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File: ■ Spirulina (*Limnospira maxima*, Sirenicapillariaceae syn. *Arthrospira maxima*, Microcoleaceae)
■ Cognitive Impairment
■ Alzheimer's Disease

102241-701

Date: November 30, 2022

RE: Improved Memory and Increased Vocabulary Demonstrated in Twelve Week Trial Involving Spirulina and Individuals with Mild Cognitive Impairment

Choi W-Y, Lee W-K, Kim T-H, et al. The effects of *Spirulina maxima* extract on memory improvement in those with mild cognitive impairment: A randomized, double-blind, placebo-controlled clinical trial. *Nutrients*. September 9, 2022;14(18):3714. doi: 10.3390/nu14183714.

As the world population ages, the prevalence of memory impairment is rising. While such impairment cannot yet be completely prevented, early interventions can slow progress and improve symptoms. Alzheimer's disease (AD), with the most severe memory losses, is mostly irreversible, increasing the importance of slowing onset and progression. Mild cognitive impairment (MCI), a transitional stage between those with and without AD, affects immediate memory, working memory, continuous attention, and selective attention. Between 1-2% of healthy individuals develop AD annually; of those with MCI, 10-15%. MCI assessment can be used as an index of early potential impairment and to register any improvements in the pre-AD stage after specific interventions.

The cyanobacterium spirulina maxima (SM; *Limnospira maxima*, Sirenicapillariaceae syn. *Arthrospira maxima*, Microcoleaceae), a green microalgae, is rich in bioactive substances and nutrients and is considered one of the best human dietary supplements (DS). *Limnospira* spp. have been studied clinically in obesity and high blood pressure. In animal models of scopolamine- and amyloid- β (A β)-induced memory impairment, an SM 70% ethanol extract (SM70EE) caused significant improvement in cognitive outcomes.

These authors used the Korean version of the Montreal Cognitive Assessment (MoCA-K) and a computer-based neurocognitive function test (CNT) in the first randomized, double-blinded, placebo-controlled clinical trial (RCT) of SM70EE on older adults to assess effects on memory function in patients with MCI. Of 100 patients assessed at Jeonbuk National University Hospital (Jeonju-si, North Jeolla Province, Republic of Korea [RoK]), 80 met inclusion criteria and were randomized to two groups of 40. Inclusion criteria were age \geq 60 years, score of 25-28 on the Korean mini-mental status examination (K-MMSE), and informed consent. Exclusion criteria were history of surgery, severe health problems, use of any drug or DS that might affect metabolism, history of allergy to medicinal plants or placebo materials, and pregnancy/lactation. Patients were asked to make no significant changes in diet or routine physical activity during the 12-week study. There were no significant between-group differences at baseline in diagnostic medical tests, demographic or lifestyle factors, vital signs, anthropometric measures, or metabolic equivalent of task test results. Of all

participants, 59 were women (28 in SM70EE; 31, placebo). Mean K-MMSE score was 26.38 ± 1.06 .

Patients consumed 1 g of either an SM70EE product (provided by the Korea Institute of Ocean Science and Technology; Jeju-si, Jeju Province, ROK) or placebo (0.5% gardenia [*Gardenia jasminoides*, Rubiaceae] pigment and 0.5% caramel color dissolved in drinking water) three times/d. Chlorophyll was a major component of SM70EE at 15.68 ± 0.76 mg/g. Visual learning, visual working memory, and verbal learning tests (CNTs) were administered, along with the MoCA-K, before the intervention, at six weeks, and at 12 weeks. Plasma levels of brain-derived neurotrophic factor (BDNF), A β , and total antioxidant capacity (TAC) were recorded at each visit. Differences in changes in outcome measures were considered statistically significant at $P < 0.05$. Safety was summarized in terms of frequency and percentage of all adverse effects (AEs) reported by participants in each group and both groups.

Data from six patients, three in each group, were not included in analysis, four of them for use of unspecified prohibited drugs and two for noncompliance, leaving 37 in each group ($T = 74$). Compliance measured by returned product count was $92.92 \pm 7.24\%$ overall, with no significant differences between or within groups. There were significant differences between groups in visual learning ($P = 0.007$) and visual working memory ($P = 0.024$) between baseline and 12 weeks that favored SM70EE. On the MoCA-K, there was a significant between-group difference in vocabulary ($P = 0.043$). There were no significant differences in BDNF and A β levels. While the between-group difference in TAC did not reach significance ($P = 0.066$), the increase in the SM70EE group suggests the need for further studies. Only one AE was reported during the study, and it was not considered to be related to the study agent. There were no statistically significant differences between groups in diagnostic medical tests, vital signs, body weight, body mass index, or metabolic equivalent of task test results at 12 weeks.

Preclinical studies indicate that SM70EE enhanced cranial nerve protection in hippocampal neuronal mouse brain cells. The memory improvement seen with SM70EE is reported to be caused by the antioxidant activity of chlorophyll and other components of SM. While in vivo studies have reported increased BDNF and A β , and improvements in other biomarkers, such changes vary greatly depending on individual health and age, as well as study species. Average age of participants in this RCT was high (68.26 ± 4.68 years). The increase in TAC with SM70EE, while not statistically significant, is similar to that reported in clinical trials of cordyceps (*Cordyceps militaris*, Cordycipiciaceae) extract. In previous studies, plasma BDNF did not differ significantly in patients with late AD from healthy individuals, while A β levels, which were not significantly different in patients with MCI vs. healthy individuals, decreased in AD. Results of this RCT indicate that SM70EE is safe and conferred significant improvements in memory function in patients with MCI. Continuous consumption of SM70EE by individuals with MCI could lead to improved memory function through improved visual memory and vocabulary and contribute to delayed progression to AD. The authors had no conflicts of interest.

—Mariann Garner-Wizard

Referenced article can be accessed at <https://www.mdpi.com/2072-6643/14/18/3714>.

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