NUTRACEUTICAL RESEARCH

Research Article

Effects on Memory Tasks and Daily Life Performance of a Dietary Supplement Made from Extract of *Bacopa Monnieri*, Astaxanthin, Phosphatidylserine, and Vitamin E in Subjects with Amnestic Mild Cognitive Impairment: A Noncomparative, Exploratory, Real-Life Study

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Received : December 19, 2025

Published : February 02, 2026

ABSTRACT

Background: Patients suffering from amnestic mild cognitive impairment are at significant risk of developing Alzheimer's disease. Since no established pharmacological treatments exist in clinical practice, emerging evidence suggests that certain supplements may help to reduce memory loss. **Aim:** to explore the opportunity of the neuroprotective capacity of a commercially available nutraceutical compound in a real-life setting. **Methods:** In this open-label, uncontrolled, observational prospective study, a combination of *Bacopa monnieri*, astaxanthin, phosphatidylserine, and vitamin E (natural mix supplement) was clinically evaluated in amnestic mild cognitive patients. A total of 100 subjects (aged 60 -79 years) underwent a battery of cognitive and daily life assessment tests. **Results:** At admission, patients had an impaired delayed recall test score of 11.84 ± 3.37. After 52 weeks of treatment with the dietary supplement, patients exhibited a statistically significant improvement ($\Delta_{T0\text{-}T2}$ = +24%; p<0.001), with overall cognitive function restored to normal (MoCA test score ranging between 25-30 points). A notable improvement of about 30% was also observed in daily activity scores. Few mild adverse events were recorded. **Conclusions:** Due to the lack of a control/placebo group, our study cannot provide definitive evidence that the supplement can slow cognitive decline. On the other hand, our study design is appropriate for early-phase setting and to estimate a possible trend. Current

DOI: https://doi.org/10.35702/nutri.10017

findings support a plausible amelioration of disease response to a nutraceutical compound in a long-term follow-up. Further randomized and controlled studies are advisable to verify this opportunity.

Keywords: Cognitive Dysfunction, Memory Disorders, Dietary Supplementation, Nutraceuticals, Pilot Study

INTRODUCTION

Mild Cognitive Impairment (MCI) affects 10 to 15% of the general population over the age of 60 [1,2]. The two primary subtypes are amnestic MCI (aMCI) and non-amnestic MCI (naMCI), with the distinction based on the presence of memory impairment. Individuals with aMCI exhibit memory loss, whereas those with naMCI show impairments in areas such as executive functions, attention, and language [3,4]. Additionally, based on the number of impaired cognitive domains, individuals can be classified into single-domain or multi-domain MCI. Among individuals with aMCI, 8 to 15% progress annually to a clear diagnosis of dementia.[5] Similarly to Alzheimer's disease, patients who meet the clinical, cognitive, and etiological criteria for MCI carrying the APOE ε4 allele are highly likely to progress to dementia in fewer years compared to an individual without these genetic characteristics [5].

Since MCI is not a neurodegenerative disease but rather a syndrome at risk of developing Alzheimer's disease within 12 months, there are no indications for pharmacological treatment. Cholinesterase inhibitors and monoclonal antibodies are prescribed but they are not approved as treatment strategy for MCI. In a recent systematic review and meta-analysis, the efficacy and safety of anti-amyloid monoclonal antibody versus acetylcholinesterase inhibitor were investigated in patients diagnosed with MCI or mild Alzheimer's disease Authors concluded that there is some evidence of mABs effect in slowing progression of cognitive decline but not exceeding the minimally important difference threshold [6].

In clinical practice, individuals with MCI may be treated with dietary supplements and are monitored every six months to assess any potential worsening and progression to Alzheimer's disease. In particular, a nutraceutical containing extracts of *Bacopa monnieri,* astaxanthin, phosphatidylserine, and vitamin E has shown potential in alleviating cognitive impairment in individuals with MCI [7].

Among the many offerings of phytotherapy, components such as *Bacopa monnieri,* astaxanthin, phosphatidylserine, and vitamin E act on some of the biological mechanisms underlying neuronal degeneration. A combination of these elements has been clinically evaluated in MCI patients, who showed a significant improvement in cognitive status after 60 days of observation [7].

It has been suggested that bacosides contribute to the repair of damaged neurons by increasing protein kinase activity, facilitating neuronal synthesis, aiding in the restoration of synaptic activity, and enhancing nerve impulse transmission [8]. It is believed that the components responsible for the cognitive effects are bacosides A and B, with the latter differing only in optical activity and likely being an artifact produced during the isolation process of bacoside A.

Bacopa monnieri is a perennial creeping medicinal plant of the Scrophulariaceae family, traditionally used in Ayurvedic medicine. It is native to India, Indochina, Australia, and Sri Lanka. The leaves are the main medicinal part and contain a variety of bioactive compounds, including triterpenoid saponins (e.g., bacoside A and B, bacopasaponins), alkaloids, flavonoids, glycosides, phytosterols, sapogenins, and related constituents. Among these, saponins are considered the primary contributors to its pharmacological activity. Clinical studies have shown that *Bacopa monnieri* supplementation is associated with improvements in verbal learning, delayed recall, memory acquisition, and anxiety reduction, supporting its characterization as a calming cognitive enhancer [9].

Astaxanthin is a carotenoid synthesized by the unicellular microalga *Haematococcus pluvialis*, which is incorporated into cellular membranes and circulating lipoproteins, and is not produced by human metabolism (dietary source). It is considered a "unique" antioxidant for cellular membranes. Furthermore, scientific studies have demonstrated that astaxanthin has neuroprotective effects and improves memory and higher brain functions [10].

In a double-blind study, oral treatment with phosphatidylserine was shown to attenuate the intensity of the ACTH and cortisol response to physical stress, without interfering with plasma levels of growth hormone (GH) and prolactin [11,12].

Vitamin E (natural α-tocopherol and synthetic α-tocopherol) protects in vitro neurons (HT22 hippocampal cells and rat cerebellar granule neurons) from cell death induced by

DOI: https://doi.org/10.35702/nutri.10017

β-amyloid protein associated with Alzheimer's disease, hydrogen peroxide, and excess glutamate (excitatory amino acid). Moreover, Vitamin E induces the activity of the oxidation-sensitive transcription factor NF-kB, which is involved in the regulation of nerve cell survival and may play a role in the neuroprotective effect of Vitamin E [13].

This pilot study aims to preliminary evaluate whether the natural mix supplement can slow down the evolution of the cognitive decline in individuals with aMCI. Furthermore, adherence to the prescription of nutraceutical therapy and tolerability were evaluated.

METHODS

Nutraceutical formulation and composition

The tested compound is detailed in **Table 1** and commercially available as a dietary supplement in tablet form. It was provided free of charge by Cristalfarma (Milan, Italy) to adult subjects enrolled in this research study at a prescription dosage of 1 tablet per day for 12 months.

Table 1. Qualitative and quantitative composition of nutraceutical compound under study

Components	Content per tablet	%NRV †
Microalgae (*Haematococcus pluvialis*) dry extract 4%	50 mg	
Astaxanthin	2 mg	
Bacopa monnieri dry extract 20%	100 mg	
Bacosides	20 mg	
Phosphatidylserine (extracted from soy)	30 mg	
Vitamin E (vegetable origin)	30 mg	250%

†NRV, nutrient reference value

Study design and participants

This was an open-label, uncontrolled, observational prospective study. Patients aged 60-80 years with definite aMCI and a Montreal Cognitive Assessment (MoCA) test (25-30 points: normal cognitive abilities, 21-24 points: mild dementia, 10-20 points: moderate dementia, ≤ 9 points: severe dementia) [14] (Italian version 8.1 of 19 Feb 2018) score ranging from 21 to 24, primarily involving deficits in the delayed recall domain, were consecutively enrolled and monitored as outpatients at five Italian Centers for Cognitive Disorders and Dementias (CDCD). This research was conducted in collaboration with AINAT, an Italian Scientific Society of territorial neurologists, which provided the aforementioned list of specialty clinics. Exclusion criteria included (i) any pre-existing rheumatic disorder, malignancy or cerebrovascular disease with a history of stroke and/or, in general, the presence of systemic conditions in which a mild cognitive impairment may coexist but do not meet the MCI criteria as defined by Petersen;1 (ii) any concomitant natural dietary supplementations to prevent cognitive decline. This study took place between November 2023 and December 2024.

The protocol was planned according to the 1964 Declaration of Helsinki and its later amendments and has obtained approval from the Ethics Committee of Foggia, Area 1. In order to participate to the study, a written informed consent was obtained from each patient.

Assessment and outcome measures

At screening phase (T0), main demographic characteristics, medical history and current medications were collected. In order to evaluate different domains of cognitive impairment and ability to perform basic self-care and more complex tasks necessary for independent living, MoCA, ADL (Activities of Daily Living, 0 = complete dependence, 6 = independence in all functions) [15] and IADL (Instrumental Activities of Daily Living, 0 = complete dependence, 6 = independence in all functions) [16] tests were respectively administered at T0 and, in case of eligible patient, after 26 (T1) and 52 (T2) weeks from the first visit. ADL test includes six activities: bathing, dressing, toileting, transferring, continence and feeding. IADL includes eight activities: using telephone, shopping, meal preparation, housekeeping, laundry, use of transportation, self-administration of drugs, and handling finances.

The primary endpoint entailed longitudinally evaluating an improvement in terms of MoCA test score (delayed recall domain) after 52 weeks of treatment which should attain a value equal or greater than 25 units in a percentage of subjects with MCI exceeding 80%. The second endpoint was to assess any possible change in the scores of ADL and IADL performance tests from the first visit to the last one. Furthermore, tolerability evaluation included monitoring of any elicited or observed adverse events.

Data analyses

Pilot studies aim to provide preliminary evidence to support a definitive trial: thus, they are based on descriptive statistics and trend estimation rather than to provide definite results.

The cohort characteristics were summarized using descriptive statistics. Pairwise comparisons in cognitive and daily life performance tests between T0 and T2 were performed using non-parametric Wilcoxon Signed-Ranks test. A p-value of less than 0.05 was considered as statistically significant. According to primary endpoint, correction for multiple testing was not performed.

Statistical analyses were performed using IBM SPSS Statistics (Version 30).

RESULTS

One hundred patients fulfilled the selection criteria and started the therapy.

Their baseline demographic/anamnestic details are summarized in **Table 2.** Overall, patients had a mean age of 68.4+4.9 years ranging from 60 to 79 and as expected the two genders were equally represented.

Table 2. Main characteristics of the 100 patients affected by Mild Cognitive Impairment

Demographics	Baseline values (n=100)
Age groups, % (n)	
60-64ys	23 (23)
65-69ys	33 (33)
70-74ys	33 (33)
75-80ys	11 (11)
Gender, female % (n)	51 (51)

The mean baseline scores of the enrolled patients were 22.46 ± 1.19, 4.54 ± 1.73, and 5.46 ± 2.35 for the MoCA, ADL, and IADL tests, respectively. The most impaired daily routine tasks were continence (n=40), mobility (n=35), and toileting activities (n=33). Regarding the IADL test items, a considerable number of patients were found to be dependent in the following activities: preparing meals (n = 53), shopping (n = 52), and taking medications properly (n = 52).

Results concerning longitudinal analysis in cognitive domains and performance tests are detailed in **Table 3.** By the end of the study, patients exhibited a significant improvement (ΔT0-T2 = +24%, p<0.001) with overall cognitive function restored to normal (MoCA test at 52 weeks ranging between 25-30 points). In particular, episodic memory improved (n=46) or remained stable (n=41) in 87% of aMCI patients.

Table 3. Summary of changes in MoCA †, ADL ‡ and IADL§ tests after 26 (T1) and 52 (T2) weeks of follow up

Cognitive test	Baseline T0, mean (SD)	T1, mean (SD)	T2, mean (SD)	Change T0 – T2(%); p-value
MoCA	22.46 (1.19)	27.22 (2,691)	27.89 (2.77)	24,01% *p<0.001*
Delayed recall	11.84 (3.37)	11.84 (3.37)	14.09 (1.49)	19,00% *p<0.001*
ADL	4.54 (1.73)	5.44 (0.91)	5.78 (0.68)	27.31% *p<0.001*
IADL	5.46 (2.35)	7.10 (1.54)	7.24 (1.48)	32.60% *p<0.001*

†MoCA, Montreal Cognitive Assessment; ‡ADL, Index of Independence in Activities of Daily Living; §IADL, Instrumental Activities of Daily Living Scale.

A considerable change in daily activities scoring was also observed (27.3 and 32.6% in ADL and IADL test, respectively).

Minor adverse events occurred more frequently during the first six months (n=12), than at the end of the study (n=4): twelve patients reported nausea, of whom three also experienced vertigo, three had vertigo alone, and one had a headache. All patients complied with the prescribed treatment, except for two who took the medication intermittently—one due to forgetfulness, and the other because of nausea.

The tolerability of the tested compound was perceived as excellent by 44% (n=44) of patients, good by 38% (n=38), fair by 14% (n=14) and poor by only 4% (n=4).

DISCUSSION

To date, MCI remains a major unmet medical need due to its high prevalence among the elderly, its substantial risk of progressing to Alzheimer's disease, and the absence of effective treatments or preventive strategies. In addition, cognitive decline can also significantly impair older adults' activities of daily living which may result in psychological fallout, restlessness, anxiety, and depression.

This was a real-world observational setting that focused on patients affected by aMCI and the opportunity to treat them with a blend *Bacopa monnieri,* astaxanthin, phosphatidylserine, and vitamin E supplement in order to delay memory decline.

The actual knowledge of nutraceuticals indicates that *Bacopa monnieri,* the main component (dry extract 20%), is well known for its antioxidant and anti-inflammatory properties, [17] with one of its primary indications being memory enhancement. Moreover, Bacopa is generally well-tolerated, with the most common side effects being gastrointestinal, including increased stool frequency, nausea, and abdominal cramps [9] A more recent triple-blinded, randomized, placebo-controlled trial showed that Bacopa monnieri alone can improve the overall cognitive performance score and some of its parameters in patients suffering from MCI after at least two months of treatment [18].

Since a mixed natural is intended to enhance the efficacy of a single-ingredient supplement, we investigated the effects of a formulation combining *Bacopa monnieri* with astaxanthin, phosphatidylserine, and vitamin E in preventing cognitive decline in individuals with aMCI. The properties of these additional components have been extensively studied and demonstrated in various clinical and non-clinical studies. Marine-derived compound like astaxanthin have demonstrated neuroprotective activity [19]. Phosphatidylserine has demonstrated the ability to slow cognitive decline in animal models. Additionally, a limited number of double-blind, placebo-controlled trials have investigated its effects, revealing improvements in memory performance among the elderly [20]. On the other hand, antioxidant properties of Vitamin E and its role in slowing down the progression of MCI are still controversial and further research involving human subjects needs to be conducted to gather evidence [21].

The efficacy of the same dietary supplement has already been established in the treatment of a broad range of cognitive domains [7]. In this study, results supported a positive trend in cognitive function among subjects with mild cognitive impairment after 60 days of supplementation. On the other hand, the novelty of the present research lies in its 12-month follow-up, extending the findings of the previous 60-day study.

In the herein reported cohort, we observed patients' improvement in overall cognitive status, specifically in mnemonic function. After one year of treatment, patients achieved normal ranges of overall MoCA test and a positive variation of delayed recall score of 19% that is a plausible result. It is important to emphasize that in this type of patient, who physiologically tend towards cognitive decline, the goal is to maintain their condition stable. MCI, especially the amnestic subtype, has been proposed as a prodromal phase of Alzheimer's disease, primarily affecting recalling information. In our real-life study, we observed a restored or at least stable mnemonic function in 87% of cases. Furthermore, follow-up assessments of both basic self-care activities and more complex tasks required for independent living revealed considerable improvement after six months of treatment, along with a decrease in variability. Of note, keeping people with MCI physically healthy is important for their cognition. One consideration should be done as the non-randomized design may have influenced the primary results. Lacks a control or placebo group is a major methodological flaw that prevents the attribution of the observed positive outcomes to

the supplement itself. Consequently, the placebo effect could not be accounted for, potentially leading to an overestimation of the true effects of this phytotherapeutic compound on patients' cognitive abilities.

On the other hand, our study design is appropriate for early-phase exploratory studies and together with the previous randomized studies, current findings might support a possible amelioration of disease response to a nutraceutical compound in a long-term follow-up. Nevertheless, within the constraints of an open-label study, the single-case design allows researchers to work with reduced variability and manage both measured and unmeasured confounders, which are primary sources of bias in controlled studies. Moreover, the compound was well tolerated, promoting better adherence to treatment among patients.

It should be noted that this is a long period of time in which each patient was exposed to different factors, some of which affected cognitive and daily functioning. In order to conclude that the study supplement caused the observed change, better control of changes in the subjects' lives - for example, physical and social activity, inclusion in courses, significant changes in diet – is needed. However, this is a real-world study, and the visit schedule was designed to mirror the standard clinical management of MCI patients.

ACKNOWLEDGEMENT

The nutraceutical compound was provided free of charge by Cristalfarma, Milan, Italy.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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