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File: ■ Sceletium (*Sceletium tortuosum*, Mesembryanthemaceae)
■ Zembrin®
■ Anxiety

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RE: Behavioral Evidence Supports the Anti-anxiety Effects of Sceletium Extract

Reay J, Wetherell MA, Morton E, Lillis J, Badmaev V. *Sceletium tortuosum* (Zembrin®) ameliorates experimentally induced anxiety in healthy volunteers. *Hum Psychopharmacol*. November 2020;35(6):1-7. doi: 10.1002/hup.2753.

Sceletium (*Sceletium tortuosum*, Mesembryanthemaceae) a plant indigenous to South Africa, traditionally used by the hunter-gatherer nomads of Kalahari to reduce pain, hunger feelings, and stress, and to enhance mental and physical performance. The long-term use of Zembrin® (HG&H Pharmaceuticals Ltd; Bryanston, South Africa), a standardized extract of sceletium, has been reported to enhance cognition and reduce anxiety. These authors conducted two placebo-controlled, double-blind trials to investigate the effects of a single dose of Zembrin on anxiety, feelings of hunger, and memory performance in healthy participants. The studies were conducted by Teesside University in Middlesbrough, United Kingdom and by Northumbria University in Newcastle-upon-Tyne, United Kingdom.

Study 1, which included 20 healthy participants (six male) aged 19.6 ± 1.09 years, measured outcomes at baseline and before and after stress induction. Study 2, which included 20 healthy participants (11 male) aged 21.3 ± 1.38 years, measured outcomes at baseline and before, during, and after stress induction. On the study visit days, all participants arrived in the morning at the study site after fasting and were randomly assigned a two-piece hard gel capsules containing either placebo (microcrystalline cellulose) or a single dose 25 mg of Zembrin. The active ingredient Zembrin is a hydroethanolic extract of aerial parts of Sceletium standardized to contain 0.35–0.45% total alkaloids: mesembrenone and mesembrenol ≥60%, and mesembrine <20%.

A 20-minute multitasking framework was used in study 1 to measure cognitive demand, negative affect, stress, and anxiety. The participants attempted to perform four tasks (visual warning, mail alert, telephone entry, and math) simultaneously; the tasks were performance-driven and varied in time, pressure, and/or difficulty. The participants attempted to achieve the highest score possible. Outcome measures of study 1 included the Perceived Stress Scale (PSS), which measured to a mild stress in multitasking exercises; the Bond-Lader Visual Analogue Scale (VAS), which confirmed stress induction and assessed treatment impact; the Hunger VAS, which measured feelings of

hunger from 0 (not hungry) to 100 (very hungry); Immediate Word Recall, which was used to determine cognitive ability; and the National Aeronautics and Space Administration Task Load Index, which measured subjective mental workload. Each outcome measure underwent an analysis of covariance (ANCOVA).

Results of study 1 revealed no statistically significant difference between placebo and the Zembrin group in changes in PSS score. Stress induction was confirmed through findings of a main effect of time on feelings of alertness (P = 0.012) and calmness (P = 0.001). No treatment effects were observed for any of the outcome measures.

Outcome measures for study 2 were the State-Trait Anxiety Inventory (STAI); which measured state anxiety, or anxiety about an event (a five-minute simulated public speaking task that followed a two-minute preparation period), and trait anxiety, or the anxiety levels; Anxiety Mood VAS (ranging from "not at all anxious" to "very anxious"); and physiological responses, heart rate and galvanic skin response.

In study 2, no statistically significant between-group differences were observed for results of the STAI (trait). Stress induction was confirmed by a trend toward a main effect of time on STAI (state) (P = 0.059), heart rate (P = 0.06), and the Anxiety Mood VAS (P = 0.043).

ANCOVA revealed a treatment by time interaction on the STAI (state) (P = 0.011), the Anxiety Mood VAS (P = 0.05), and heart rate (P = 0.025). Post hoc analysis revealed between-group statistically significant differences before the induction of stress, with anxiety levels significantly lower on the STIA (state) (P = 0.009) and VA anxiety scale (P = 0.024) in the Zembrin group compared with placebo.

One important difference between the current and the literature cited study protocols is a longer treatment regiment, and older population which was assessed for different cognitive functioning (i.e., executive functioning). In addition, the stressor in study 1 may have been too mild to produce a treatment effect in the subjective, self-reported outcome measures. The authors recommend that future studies should consider using protocols that elicit stronger stress responses.

The current study provides the first behavioral evidence that a single 25 mg dose of standardized extract of sceletium (Zembrin) can ameliorate subjective and physiological indicators of stress/anxiety during a controlled laboratory stress protocol in young healthy participants. The stressor may have been too mild to produce a treatment effect in the subjective, self-reported outcome measures, and the two studies were underpowered as placebo-controlled studies with only 20 subjects in each study.

"We provide the first tentative behavioral evidence to support the anxiolytic properties of *Sceletium tortuosum* (25 mg Zembrin®)," conclude the authors.

The authors report no conflicts of interest.

—Shari Henson

The American Botanical Council has chosen not to reprint the original article.