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File: ■ Sceletium (*Sceletium tortuosum*, Aizoaceae)
■ Cognition
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RE: Sceletium Improves Cognitive Flexibility and Executive Function in Healthy Adults

Chiu S, Gericke N, Farina-Woodbury M, et al. Proof-of-concept randomized controlled study of cognition effects of the proprietary extract *Sceletium tortuosum* (Zembrin) targeting phosphodiesterase-4 in cognitively healthy subjects: implications for Alzheimer's dementia. *Evid Based Complement Alternat Med*. 2014;2014:682014. doi: 10.1155/2014/682014.

Sceletium (*Sceletium tortuosum*, Aizoaceae) is a succulent plant commonly found in South Africa. In vitro studies show that sceletium inhibits phosphodiesterase-4 (PDE4), an enzyme involved in memory impairment. The authors hypothesize that sceletium can enhance cognition in healthy subjects. The purpose of this proof-of-concept (pilot), randomized, placebo-controlled, crossover study was to evaluate the neurocognitive effects of sceletium in healthy subjects.

Healthy subjects (n = 21, aged 45-61 years) were recruited through advertisements to participate in this study conducted in San Juan, Puerto Rico. Subjects were excluded if they had any significant and untreated medical disorders (i.e., severe uncontrolled or marginally controlled diabetes mellitus, recent myocardial ischemia or infarction, unstable angina, uncontrolled hypertension, renal failure, serious renal diseases, chronic active hepatitis, acute hepatitis, cirrhosis, AIDS, malignancy, neurological disorders, epilepsy, recent cerebrovascular disease, or recent traumatic brain injury); active suicidal risk; psychiatric disorders; were pregnant; a Hamilton depression rating scale (HAM-D) score ≥ 8; or a body mass index (BMI) ≥ 30.

For 3 weeks, subjects received either placebo or 25 mg sceletium (Zembrin®; HG&H Pharmaceuticals; Bryanston, South Africa) aerial extract. The active ingredient of Zembrin is a 2:1 dry aqueous-ethanolic extract of the entire aboveground portions of naturally occurring sceletium, with an alkaloid content not less than 0.38% by weight and containing the 4 active alkaloids mesembrenone, mesembrenol, mesembranol, and mesembrine. The HG&H Pharmaceuticals website states, "All clinical and preclinical research on Zembrin® applies only to this proprietary standardized *Sceletium* extract, and not to other *Sceletium*-based products." After a 3-week washout period, subjects

were crossed over to the alternate treatment. At baseline and weeks 3, 6, and 9, a battery of neuropsychological tests (CNS Vital SignR test) was used to measure the changes in 9 cognitive domains; specifically, composite memory, verbal memory, visual memory, processing speed, executive function, psychomotor speed, reaction, complex attention, and cognitive flexibility were assessed. The subjects also completed the HAM-D questionnaire.

After 3 weeks of treatment, there was a significant improvement in cognitive flexibility ($P < 0.022$) and executive function ($P < 0.032$) with Zembrin treatment compared with placebo. There were no significant changes in the other domains. Statistical analyses to determine the clinical significance of the results (Cohen's *d* statistic) indicated that Zembrin treatment had a moderate effect on cognitive and executive function, a strong effect on processing speed, and a small effect on psychomotor speed and attention. The change on the overall HAM-D scale compared to baseline did not significantly differ between treatment and placebo, although the Zembrin group reported a significant improvement on the sleep quality subscale (onset of sleep) compared with the placebo group ($P = 0.049$).

The sceletium was well tolerated. In regard to safety, there were no significant changes in blood pressure, pulse, temperature, or weight. A total of 9.5% of the Zembrin group reported transient gastrointestinal discomfort compared to 4.2% of the placebo group; however, the supervising clinician did not think the effect was directly related to Zembrin. Kendall's tau *c* coefficient was used to assess changes in the frequency and intensity of the complaints and symptoms listed in the treatment-emergent adverse events (TEAE) scale. There was a moderate association between Zembrin and an improvement in irritability, drowsiness, memory problems, anxiety, confusion, skin irritation, chest pain, stool discoloration, and poor hearing.

The authors conclude that Zembrin significantly enhanced executive function and cognitive flexibility in healthy subjects. Executive function includes working memory, attention control, response inhibition, and concept formulation. Problems with working memory are present in the earliest stages of Alzheimer's disease, before significant memory deficits appear. The authors hypothesize that the improvements may be due to Zembrin modulating the PDE4-cyclic adenosine monophosphate (cAMP)-response element-binding protein (CREB) cascade, which is involved in the regulation of cognition, the sleep-wakefulness cycle, and moods. Acknowledged limitations of the study are the small sample size, short treatment duration, and single dose. The authors intend to "further investigate whether Zembrin can delay or reverse the course of age-related cognitive decline and AD [Alzheimer's disease] as well as prevent the conversion from MCI [mild cognitive impairment] to AD." Presumably, they will carry out a dose-ranging study before conducting the larger, longer-term trials necessary to evaluate efficacy and safety in elderly adults.

—Heather S. Oliff, PhD

Referenced article can be found at http://www.hindawi.com/journals/ecam/2014/682014/.