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File: ■ Prickly Pear (*Opuntia ficus-indica*, Cactaceae)
■ Cognitive Function

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RE: Effects of Prickly Pear on Cognitive Function in Older Adults

Han EH, Lim MK, Lee S, et al. Efficacy of ethanolic extract of *Opuntia ficus-indica* var. *saboten* stems for improving cognitive function in elderly subjects 55-85 years of age: a randomized, double-blind, placebo-controlled study. *J Med Food*. November 2020;23(11):1146-1154. doi: 10.1089/jmf.2019.4678.

Neurodegenerative diseases, such as Alzheimer's, Parkinson's, Huntington's diseases are a serious health issue in elderly populations. While aging can cause mild cognitive decline, these neurodegenerative diseases are induced by oxidative stress, brain injury, and neuronal inflammation leading to dementia. Prickly pear (*Opuntia ficus-indica*, Cactaceae) has demonstrated neuroprotective and anti-inflammatory properties in preclinical studies, suggesting potential application for enhancing cognitive function in adults. Therefore, the purpose of this randomized, double-blind, placebo-controlled trial was to examine the effects of OFE (an ethanolic extract of prickly pear var. *saboten* stem and dextrin, 1:1 per weight) on cognitive function in older adults.

The patients were recruited from three psychiatric departments at university hospitals in Seoul, Korea. Eligibility criteria were age 55 – 85 years; ability to read; score of > 1.0 in word list memory, word list recall, or word list recognition in the Consortium to Establish a Registry for Alzheimer's Disease-Korean version-Neuropsychological Battery (CERAD-K-NP); and adherence to the study protocol. The patients were randomly assigned to receive OFE (0.96 g/tablet, containing 0.48 grams of the extract) or placebo (0.96 g/tablet containing 0.48 g of cellulose, microcrystalline and insoluble fiber; DuPont Nutrition USA, Inc; Wilmington, Delaware). To prepare the OFE extract, prickly pear (var. *saboten*) stems were collected in Jeju Island, Korea. The dried stems were ground into a powder (160 kg), which was extracted with 2,400 L of 70% ethanol at 80°C (176°F) for two hours. The extracts were filtered and concentrated to 15° – 20° Brix. For the test sample, the ethanolic extract was mixed with dextrin (Daesang; Soul, Korea) in a 1:1 ratio per weight (OFE) and sterilized at 95°C (203°F) for one hour before being spray dried and passed through a 60-mesh sieve. The prepared OFE was tested for dihydrokaempferol (0.506 mg/g) as the marker compound.

The patients visited the clinic and were screened for eligibility (visit 1). After randomizing the included patients, they were instructed to take two tablets of their assigned treatment

(visit 2, baseline), and then daily for 12 weeks. Subsequent visits were on day 42 ± 7 (visit 3) and day 84 ± 5 (visit 4). The efficacy of the treatments was assessed each visit using the Alzheimer's Disease Assessment Scale-Korean version (ADAS-K), Alzheimer's Disease Assessment Scale-Korean version-cognitive subscale (ADAS-K-cog), Alzheimer's Disease Cooperative-Activities of Daily Living (ADCS-ADL), Visual Continuous Performance Test (CPT), and Short-form Geriatric Depression Scale (SGDS). Safety was assessed by adverse events and by blood tests, vital signs, and electrocardiograms.

Of the 100 patients recruited 81 patients (OFE n = 41, placebo n = 40) completed the 12-week trial. Age, exercise activity, and smoking status were not significantly different between the groups. The proportion of patients with comorbid illness and clinical history were similar between the OFE- and placebo-treated groups.* There were no significant differences between the two groups for ADAS-cog, ADAS-memory, ADAS-K, ADCS-ADL, and SGDS. Subgroup analysis of patients ≤ 70 years of age revealed a significant decrease in overall ADAS-cog (P = 0.0394), ADAS-memory (P = 0.0419), and ADAS-K (P = 0.0475) after 12 weeks of administration with OFE compared with placebo. No significant differences were found between the groups for visual CPT score, including after sub-analysis of patients ≤ 70 years of age. The sub-analysis of patients > 70 years, however, demonstrated an increase in correct responses and a decrease in errors of omission (both P = 0.0222) in the OFE group compared with placebo. Significant differences in adverse events were not observed between the groups, with no serious adverse events reported.

While there was no significant difference between the OFE and placebo groups on enhancing overall cognitive function, twelve weeks of OFE supplementation showed age-dependent efficacy for improving cognitive function. Patients ≤ 70 demonstrated improvements in ADAS-cog, ADAS-memory, and ADAS-K, whereas patients >70 showed improvements in correct responses and less errors of omission in visual CPT. The differential age-dependent effects on cognitive function with OFE may be explained by brain plasticity, which tends to decrease with age. The authors cite limitations related to the lack of pharmacokinetic studies and limited number of subjects. In either case, the authors suggest OFE might serve as an ingredient for functional food development to prevent cognitive decline in people ≤ 70 years of age, acknowledging that advancing dementia cannot be reversed.

The authors report no conflicts of interest.

–Gavin Van De Walle, MS, RDN

* …which may be an explanation for the non-difference between verum and placebo. However, since the differences between age-strata are pronounced by the authors, it would have been appropriate for them to address possible differences between age groups likewise. The idea is not too far-fetched that age-groups would likely be different regarding comorbidities/(co)medications. From a properly planned and conducted study, one would expect that comorbidities as well as comedications are a subject of inclusion criteria and/or randomization strategies and would be made transparent.

Peer Review Comments

The recruitment protocol and initial eligibility criteria are not clear. Were the patients hospitalized and included in the study when leaving the hospital? Or was the study performed using the hospital ambulance as a study center but with outpatients?

Overall, the study is interesting but suffers – like so many studies in the field - from poor transparency regarding major methodological cornerstones, leaving it open whether the flaw is only the transparency of the methodology or the methodology itself.

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