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File: ▪ Sceletium (*Sceletium tortuosum*)
▪ Zembrin®
▪ Safety

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RE: Zembrin® (Sceletium Extract) Is Safe and Well Tolerated in a Trial in Healthy Adults

Nell H, Siebert M, Chellan P, Gericke N. A randomized, double-blind, parallel-group, placebo-controlled trial of extract *Sceletium tortuosum* (Zembrin®) in healthy adults. *J Altern Complement Med*. February 26, 2013; [epub ahead of print]. doi: 10.1089/acm.2012.0185.

Sceletium (*Sceletium tortuosum*) has a long history of use as a medicinal plant in South Africa, home to these authors. In 1728, it was proclaimed "the greatest cheerer of the spirits, and the noblest restorative in the world."[1] According to the authors, sceletium is used to relieve thirst, hunger, and fatigue, and for its restorative, mood-elevating, and sedative effects, including its therapeutic use for anxiety and depression. Intoxication and euphoria are also reported with its use.[2] In case studies, anxiolytic and antidepressant activities have been observed with consumption of sceletium tablets and capsules.[3] These authors conducted a randomized, double-blind, parallel-group, placebo-controlled trial to evaluate the safety and tolerability of two different doses of Zembrin® (extract manufactured by Gehrlicher GmbH; Eurasburg, Germany; capsules manufactured by Pharmaceutical Contractors [Pty] Ltd.; Isando, South Africa), a proprietary commercial dry extract of sceletium, in healthy adults.

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. Safe daily doses of sceletium raw material are reported to range from 50 mg to 5,000 mg. The authors selected low doses of 8 mg and 25 mg of Zembrin (equivalent to 16 mg and 50 mg, respectively, of sceletium), considering the doses to be safe and to have potential for inclusion in functional food and dietary supplement products. The Zembrin used in this study was standardized to 0.4% W/W total for the 4 alkaloids mesembrenol, mesembrenone, mesembrine, and mesembranol. Each gelatin capsule contained 0 mg, 8 mg, or 25 mg of sceletium dry extract, as well as various excipients.

A screening visit was followed by a 2-week placebo run-in period during which 37 subjects recorded their daily use of placebo medication to assess compliance. At visit 3,

the subjects were randomly assigned to 1 of the following 3 treatment groups for 3 months: 12 subjects were allocated to the 8 mg Zembrin group, 12 to the 25 mg Zembrin group, and 13 to the placebo group. All but 1 subject completed the trial. The 37 healthy men and nonpregnant women (no gender differentiation provided) were aged between 18 and 55 years, weighed >50 kg (>110.2 lb), and had a body mass index ranging from 18.5 to 29.9 kg/m^2.

Visits 3, 4, 5, and 6 were scheduled monthly. Safety assessments performed at the screening visit and at visits 4, 5, and 6 included vital signs, physical examination, laboratory test, 12-lead electrocardiogram (ECG), and the recording of adverse events (AEs). At visits 2, 3, 4, and 5, the subjects were given a diary and asked to record the occurrence of AEs, their daily use of the study product, and the intake of other medications.

The authors report that the greatest incidence of AEs occurred in the placebo group, followed by the 25 mg and 8 mg Zembrin groups. Twenty-two of the 37 total assigned subjects (59%) experienced at least 1 AE. Four of the 12 subjects (33.3%) in the 8 mg group reported 6 AEs. Seven of the 12 subjects (58.3%) in the 25 mg group reported 14 AEs, and 11 of the 13 subjects (84.6%) in the placebo group reported 22 AEs.

Headache was the most common AE, with 8 incidences reported by 7 of the 37 subjects (18.9%). Of those, 4 occurred in 4 subjects in the placebo group, 3 in 2 subjects in the 25 mg Zembrin group, and 1 in 1 subject in the 8 mg Zembrin group. Other AEs included abdominal pain (5 incidences in 3 of the 13 subjects in the placebo group), upper respiratory tract infection (4 incidences in 4 of the 13 subjects who received placebo), and influenza (3 incidences in 3 subjects; 1 from each group).

All but 2 AEs were mild or moderate and were considered unrelated to the study medication. The 2 severe AEs were reported in the placebo group. One subject reported abdominal pain, which was considered as possibly related to the study product; and 1 subject who complained of headache, which was considered as probably related to the study product, withdrew from the trial.

The authors reported no marked, clinically relevant differences in the changes in vital signs among the 3 treatments, except for a difference in diastolic blood pressure (DBP) between the placebo and the 8 mg Zembrin groups. In those in the 8 mg group, a mean increase in DBP of 1.92 mmHg occurred from the screening visit to visit 6; the subjects in the placebo group experienced a mean decrease in DBP of 6.17 mmHg. This resulted in a mean difference of 8.08 mmHg (95% confidence interval: 1.51-14.65) between those 2 treatments (P=0.02). No such significant difference in DBP was seen between the 25 mg Zembrin group and the placebo group.

Other safety results showed no differences among the 3 treatments in ECG or physical examination findings during the 3 months, and no significant changes were observed in laboratory parameters or in body weight.

Five subjects offered positive comments about changes in their health. These comments from 1 subject (8.3%) in the 8 mg Zembrin group, 3 subjects (25%) in the 25 mg Zembrin group, and 1 subject (7.7%) in the placebo group included sleeping better at night, coping better with stressful situations, and feeling better in general.

According to the authors, the spectrum of sceletium uses suggests a dose response. The lowest doses are ingested at the food side of the spectrum, higher doses at the botanical medicine side, and the highest doses at the intoxicating end of the spectrum. "In addition to dose-response for total alkaloid content, the alkaloid composition is likely to be a key factor that determines effects and adverse effects," write the authors.

The results of this trial show that both treatments of Zembrin at doses of 8 mg and 25 mg once daily for 3 months were well tolerated and safe.

One of the authors (Nigel Gericke) discloses that he is the Director of Medical and Scientific Affairs of HG&H Pharmaceuticals (Pty) Ltd, the company that developed Zembrin.

– *Shari Henson*

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