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Original Paper

Effect of ashwagandha (*Withania somnifera*) extract with Sominone (Somin-On™) to improve memory in adults with mild cognitive impairment: A randomized, double-blind, placebo-controlled study

Journal of Psychopharmacology
1–14
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DOI: 10.1177/02698811251324377
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Abstract

Background: Mild cognitive impairment (MCI) is a condition in which people have memory or thinking problems than other people of their age. This study evaluated the effectiveness and safety of ashwagandha extract standardized with Sominone (Somin-On™) in enhancing memory and cognitive functioning in adults with MCI.

Methods: In this randomized double-blind, placebo-controlled pilot study, 40 subjects with MCI were randomized in a 1:1 ratio to receive either Somin-On™ (250 mg daily) or a placebo for 60 days. The outcome measures, improvement in memory and other cognitive functions after 30 and 60 days were assessed using Montreal Cognitive Assessment (MoCA); Mini–mental state examination (MMSE); Wechsler Memory Scale-III (WMS-III)); and Shepard mental rotation task.

Results: Subjects treated with Somin-On™ showed significant improvements in immediate memory, general memory, working memory and visuospatial processing and the response assessed using WMS-III after 30 and 60 days outperforming the placebo group. Scores on the Shepard Mental Rotation test in Somin-On™ group showed a significant rise by 12.22% at 30 days and 31.67% at 60 days, from baseline. Significant improvement was observed with Somin-On™ in memory assessment scales viz. MoCA (7.83% at 30 days and 14.77% at 60 days, from baseline) and MMSE (9.26% at 30 days and 19.21% at 60 days, from baseline) compared to placebo group.

Conclusions: The supplementation of Somin-On™ is an effective therapy to improve the immediate, general and working memory, as well as cognitive functions like attention and information processing speed in adults with MCI.

Keywords

Ashwagandha (*Withania somnifera*), memory, Sominone, Shepard mental rotation task, mild cognitive impairment, mini–mental state examination, Wechsler Memory Scale

Introduction

Mild cognitive impairment (MCI) is a neurocognitive disorder which involves cognitive impairments beyond those expected based on an individual's age and education but which were not significant enough to interfere with instrumental activities of daily living. MCI may occur as a transitional stage between normal aging and dementia, especially Alzheimer's disease (AD). It includes both memory and non-memory impairments. The cause of the disorder remains unclear, as well as both its prevention and treatment, with some 50% of people diagnosed with it going on to develop AD within 5 years. The diagnosis can also serve as an early indicator for other types of dementia, although MCI may remain stable or even remit. MCI was defined by the following criteria: (1) a subjective complaint of a memory disturbance (preferably supported by an informant); (2) objective evidence of a memory deficit; (3) generally preserved cognitive functions; (4) intact activities of daily living (ADL); and (5) the absence of dementia (Gjøra et al., 2021; Hemmy et al., 2020; Song et al., 2020; Warren et al., 2022).

MCI often involves the same types of brain changes seen in AD or other forms of dementia. In MCI, those changes occur at a lesser degree. The prevalence of MCI varies by age (Bai et al., 2022; Lau et al., 2021; van de Mortel et al., 2021). The prevalence of MCI among different age groups was as follows: 6.7% for ages 60–64; 8.4% for ages 65–69, 10.1% for ages 70–74, 14.8% for ages 75–79 and 25.2% for ages 80–84 (Chao, 2020). Globally, approximately 16% of the population over the age of 70 experiences some type of MCI (Brito et al., 2023).

Cognitive impairment may affect ADLs for patients and their families (Morley et al., 2015; Panghal et al., 2022). MCI which is

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a condition between normal cognitive aging and dementia usually does not affect ADLs (Langa and Levine, 2014), although MCI is considered as an early sign of serious memory impairment. Currently, there is no approved medication or standard of treatment available for MCI (Perng et al., 2018), making the development of therapeutic strategies an unmet need.. While MCI can't be prevented, research suggests that some lifestyle factors may lower the risk of getting MCI such as limiting exposure to air pollution, reducing alcohol consumption, reducing the risk of head injury, stimulating your mind with puzzles, games and memory training (Han and Jia, 2022; Tzivian et al., 2016; Xue et al., 2021). Physicians also recommend lifestyle modifications, such as regular exercise, a diet low in fat and rich in fruits and vegetables, omega3 fatty acids, to promote good overall health and may play a role in good cognitive health (Bhatti et al., 2020; Dominguez et al., 2021; Jackson et al., 2016; Phillips, 2017; Roman et al., 2019).

Ayurveda, a traditional system of medicine practiced in India for thousands of years, recommends the use of herbal therapies to aid memory and cognition (Kulkarni et al., 2012; Mehla et al., 2020; Rao et al., 2012). Ashwagandha (*Withania somnifera*) is a traditional herb that is widely used to manage stress, anxiety and cognitive function (Gkotzamanis and Panagiotakos, 2020; Lorca et al., 2023; Uddin et al., 2019). Efficacy of Ashwagandha extract has been reported in various neurodegenerative disorders such as AD, Parkinson's disease and Huntington's disease in preclinical studies (Kurapati et al., 2013; Nagashayana et al., 2000; RajaSankar et al., 2009). In experimental models, Ashwagandha extract has reduced oxidative stress and mitochondrial dysfunction, contributing to its neuroprotective and anti-degenerative properties (Manchanda and Kaur, 2017). Additionally, Ashwagandha supplementation has been reported to enhance memory and improve cognitive functions in animal studies (Naidu et al., 2006; Schliebs et al., 1997).

One of ashwagandha's prescribed applications is for treatment of memory and cognitive deficit following injury, illness or simply old age (Singh and Udupa, 1993). Preclinical studies have indicated a potential role of ashwagandha as a nootropic, promoting cognitive function and enhancing memory (Dhuley, 2001; Naidu et al., 2006), presumably due to its cholinomimetic activity (Schliebs et al., 1997).

Sominone, an active metabolite of withanoside IV derived from the roots of Withania somnifera, has been extensively studied for its potential benefits in enhancing memory and cognitive functions, particularly in the context of AD. Sominone has been shown to enhance neurite outgrowth and improve spatial memory in normal mice. The study identified that sominone mediates its effects through the neurotrophic factor receptor, RET. This suggests that sominone could play a role in neurogenesis and cognitive enhancement by interacting with specific neurotrophic pathways (Tohda and Joyashiki, 2009). In a severe AD model using 5XFAD mice, sominone significantly improved object recognition memory and increased axonal density in the frontal and parietal cortices. Interestingly, these improvements were observed without a reduction in amyloid plaque numbers or neuroinflammation, indicating that Sominone's beneficial effects on memory might be independent of these common AD pathological markers. Additionally, in cultured cortical neurons, Sominone was able to recover axonal length reduced by amyloid-beta treatment, further supporting its role in neuronal repair and cognitive function (Joyashiki et al., 2011). Another study demonstrated that withanoside IV and its active metabolite, sominone, could attenuate neurodegeneration induced by amyloid-beta (Aβ(25–35)) in mice. Oral administration of withanoside IV significantly improved memory deficits and prevented the loss of axons, dendrites and synapses. Sominone was identified as the main active metabolite responsible for these effects, as it induced significant axonal and dendritic regeneration and synaptic reconstruction in cultured rat cortical neurons damaged by amyloid-beta. This highlights Sominone's potential in ameliorating neuronal dysfunction and promoting neural network reconstruction in AD (Kuboyama et al., 2006).

Our prospective, randomized, double-blind, placebo-controlled pilot study was designed to evaluate the efficacy and safety of Ashwagandha extract standardized with Sominone (Somin-On™) in improving memory and cognition in adults with MCI. The choice of this dose was derived from preclinical studies conducted in male Sprague Dawley rats, where equivalent dosages (22.5 mg/kg body weight in rats) demonstrated significant cognitive-enhancing effects in animal models (unpublished data). While extrapolating rat dose to human dose, 22.5 mg/kg in rats is equivalent to 250 mg for an adult human (Nair and Jacob, 2016). These findings provide a scientific rationale for further investigation in humans, thereby supporting its potential benefits and confirming its safety and efficacy in adults with MCI.

Materials and methods

This 60-day prospective clinical trial was conducted using a random-assignment, parallel-group, single-center, double-blind, placebo-controlled design to evaluate the effect of Somin-On™ in adults with MCI. The study was conducted at Hi Tech Hospital and Trauma Center, Jhansi, Uttar Pradesh, India, after getting ethical clearance from the institutional ethics committee. The protocol of the study was not modified after the trial's commencement.

Participant selection

Inclusion in the present study required participants to have mild, subjective symptoms of memory impairment, be between 25 and 65 years old and meet he following criteria: a Mini–Mental State Examination (MMSE) score of 20–23, Montreal Cognitive Assessment (MoCA) score of 18–25 and a Vitamin B12 (Serum) level of 200–900 pg/mL. Additionally, participants were required to have no impairment in social and occupational functioning and the ability, an instrumental activities of Daily Life (IADL) score of >6, a Clinical Dementia Rating (CDR) Global SCORE of <0.5 and a willingness to provide informed consent. Exclusion criteria included known neuropsychiatric conditions, persistent endocrine disorders, uncontrolled hypertension or diabetes mellitus, drug dependence or addiction, use of alcohol, psychotropic drugs or alternative medicines for memory enhancement or any severe co-morbid medical condition. Pregnant or lactating women and participants with a known history of hypersensitivity were excluded from the study. Participants who were already users of nootropic agents, including ashwagandha or anticholinesterase drugs, were excluded from the study. Medications that

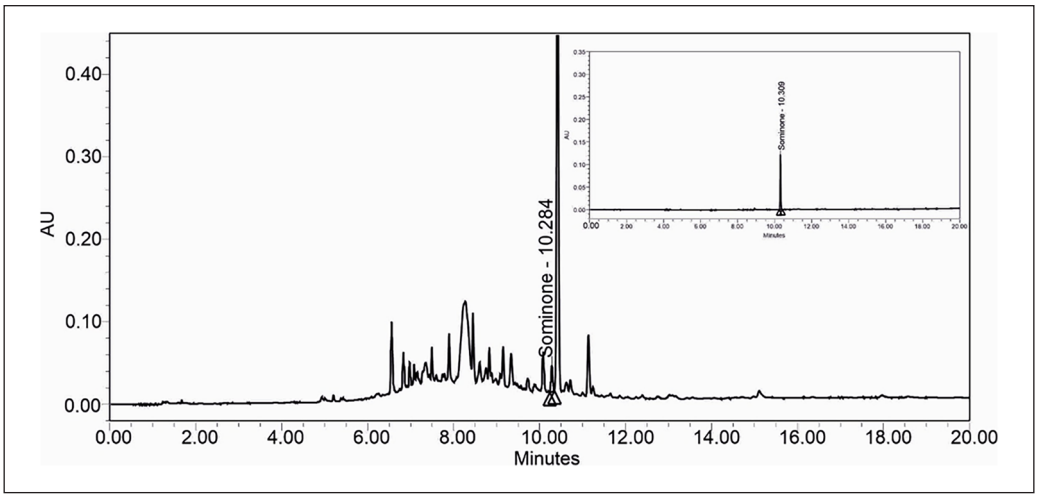


Figure 1. HPLC chromatogram of sominone in Somin-On™ (Sominone at 220 nm wavelength). (Inset: HPLC chromatogram of sominone standard at 220 nm).

could affect the outcome of the study were prohibited during the study. Subjects with a history of brain disorders, use of any type of dementia delaying medication, head trauma with post-traumatic loss of consciousness for at least 30 min during the lifespan and brain-damaged subjects were excluded from the study.

Ethical consideration

The study was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki and the Ethical Guidelines for Biomedical Research on Human Subjects, issued by the Indian Council of Medical Research and New Drugs and Clinical Trials Rules 2019. The Institutional Review Board's approval was obtained from Nirmal Hospital Institutional Ethics Committee, Jhansi, India. The ethical committee approval number was ECR/325/Inst/UP/2013/RR-19. Ethics Committee notifications as per Good Clinical Practice Guidelines, issued by the Central Drugs Standard Control Organization, and the Ethical Guidelines for Biomedical Research on Human Subjects, issued by the Indian Council of Medical Research, were followed. This study was registered on Clinical Trials Registry-India (CTRI) on 22/03/2023 (Registration No. CTRI/2023/03/050974). Informed consent was obtained from each participant prior to study enrolment.

Investigational product-randomization and blinding

The investigational product (IP) was 250 mg of *Withania somnifera* extract, standardized to contain not less than (NLT) 2% Sominone (Somin-On™; Arjuna Natural Pvt. Ltd., Aluva, India). Botanically identified ashwagandha (*Withania somnifera*) were collected and cleaned, then extracted by refluxing with ethanol. This extract was fractionated into different portions using liquid-liquid partition and solid-liquid phase partition. The final fraction contains Sominone, known for improving cognition, along with Withanolides (*Withanolide glycosides* and *Withanolide aglycones*). The extract is then concentrated and dried to a powder form and standardized to contain NLT 2% Sominone (Figure 1). The composition of Somin-On™ is mentioned in Table 1.

Table 1. Composition of Somin-On™.

Parameters	Assay values
Sominone	NLT 2%
Withanoside IV	NLT 1%
Total withanolide	NLT 10%
Moisture	NMT 5%
Ash content	NMT 5%
Fat content	NMT 3%
Dietary fiber	NLT 1%
Carbohydrate	35–45%
Polyphenol	5–8%

NLT: not less than; NMT: not more than.

The placebo group received an identical placebo containing microcrystalline cellulose powder capsule. Both the groups took their respective interventions orally once daily for 60 days. The capsules were packed and dispensed in identical airtight bottles labelled by randomization codes All the participants were assigned an identification number based on their enrolment. The study was a double-blind one, that is, doctors and subjects were unaware of patients receiving the treatment and the placebo. The contact details of the investigator and reviewing ethics committee were also provided to the participants to report the adverse event(s), if any. The participants were instructed to avoid concomitant use of any other supplement, nootropics or psychoactive drugs.

Study procedure

Only those subjects who passed the inclusion/exclusion criteria were considered for the baseline score assessment. The study was initiated with a screening visit followed by a 60-day treatment period. The 1st day was for screening purposes. During the screening visit, a brief medical history was obtained from each subject. A general physical examination was conducted, and baseline measurements, including body weight, BMI and vital parameters, were recorded; additionally, study-specific questionnaire – MMSE, MOCA, IADL, CDR, WMS III and

Shepard Mental Rotation Task – were administered, and preliminary laboratory parameters were completed. The inclusion/exclusion criteria have been checked and screen failures noted. Baseline scores were taken only if the subjects passed the inclusion/exclusion criteria. They were randomized to the Somin-On™ or the placebo group in a double-blinded manner. The IPs were dispensed by the pharmacist according to the allocation concealed randomization list and the randomized subjects were instructed to take one capsule daily after breakfast for 60 consecutive days. The day 30 visit is considered as the interim visit where all the study-specific parameters were checked again and the IPs were provided for the next 30 days and also evaluated study compliance. The day 60 was the final visit when the final assessments of efficacy (MMSE, MOCA, WMS III and Shepard Mental Rotation Task) and safety endpoints (biochemical tests) were completed, and the subject was asked for compliance.

Outcome measures

The primary outcomes were the change (baseline to 30-day and 60-day) in cognition function assessed using outcome measures, WMS-III and Shepard Mental Rotation Task.

The secondary outcomes were the change (baseline to 30-day and 60-day) in MoCA and MMSE scores.

Safety assessment

Safety and tolerability of IPs were assessed at 30-day and 60-day through an investigator-participant discussion and querying the adverse effect(s) as treatment-emergent adverse events and the biochemical parameters such as Complete Blood Count, Renal Function Test, Vitamin B12 and Liver Function Test. Participants were also requested to contact the researchers immediately if any adverse effect(s) were experienced.

Study assessments

Wechsler Memory Scale–III. The WMS-III is an individually administered battery of 11 subtests of learning, memory and working memory. Six of the subtests are included in the core battery, and five subtests are considered optional I supplemental. Only six of the WMS-III subtests are considered primary. (Logical Memory I and II, Verbal Paired Associates I and II, Letter-Number Sequencing are in Auditory presentation and Faces I and II, Family Pictures I and II and Spatial Span are in visual presentation), and all must be administered in order to calculate the WMS-III index scores. The primary subtests can be administered in 30–35 min. The Family Pictures subtest is new to the WMS-III and is purported to be the visual analogue to the Logical Memory subtest. The WMS-III Faces subtest uses a recognition paradigm to assess visual immediate and visual delayed memory. The Letter-Number Sequencing subtest is new to the WMS-III and is a measure of auditory working memory. The WMS-III provides for the calculation of eight primary index scores and four Auditory Process Composite scores. The primary indexes are considered by the publishers to be core to evaluating memory functioning, whereas the Auditory Process Composites are considered supplementary scales to better isolate and characterize various processes in memory functioning, such as single-trial learning versus learning over trials, retention and retrieval.

Eight primary indices are (1) The Auditory Immediate Index (Logical Memory I and Verbal Paired Associates I), (2) Visual Immediate Index (Faces I and Family Pictures I), (3) Immediate Memory Index (Logical Memory I, Verbal Paired Associates I, Faces I and Family Pictures I), (4) Auditory Delayed Index (Logical Memory II and Verbal Paired Associates II), (5) Visual Delayed Index (Faces II and Family Pictures II), (6) Auditory Recognition Delayed Index (Logical Memory II Recognition and Verbal Paired Associates II Recognition), (7) General Memory Index (Logical Memory II, Verbal Paired Associates II, Faces II and Family Pictures II, Logical Memory II Recognition and Verbal Paired Associates II Recognition) and (8) Working Memory Index (Letter Number Sequencing and Spatial Span).

The raw score for each subtest administered is computed first. The raw score is the sum of points earned on a subtest. To interpret an examinee's performance, the raw scores must be translated into standard scores (either scaled scores or Indexes). The Index scores are obtained by summing the scaled scores that comprise the specific Index as given in the WMS-III Administration and Scoring Manual (Brooks et al., 2008; Tulsky et al., 2003).

Shepard mental rotation task. This test assesses the subject's cognitive rate of spatial processing. The subject is asked to compare images of two objects or letters, often rotated along a particular axis, and state whether the two are the same or are mirror images. In classic mental rotation experiments, participants decide whether two figures are the same or mirror images of one another. The time to do so shows a linear relationship between the two figures' initial angular disparity and both response time and accuracy (Shepard and Metzler, 1971).

Montreal cognitive assessment. MoCA is a widely used screening assessment for detecting cognitive impairment. It was created in 1996 by Ziad Nasreddine in Montreal, Quebec. It was validated in the setting of MCI and has subsequently been adopted in numerous other settings clinically. This test consists of 30 points and takes 10 min to complete. The Montreal test is performed in seven steps which may change in some countries dependent on education and culture. The MoCA Test was validated as a highly sensitive tool for early detection of MCI (Freitas et al., 2013; Li et al., 2018). MoCA has been subsequently adopted in clinical settings around the world and is widely used as a scale in academic and non-academic research. The sensitivity of MoCA for detecting MCI is 90%, compared to 18% for the MMSE. The basics of this test include short-term memory, executable performance, attention, focus and more. MoCA scores range between 0 and 30. A score of 26 or over is normal (Kaul et al., 2022).

Mini–mental state examination. MMSE or Folstein test is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. It is commonly used in medicine and allied health to screen for dementia. It is also used to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over time, making it an effective way to document

an individual's response to treatment. The MMSE's purpose has been not, on its own, to provide a diagnosis for any particular nosological entity. Administration of the test takes between 5 and 10 min and examines functions include simple questions and problems in a number of areas: the time and place of the test, repeating lists of words, arithmetic such as the serial sevens, language use and comprehension and basic motor skills. Any score of 24 or more (out of 30) indicates normal cognition. Below this, scores can indicate severe (⩽9 points), moderate (10–18 points) or mild (19–23 points) cognitive impairment (Kurlowicz and Wallace, 1999).

Statistical analysis

An arbitrary sample size was considered for this study. Descriptive statistics were performed for all demographics of the study participants. A Shapiro–Wilk test of normality was conducted on the cognitive function data to understand the distribution of the data and to check the assumptions required for statistical analysis. Considering the assumption of data distribution, within-group analysis using non-parametric paired *t*-test (Wilcoxon signed rank test) was conducted to understand the variability in different cognitive functions like MoCA, MMSE, Shepard mental rotation and sub groups of immediate memory, general memory, working memory, visuospatial processing and response at day 30 and day 60 from baseline, among the Somin-On™ and placebo groups. A within-group comparison was also made to understand any variability in cognitive functions at day 60 compared to day 30 in both Somin-On™ and placebo groups. The observations during day 30 and day 60 were initially adjusted to the baseline observations. The baseline adjusted observations from the cognitive function test obtained for the two groups at day 30 and day 60 were compared for any significant variability using Mann–Whitney *U* test. Statistical test to understand the variability in safety parameters at day 60 from baseline in the Somin-On™ and placebo group was done either by paired *t*-test analysis and in conditions where the normality assumption is not met, an equivalent non-parametric method (Wilcoxon signed rank test) was used. Shapiro–Wilk analysis revealed that except monocytes, eosinophils, bilirubin and basophils, all other variables meet the assumption of normality. All statistical analysis was conducted using SPSS16.0 (SPSS Inc., Chicago, IL, USA) at 95% level of significance.

Results

Of the 46 subjects screened, 40 subjects who met the inclusion criteria were randomized; 20 each in Somin-On™ and placebo group (Figure 2). Among them, the mean (SD) age of the Somin-On™ group was 36.400 (7.910) years and 34.300 (6.914) for the placebo group. In Somin-On™ group, 65% of participants were male and 35% were female, whereas 55% were male and 45% female in the placebo group. The baseline characteristics of participants were comparable in both groups and presented in Table 2.

Analysis of immediate memory, general memory, working memory, visuospatial processing and response, Shepard mental rotation task, MoCA and MMSE parameters within placebo and Somin-On™ group during 30th and 60th day using Mann–Whitney *U* analysis compared to the baseline showed efficient improvement in Somin-On™ group during the 30th and 60th days, compared to the variability observed in the placebo group for those periods (Table 3). Between-group analysis conducted on the baseline-adjusted observations using Mann–Whitney *U* test showed significantly higher performance of Somin-On™ at day 30 compared to placebo group in improving immediate memory (logical memory I: Mann–Whitney $U=123.5$, $p=0.003$; verbal paired associate I: Mann–Whitney $U=140$, $p=0.009$; faces I: Mann–Whitney $U=161.5$, $p=0.045$), general memory (logical memory II: Mann–Whitney $U=97$, $p=0.001$; verbal paired associate II: Mann–Whitney $U=59$, $p<0.001$; faces II: Mann–Whitney $U=123$, $p=0.038$), working memory (letter number sequencing: Mann–Whitney $U=55.5$, $p<0.001$; spatial span: Mann–Whitney $U=41.5$, $p<0.001$), visuospatial processing and response (visual reproduction I: Mann–Whitney $U=122.5$, $p=0.035$; visual reproduction II: Mann–Whitney $U=121$, $p=0.033$), Shepard mental rotation task (Mann–Whitney $U=56.5$, $p<0.001$), MoCA (Mann–Whitney $U=32$, $p<0.001$) and MMSE (Mann–Whitney $U=76$, $p=0.001$). The variability observed in immediate memory (family pictures I: Mann–Whitney $U=199.5$, $p=0.989$) and general memory (family picture II: Mann–Whitney $U=190$, $p=03.799$) was not statistically significant, whereas, during day 60, the Somin-On™ group showed statistically significant improvement from baseline ($p<0.05$) in Shepard mental rotation task, MoCA, MMSE and all subgroups of immediate memory, general memory, working memory, visuospatial processing and response compared to the placebo group. Details of the efficacy analysis between Somin-On™ and placebo group are provided in Table 4.

The improved efficiency of the Somin-On™ group in enhancing cognitive functions during the study period is illustrated in Figures 3–6. The Wechsler Memory Scale III assessment was conducted in four major domains: Immediate Memory, General Memory, Working Memory, and Visuospatial Processing and Response. The overall percentage change in these four domains was notable in the Somin-On™ group. For Immediate Memory, the Somin-On™ group showed a percentage change of 1.65% at day 30 and 7.43% at day 60, compared to −0.06% and −0.71% in the placebo group, respectively. General Memory in the Somin-On™ group improved by 4.97% at day 30 and 14.66% at day 60, while the placebo group only showed changes of 0.75% and 2.07%, respectively. Working Memory showed a significant increase of 10.05% at day 30 and 18.46% at day 60 in the Somin-On™ group, compared to 0.56% and 0.84% in the placebo group. Lastly, Visuospatial Processing and Response improved by 6.67% at day 30 and 14.4% at day 60 in the Somin-On™ group compared to 1.06% and 0.54% in the placebo group. No significant changes were observed in laboratory parameters in both the Somin-On™ and placebo groups after 60 days (Table 5). In this study, no adverse events were reported, indicating the safety of the intervention. These results demonstrate the safety and efficacy of Somin-On™ in enhancing various aspects of memory and cognition in adults with MCI over a 60-day period.

Discussion

The study was a randomized, double blind, placebo-controlled study to assess the effect of (Somin-On™) for 60 days in adults with MCI. The cognitive assessments were performed using

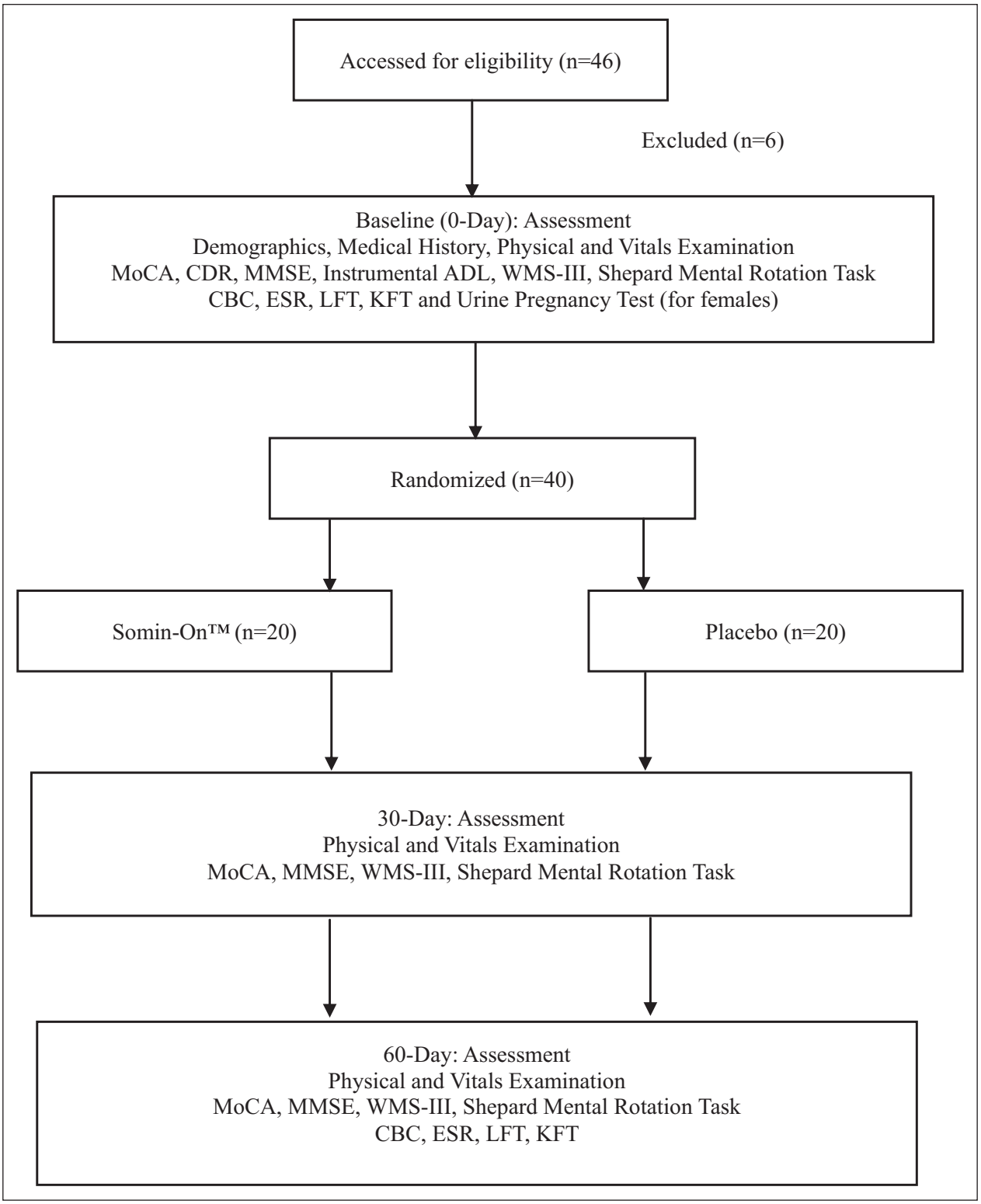


Figure 2. Consort flowchart.

WMS-III, Shepard mental rotation task, MoCA and MMSE. Our study results showed that daily administration of (Somin-On™) capsule (250 mg, once a day) is associated with significant improvement in memory in adult participants with MCI.

There are reports stating the strong association of stress and sleep deprivation with cognitive impairment in humans (Miller, 2015). Presently, there is no approved drug for the treatment of MCI (Petersen et al., 2018). However, the expert consensus

Table 2. Demographic and other baseline characteristics.

Parameter	Somin-On™	Placebo
	Mean ± SD	Mean ± SD
Population (*n*)		
Total	20	20
Male	13	11
Female	7	9
Age (years)		
Total	36.400 ± 7.910	34.300 ± 6.914
Male	36.231 ± 7.073	34.818 ± 7.935
Female	36.714 ± 9.895	33.667 ± 5.831
Height (cm)		
Total	160.000 ± 7.079	161.700 ± 6.010
Male	164.385 ± 4.011	166.091 ± 3.859
Female	151.857 ± 2.734	156.333 ± 2.872
Weight (kg)		
Total	62.000 ± 7.532	62.650 ± 7.271
Male	65.000 ± 6.782	67.455 ± 4.655
Female	56.429 ± 5.653	56.778 ± 5.286
IADL		
Total	7.250 ± 0.444	7.450 ± 0.510
Male	7.231 ± 0.439	7.455 ± 0.522
Female	7.286 ± 0.488	7.444 ± 0.527
CDR		
Total	0	0
Male	0	0
Female	0	0
MoCA		
Total	22.350 ± 1.226	22.200 ± 1.196
Male	22.385 ± 1.387	22.273 ± 0.905
Female	22.286 ± 0.951	22.111 ± 1.537
MMSE		
Total	21.600 ± 0.503	21.650 ± 0.489
Male	21.615 ± 0.506	21.545 ± 0.522
Female	21.571 ± 0.535	21.778 ± 0.441
Vit. B12		
Total	268.335 ± 42.309	261.010 ± 35.704
Male	274.377 ± 44.524	266.664 ± 34.965
Female	257.114 ± 38.441	254.100 ± 37.439

recommended the use of cognitive trainings, regular exercise and clinically established herbal supplements for the management of MCI (Kandiah et al., 2021).

Ashwagandha is majorly composed of alkaloids and steroidal lactones (Chauhan and Mehla, 2015). After oral administration, Sominone is the main active metabolite of Withanoside IV (an alkaloid of Ashwagandha) (Tohda and Joyashiki, 2009). In mice model, Sominone was found to increase the outgrowth of neurite and spatial memory through modulation of RET, a neurotrophic factor receptor (Tohda and Joyashiki, 2009).

The bioactive molecules including Withanolides of Ashwagandha have also exhibited their neuroprotective effect via modulation of Nuclear factor-kappa B (NF-kB) (Grover et al., 2010), attenuation of neuronal excitotoxicity (Parihar and Hemnani, 2003) and reduction of damage caused by oxidative stress (Chaudhary et al., 2003), thereby proposing a potential role of ashwagandha in cognitive restoration. Other animal studies have reported the reversal of cognitive impairment via prevention from hypoxia and/or stress induced hippocampal degeneration (Baitharu et al., 2013; Jain et al., 2001), cholinergic enhancement (Bhattacharya and Kumar, 1997) and clearance of Aβ through low-density lipoprotein receptor modulation (Sehgal et al., 2012). Here, in our study, we assume that any of the above-explained mechanisms may be responsible for improved cognitive functioning by ashwagandha in MCI population.

There are various reports which supports the nootropic activity of ashwagandha in preclinical and clinical settings (Lorca et al., 2023; Xing et al., 2022). However, there is scanty of clinical evidences on its efficacy in MCI patients. The left temporo-parietal cortex part of brain controls the immediate (sensory) memory (Baldo et al., 2012), while working memory is processed by fronto-parietal brain regions (Chai et al., 2018). Long-term (general) memory is primarily regulated by hippocampus and medial temporal lobes (Eichenbaum, 2004). The LM I, VPA I, Faces I and FP I subtests of the WMS-III measure immediate memory, while LM II, VPA II, Faces II and FP II subtests measure audio-visual declarative long-term memory and LNS with spatial span subtests of the WMS-III measures working memory (Tulsky et al., 2003). In the present study, increased score of WMS-III subtests indicates a significant improvement in immediate ($p < 0.001$), long-term ($p < 0.001$) and working memory ($p < 0.001$) with (Somin-On™) treatment as compared to placebo. Our findings were similar to a previous report from India except Letter-Number Sequencing (LNS) subtest (Choudhary et al., 2017), where author reported no significant effect in visual reproduction I, II subtests and MRT while it was significantly improved in our study. In support of our finding, another study reported the evidence of ashwagandha in improving working memory when administered as once daily dose (Xing et al., 2022).

In our study, we also used MRT to assess the working memory and reported (Somin-On™) treatment was associated with significantly improved visuospatial performance ($p < 0.001$). Mental rotation has been persistently linked to intelligence tests, as evidenced by the pivotal works by Shepard and Metzler (1971) and Rovet and Netley (1982). Accordingly, authors have suggested incorporating mental rotation training into the educational curricula to improve visuospatial intelligence and performance rather than completely relying on visuospatial ability (Anomal et al., 2023). We did not record the educational status and its correlation with visuospatial performance though working memory was significantly improved based on MRT. Further, our findings of MRT are supported by working memory subtests of the WMS-III.

We used MMSE for participant screening and to determine the degree of cognitive impairment. (Somin-On™) treatment showed an increase ($p < 0.001$) in MMSE score supporting improvement in cognitive functions. As per the recent recommendation by CSIR-NIScPR (India), MMSE is sensitive for assessing general memory but limitation for evaluating executive functioning problems. However, MoCA is more reliable than MMSE in MCI screening (Dong et al., 2012; Hoops et al., 2009), and evaluation of verbal, memory, visuospatial and executive

Table 3. Within-group analysis comparing the variability of cognitive functions between baseline, day 30 and day 60 for Somin-On™ group and placebo group.

Group	Parameter		Baseline		30-day		Baseline to 30-day		60-day		Baseline to 60-day		30-day to 60-day	
			Mean	SD	Mean	SD	% Change (test statistic)	*p*-Value	Mean	SD	% Change (test statistic)	*p*-Value	% Change (test statistic)	*p*-Value
Somin-On™	WMS III – Immediate memory	Logical memory I	104.25	6.129	107	4.413	2.638 (–2.43)	0.015	111	4.168	6.475 (–3.14)	0.002	3.738 (–2.54)	0.011
		Verbal paired associate I	101	2.052	103.75	4.253	2.723 (–2.33)	0.02	108	3.770	6.931 (–3.57)	<0.001	4.096 (–2.75)	0.006
		Faces I	102.75	2.552	103.5	3.285	0.730 (–1.73)	0.083	110	4.588	7.056 (–3.46)	0.001	6.280 (–3.27)	0.001
		Family pictures I	100	0.000	100.5	2.236	0.500 (–1)	0.32	109.25	7.482	9.250 (–3.35)	0.001	8.706 (–3.23)	0.001
	WMS III –General memory	Logical memory II	95.75	4.375	100.5	3.204	4.961 (–2.98)	0.003	108	5.231	12.794 (–3.65)	<0.001	7.463 (–3.45)	0.001
		Verbal paired associate II	88.5	4.007	98.25	4.375	11.017 (–3.59)	<0.001	105.5	5.596	19.209 (–3.96)	<0.001	7.379 (–2.96)	0.003
		Faces II	95.75	5.447	99.25	4.064	3.655 (–2.89)	0.004	109.5	6.262	14.360 (–3.77)	<0.001	10.327 (–3.57)	<0.001
		Family pictures II	99.75	1.118	100	0.000	0.251 (–1)	0.32	112	6.156	12.281 (–3.76)	<0.001	12.000 (–3.76)	<0.001
	WMS III – Working memory	Letter number sequencing	93.25	4.064	100	5.130	7.239 (–3.46)	0.001	108.5	4.007	16.354 (–3.96)	<0.001	8.500 (–3.66)	<0.001
		Spatial span	87.5	3.441	98.75	5.821	12.857 (–3.65)	<0.001	105.5	5.826	20.571 (–3.95)	<0.001	6.835 (–2.82)	0.005
	Visuospatial processing and response	Visual reproduction I	93.25	6.935	100	5.620	7.239 (–2.96)	0.003	106.25	4.833	13.941 (–3.64)	<0.001	6.250 (–3.11)	0.002
		Visual reproduction II	94.25	5.200	100	6.882	6.101 (–2.83)	0.005	108.25	5.684	14.854 (–3.86)	<0.001	8.250 (–3.297)	0.001
	Shepard mental rotation task		11.05	0.945	12.4	1.142	12.217 (–3.72)	<0.001	14.55	1.234	31.674 (–3.95)	<0.001	17.339 (–3.75)	<0.001
	MoCA		22.35	1.226	24.1	0.887	7.830 (–3.43)	0.001	25.65	1.348	14.765 (–3.77)	<0.001	6.432 (–3.52)	<0.001
	MMSE		21.6	0.503	23.6	1.095	9.259 (–3.58)	<0.001	25.75	1.251	19.213 (–3.94)	<0.001	9.110 (–3.87)	<0.001
Placebo	WMS III – Immediate memory	Logical memory I	106.25	4.552	106	4.472	–0.235 (–1)	0.32	104	4.168	–2.118 (–2.17)	0.03	–1.887 (–1.99)	0.046
		Verbal paired associate I	101.75	2.447	101.75	2.447	0.000 (0.000)	1	100.75	2.936	–0.983 (–1.3)	0.194	–0.983 (–1.3)	0.194
		Faces I	103.25	2.447	103	2.513	–0.242 (–1)	0.32	103	2.991	–0.242 (–0.577)	0.56	0.000 (0.000)	1
		Family pictures I	100	0.000	100.25	1.118	0.250 (–1)	0.33	100.5	3.591	0.500 (–0.63)	0.53	0.249 (–0.33)	0.74
	WMS III – General memory	Logical memory II	94.75	4.128	95	4.292	0.264 (–1)	0.32	96	4.472	1.319 (–1.89)	0.059	1.053 (–1.63)	0.102
		Verbal paired associate II	89	3.839	90.25	5.250	1.404 (–1.63)	0.102	91.25	5.821	2.528 (–2.07)	0.038	1.108 (–1.63)	0.102
		Faces II	94.75	4.435	96	5.525	1.319 (–1.34)	0.18	97.75	5.955	3.166 (–2.15)	0.031	1.823 (–1.73)	0.084
		Family pictures II	100	0.000	100	0.000	0.000 (0.000)	1	101.25	2.751	1.250 (–1.89)	0.059	1.250 (–1.89)	0.059
	WMS III – Working memory	Letter number sequencing	93.75	3.193	94	3.479	0.267 (–1)	0.32	94.25	3.354	0.533 (–0.63)	0.53	0.266 (–0.33)	0.74
		Spatial span	87.5	3.804	88.25	4.667	0.857 (–1)	0.32	88.5	4.617	1.143 (–1.134)	0.257	0.283 (–0.58)	0.564
	WMS III – Visuospatial processing and response	Visual reproduction I	92.25	4.993	93.75	4.833	1.626 (–2.12)	0.034	93.25	4.940	1.084 (–1.41)	0.157	–0.533 (–1)	0.317
		Visual reproduction II	94.25	4.064	95.25	4.435	1.061 (–1.63)	0.102	94.25	4.667	0.000 (0.000)	1	–1.050 (–1.07)	0.285
	Shepard mental rotation task		10.85	1.040	10.8	0.951	–0.461 (–0.31)	0.76	9.85	1.309	–9.217 (–2.575)	0.01	–8.796 (–2.54)	0.011
	MoCA		22.2	1.196	22.1	1.210	–0.450 (–0.82)	0.41	22.4	1.095	0.901 (–0.665)	0.51	1.357 (–1.112)	0.266
	MMSE		21.65	0.489	22.1	1.334	2.079 (–1.73)	0.084	22.25	0.910	2.771 (–2.67)	0.008	0.679 (–0.78)	0.439

Non-parametric paired *t*-test (Wilcoxon signed rank test) was used to understand the within variability among the Somin-On™ group ($n=20$) and placebo group ($n=20$). Test statistics represented here is the *Z*-score.

Table 4. Analysis comparing the variability of cognitive functions at day 30 and day 60 from baseline between Somin-On™ and placebo groups.

Parameter			30-day						60-day					
			Placebo		Somin-On™		Placebo vs Somin-On™		Placebo		Somin-On™		Placebo vs Somin-On™	
			Mean	SD	Mean	SD	Mean diff. (test statistic)	*p*-Value	Mean	SD	Mean	SD	Mean diff. (test statistic)	*p*-Value
WMS III	Immediate memory	Logical memory I	−0.25	1.118	2.75	4.128	3 (123.5)	0.003	−2.25	4.128	6.75	7.122	9 (59)	<0.001
		Verbal paired associate I	0	0	2.75	4.435	2.75 (140)	0.009	−1	3.479	7	4.702	8 (-4.55)	<0.001
		Faces I	−0.25	1.118	0.75	1.832	1 (161.5)	0.045	−0.25	1.970	7.25	5.730	7.5 (50)	<0.001
		Family pictures I	0.25	1.118	0.5	2.236	0.25 (199.5)	0.989	0.5	3.591	9.25	7.482	8.75 (69)	<0.001
	General memory	Logical memory II	0.25	1.118	4.75	5.250	4.5 (97)	0.001	1.25	2.751	12.25	8.188	11 (46)	<0.001
		Verbal paired associate II	1.667	4.082	7.75	6.172	6.083 (59)	<0.001	2.25	4.723	17	6.366	14.75 (18.5)	<0.001
		Faces II	1.25	4.552	3.5	4.007	2.25 (123)	0.038	3	5.938	13.75	8.091	10.75 (56)	<0.001
		Family pictures II	0	0	0.25	1.118	0.25 (190)	0.799	1.25	2.751	12.25	6.172	11 (31.5)	<0.001
	Working memory	Letter number sequencing	0.25	1.118	6.75	5.200	6.5 (55.5)	<0.001	0.5	3.591	15.25	5.955	14.75 (5.5)	<0.001
		Spatial span	0.75	3.354	11.25	6.859	10.5 (41.5)	<0.001	0.25	1.970	6.75	7.993	6.5 (107)	0.011
	Visuospatial processing and response	Visual reproduction I	1.5	2.856	6.75	7.482	5.25 (122.5)	0.035	1	3.078	13	8.796	12 (45.5)	<0.001
		Visual reproduction II	1	2.616	5.75	6.742	4.75 (121)	0.033	0	5.130	14	6.996	14 (19.5)	<0.001
Shepard mental rotation task			−0.05	0.887	1.35	0.933	1.4 (56.5)	<0.001	−1	1.451	3.5	1.469	4.5 (8)	<0.001
MoCA			−0.1	0.553	1.7	1.380	1.8 (32)	<0.001	0.2	1.196	3.3	1.922	3.1 (41)	<0.001
MMSE			0.45	1.146	2	1.257	1.55 (76)	0.001	0.6	0.883	4.15	1.387	3.55 (4.5)	<0.001

Non-parametric independent sample *t*-test (Mann–Whitney *U* test) was used to understand the variability between Somin-On™ group ($n=20$) and Placebo group ($n=20$). Test statistic represented here is the Mann–Whitney *U* score.

Table 5. Comparison of safety parameters at day 60 from baseline for the Somin-On™ group and placebo group.

Parameter	Placebo								Somin-On™							
	Baseline			Day 60			Day 60 to baseline (test statistic)	Within group	Baseline			Day 60			Day 60 to baseline	Within group
	Mean	SD	SE	Mean	SD	SE	% Change	*p*-Value	Mean	SD	SE	Mean	SD	SE	% Change	*p*-Value
Hb	13.795	0.831	0.186	13.930	0.837	0.187	0.979 (–1.89)	0.075	13.840	0.982	0.219	13.895	0.928	0.207	0.397 (–0.74)	0.471
RBC	4.864	0.198	0.044	4.939	0.213	0.048	1.532 (–2.03)	0.057	4.881	0.236	0.053	4.952	0.269	0.060	1.465 (–1.93)	0.068
WBC	6250.000	745.160	166.623	6105.000	673.150	150.521	–2.320 (0.941)	0.359	6370.000	860.294	192.368	6360.000	744.382	166.449	–0.157 (0.155)	0.878
Neutrophils	61.650	6.761	1.512	61.250	6.086	1.361	–0.649 (0.383)	0.706	62.500	6.262	1.400	59.850	6.839	1.529	–4.240 (1.561)	0.135
Lymphocytes	30.700	5.342	1.195	30.850	4.870	1.089	0.489 (–0.158)	0.876	30.900	6.423	1.436	33.050	5.763	1.289	6.958 (–1.351)	0.193
Monocytes	4.950	1.638	0.366	5.150	1.843	0.412	4.040 (–0.73)	0.463	4.000	1.298	0.290	4.850	1.565	0.350	21.250 (–1.792)	0.073
Eosinophils	2.200	0.894	0.200	2.200	0.616	0.138	0.000 (0.000)	1.000	2.100	0.641	0.143	2.250	0.716	0.160	7.143 (–1)	0.317
Basophils	0.600	0.503	0.112	0.550	0.510	0.114	–8.333 (–0.45)	0.655	0.500	0.513	0.115	0.500	0.513	0.115	0.000 (0.00)	1.000
Haematocrit	41.950	2.373	0.531	42.030	2.387	0.534	0.191 (–0.282)	0.781	42.335	2.398	0.536	42.110	2.510	0.561	–0.531 (0.917)	0.370
MCH	28.351	1.107	0.248	28.217	1.122	0.251	–0.473 (0.785)	0.442	28.330	1.005	0.225	28.051	0.942	0.211	–0.985 (2.011)	0.059
MCHC	32.880	0.682	0.153	33.137	0.572	0.128	0.782 (–1.39)	0.180	32.666	0.749	0.168	32.874	0.419	0.094	0.637 (1.52)	0.148
ESR	6.150	2.084	0.466	6.150	1.182	0.264	0.000 (0.00)	1.000	86.732	2.361	0.528	86.526	2.385	0.533	–0.238 (0.698)	0.494
Total bilirubin	0.670	0.093	0.021	0.677	0.096	0.022	0.970 (–0.79)	0.432	6.000	2.406	0.538	5.700	1.418	0.317	–5.000 (–1.177)	0.239
Bilirubin direct	0.269	0.092	0.021	0.277	0.047	0.011	2.980 (–0.459)	0.652	0.684	0.101	0.023	0.664	0.104	0.023	–2.924 (0.337)	0.740
Bilirubin indirect	0.402	0.141	0.032	0.393	0.069	0.015	–2.242 (0.381)	0.707	0.265	0.126	0.028	0.256	0.053	0.012	–3.585 (1.47)	0.159
AST_SGOT	28.184	7.611	1.702	26.988	6.546	1.464	–4.244 (1.38)	0.183	0.419	0.127	0.029	0.394	0.102	0.023	–5.967 (0.53)	0.602
ALT_SGPT	29.357	12.582	2.814	28.957	8.686	1.942	–1.364 (0.29)	0.775	25.436	6.235	1.394	24.861	5.357	1.198	–2.261 (0.947)	0.355
Serum creatinine	0.711	0.109	0.024	0.741	0.092	0.021	4.219 (–1.6)	0.126	27.471	9.204	2.058	25.685	5.337	1.193	–6.501 (1.98)	0.052
BUN	11.103	1.161	0.260	10.774	0.964	0.216	–2.963 (1.85)	0.080	75.597	17.389	3.888	75.954	17.102	3.824	0.472 (0.315)	0.756
MCV	85.971	2.570	0.575	85.318	3.019	0.675	–0.760 (1.93)	0.069	0.683	0.091	0.020	0.690	0.087	0.020	1.099 (1.08)	0.201
Alkaline phosphatase	82.753	18.678	4.177	82.651	18.345	4.102	–0.123 (0.184)	0.856	11.447	1.801	0.403	11.411	1.712	0.383	–0.319 (0.92)	0.307
Vitamin B12	261.010	35.704	7.984	262.587	35.032	7.833	0.604 (–1.32)	0.202	268.335	42.309	9.461	269.353	40.508	9.058	0.379 (–1.11)	0.283

*Based on the assumption of normality paired-*t* test or equivalent Wilcoxon signed rank test was used to check any variability in safety parameters during the study in both Somin-On™ group ($n=20$) and Placebo group ($n=20$). Test statistic represented here are *t*-value for paired *t*-test and *Z* score for Wilcoxon signed rank test.

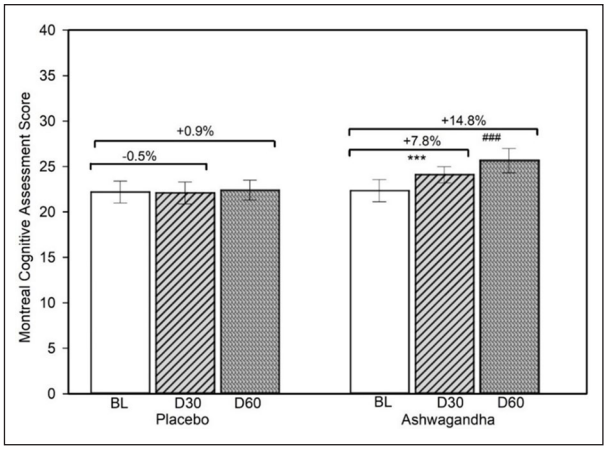


Figure 3. Montreal cognitive assessment (MoCA) in placebo ($n=20$) and ashwagandha (Somin-On™) ($n=20$) groups during the study.
BL: baseline; D30: day 30; D60: day 60.
$^{***}p<0.001$ at day 30, $^{###}p<0.001$ at day 60.

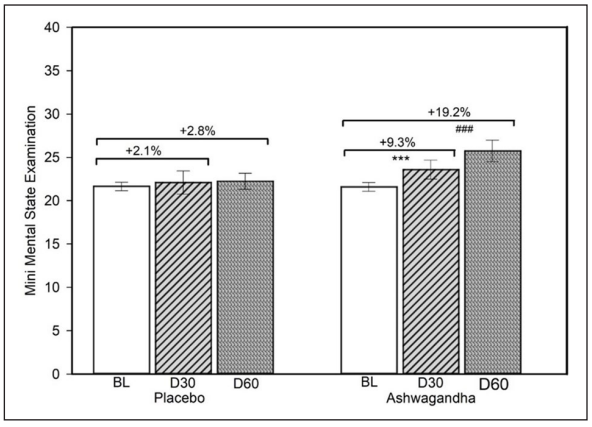


Figure 4. Mini mental state examination (MMSE) in placebo ($n=20$) and ashwagandha (Somin-On™) ($n=20$) groups during the study.
BL: baseline; D30: day 30; D60: day 60.
$^{***}p<0.001$ at day 30, $^{###}p<0.001$ at day 60.

function with time and place orientation. In our study, the MoCA score was significantly enhanced at 30 and 60-day ($p<0.001$) with (Somin-On™) treatment as compared to placebo.

The reduced visuospatial working memory is an early sign of MCI which may be due to shrinkage/atrophy of the hippocampus led to deleterious effect on visual-grapheme-phoneme conversion (Alescio-Lautier et al., 2007; Edwards and Anderson, 2014). The significant improvement in visuospatial working memory in our study indicates a positive effect of (Somin-On™) on

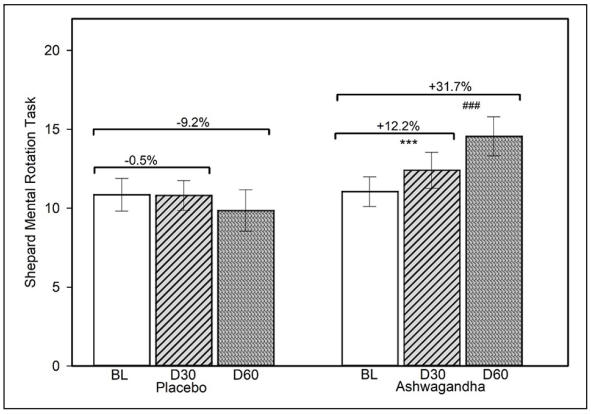


Figure 5. Shepard Mental Rotation Task in placebo ($n=20$) and ashwagandha (Somin-On™) ($n=20$) groups during the study.
BL: baseline; D30: day 30; D60: day 60.
$^{***}p<0.001$ at day 30, $^{###}p<0.001$ at day 60.

visual-grapheme-phoneme conversion at hippocampus fusiform gyrus. Studies have reported that improved working memory results in the effective conversion of short-term memory into long-term memory (Alescio-Lautier et al., 2007; Missonnier et al., 2007; Yetkin et al., 2006). Our study findings also support the theory of improvement in long-term memory due to enhanced working memory and the findings were consistent when assessment was performed by various cognitive tools (WMS-III, Shepard mental rotation test, MoCA and MMSE). Therefore, the regular supplementation of (Somin-On™) may lead to improved cognitive function through improved immediate, general and working memory in adult MCI population.

Despite the significant findings, the study has several limitations, including a small sample size and a short duration. Additionally, the study did not incorporate biomarkers or brain imaging (MRI, CT) to further elucidate cognitive changes. Future studies with larger sample sizes are necessary to confirm the findings of supplementation of (Somin-On™) in participants with MCI. Moreover, while this study focused on a comparison with a placebo, another limitation is the lack of effective control group receiving an extract of *Withania somnifera.* Future comparative studies could provide a better understanding of the specific contributions of Sominone and other components.

Conclusion

The results suggest that the therapy with ashwagandha extract standardized with Sominone (Somin-On™) has led to significant improvements in enhancing both immediate and general memory in people with MCI as well as improving cognitive function, such as attention, and information processing speed.

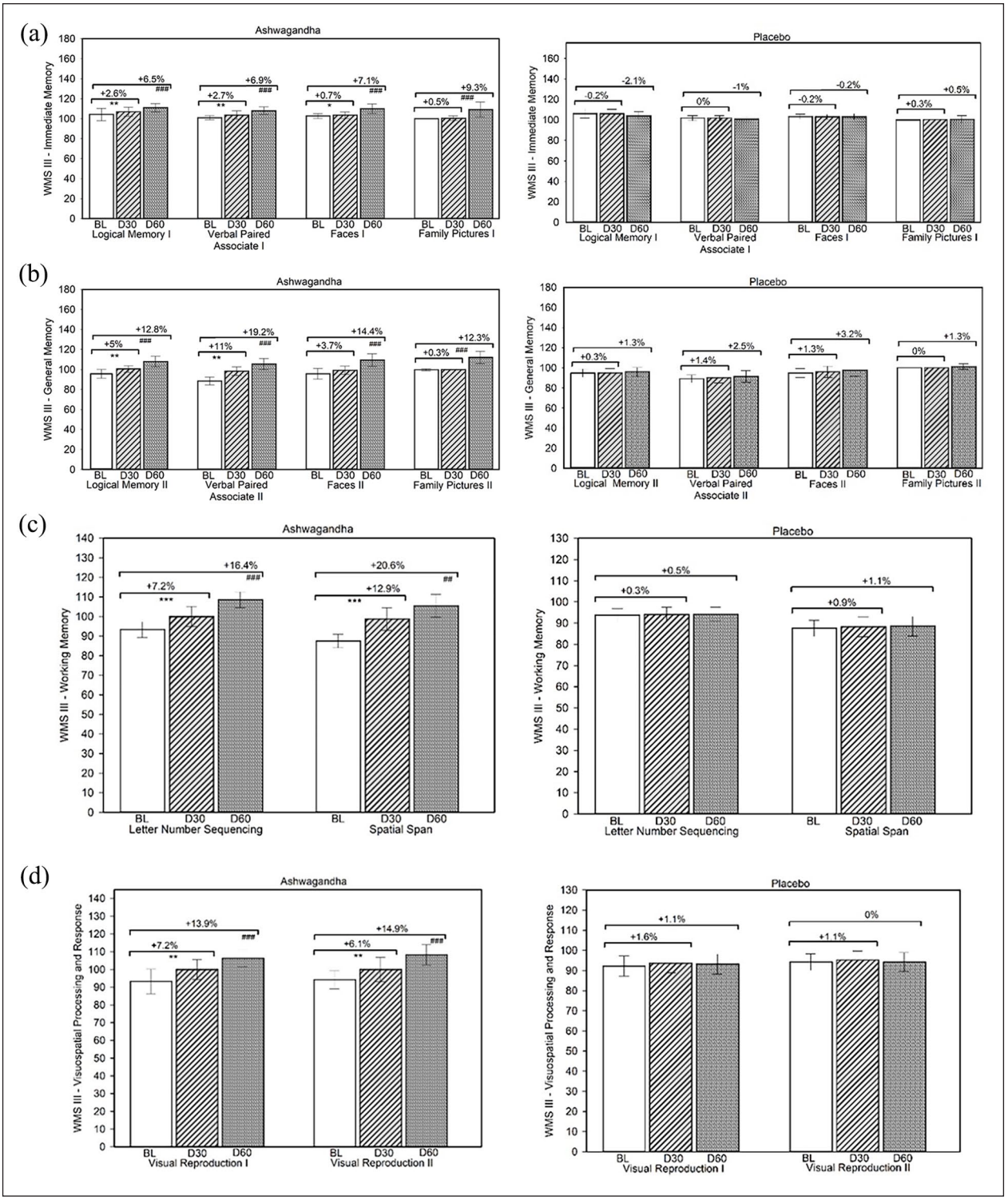


Figure 6. Wechsler Memory Scale–III (a) Immediate memory, (b) General memory (c) Working memory (d) Visuospatial Processing and Response in placebo ($n=20$) and ashwagandha (Somin-On™) ($n=20$) groups during the study.

BL: baseline; D30: day 30; D60: day 60.

*$p<0.05$ at day 30, **$p<0.01$ at day 30, ***$p<0.001$ at day 30, $^{\#}p<0.05$ at day 60, $^{\#\#}p<0.01$ at day 60, $^{\#\#\#}p<0.001$ at day 60.

Acknowledgements

The authors thank Arjuna Natural Pvt. Ltd. Aluva, India for supplying the ashwagandha extract (Somin-On™) and placebo capsules used in the study. The authors thank all the study participants who participated in the study.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the institutional ethics committee of Nirmal Hospital, Jhansi (Date of Approval 15 March 2023). The clinical trial was prospectively registered in Clinical Trial Registry of India with registration number CTRI/2023/03/050974 on 22 March 2023. Before participating in the study, a written voluntary Informed consent form was signed by all the participating subjects.

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