and to identify whether the intervention can delay or prevent the development into dementia. Further research using more people in larger-scale trials with longer follow-up durations would give us a more definitive answer when it comes to the long-term effectiveness and safety of using BM-Std as part of a cognitive training program to prevent Alzheimer and other types of dementia.

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Conflicts of interest

The authors have no conflicts of interest to declare

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