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Original Article

A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial of Extract *Sceletium tortuosum* (Zembrin) in Healthy Adults

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Abstract

Objectives: The objective of the study was to evaluate the safety and tolerability of two doses (8 mg and 25 mg once daily) of a 2:1 standardized extract of the South African medicinal plant *Sceletium tortuosum* (L.) N.E. Br., trademarked Zembrin®, in healthy adult volunteers over a three-month period.
Design: This was a randomized, double-blind, parallel-group, placebo-controlled single center study.
Setting: Tiervlei Trial Centre, Karl Bremer Hospital, Bellville, Cape Town, South Africa.
Participants: The study took place between February 2 and July 27, 2009. Thirty-seven healthy adults were recruited from the general population.
Intervention: Participants were randomized to receive either one of two doses of study medication, or an identical placebo, taken once daily for 3 months. Of the 37 subjects, 12, 12, and 13 subjects received 8 mg extract *Sceletium tortuosum* (Zembrin®), 25 mg extract *Sceletium tortuosum* (Zembrin®), and placebo treatment, respectively.
Outcome measures: No efficacy variables were assessed. The safety and tolerability variables comprised of vital signs, physical examination, 12-lead electrocardiogram (ECG), laboratory assessments (hematology, biochemistry, and urinalysis), and the recording of adverse events (AEs).
Results: There were no apparent differences between the three treatments with regard to vital signs, 12-lead ECG, body weight, and physical examination from screening to the end of the 3-month treatment period. No significant changes were observed in hematology or biochemistry parameters between initial screening and the end of the study. Both doses of extract *Sceletium tortuosum* (Zembrin®) were well-tolerated. The most commonly reported AE was headache, followed by abdominal pain and upper respiratory tract infections, all with greater incidence in the placebo group than in the treatment groups. Unsolicited positive effects on well-being were noted in patient diaries by some participants taking extract *Sceletium tortuosum* (Zembrin®), including improved coping with stress and sleep.
Conclusion: Both doses of extract *Sceletium tortuosum* (Zembrin®) (8 mg and 25 mg) were well tolerated when used by healthy human subjects once daily for 3 months.

Introduction

Sceletium tortuosum (L.) N.E. Br., family Mesembryathemaceae, known as *kanna* in Nama, *kougoed* in Afrikaans, and *Sceletium* in English, has one of the oldest documented histories of use of any South African medicinal plant. The earliest written records of the use of this plant date to 1662 and 1685.[1–9] In 1738, Peter Kolben stated that *Sceletium* was "the greatest cheerer of the spirits, and the noblest restorative in the world."[10] The vernacular name "kougoed" was first documented in 1830,[4] alluding to the well-known Nama practice of chewing this plant. In 1928, Laidler stated that *Sceletium* was prized by Europeans as a ginseng-like herb.[11] More recently, in 1971, Herre reported that storekeepers in Namaqualand bought *Sceletium* from the locals and resold it.[8] In 1994, Rood stated that *Sceletium* was a good calming herb.[3] Smith et al. reported negative side effects including headaches, listlessness, loss of appetite, and depression after the chewing of *Sceletium tortuosum* leaves.[1] Gericke & Viljoen reported *Sceletium tortuosum* ingestion resulting in mood elevation and transient euphoria, as well as sedative and anxiolytic activities.[13] Gericke reported on the

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first clinical case studies where anxiolytic and antidepressant activities were reported for tablets and capsules of *Sceletium tortuosum*.[12]

United States Patent 6,288,104 discloses the use of mesembrine and related compounds as serotonin-uptake inhibitors,[15] and *in-vitro* serotonin-uptake inhibitory activity was independently confirmed for mesembrine by Professor Alan Harvey of Strathclyde Institute of Drug Research.[13] Mesembrine-HCl has been demonstrated as a weak inhibitor of phosphodiesterase-4 (PDE4).[13] Mesembrine has been demonstrated to be a highly selective inhibitor of the 5-HT transporter (Ki 1.4 nM), while mesembrenone has been demonstrated to be a potent dual inhibitor of the 5-HT transporter and of PDE4 , with the IC50's $<1\ \mu M$. Zembrin®, a proprietary commercial dry extract of *Sceletium tortuosum*, was demonstrated to be a potent blocker in 5-HT transporter binding assays (IC50 4.3 $\mu g/ml$) and had powerful inhibitory effects on phosphodiesterase 4 (PDE4) (IC50 8.5 $\mu g/ml$).[16]

The total crude alkaloid content of *Sceletium tortuosum* is highly variable, ranging from 0.05% to 2.3%.[13,14] The alkaloid content of tablets and capsules of *Sceletium tortuosum* has been reported by Van Wyk and Wink to be in the range of 1–4 mg.[6] While mesembrine has been reported to be a main compound of *Sceletium tortuosum*,[6] the alkaloid composition of *Sceletium* raw material is complex,[13,14] and this is further complicated by reports that post-harvesting interventions such as traditional fermentation may alter the alkaloid composition of dry plant material.[13] It is clear that in order to address the variability in total alkaloid content and alkaloid composition, plant material or extracts used in scientific research on *Sceletium tortuosum* should be conducted on plant material or extracts with a known total alkaloid content, with the alkaloid composition characterized for the major alkaloids present. Since there is documented historical use of tinctures of *Sceletium tortuosum* by colonists of the Cape of Good Hope dating back to at least 1868, [13] aqueous-ethanolic extracts of the plant can be regarded as a useful departure point for further research.

The active ingredient of the investigational product (IP), extract *Sceletium tortuosum* (Zembrin®), is a 2:1 dry aqueous–ethanolic extract of the entire aboveground portions of a cultivated selection of naturally occurring *Sceletium tortuosum* (L.) N.E.Br. of the family Mesembryanthemaceae, with a total alkaloid content not less than 0.38% by weight. The relative amount of the three key mesembrine-alkaloids in the extract, quantified by high pressure liquid chromatography (HPLC) analysis against validated analytical reference compounds, conforms to the profile: mesembrenone + mesembrenol >70%, mesembrine <20%; the minor compound mesembranol is present.

Daily doses of *Sceletium tortuosum* raw material that have been reported to have been safely ingested by humans are very broad, ranging from 50 mg[12] to 5000 mg.[5] It was therefore anticipated that the low doses of extract *Sceletium tortuosum* (Zembrin®) selected for this study—8 mg and 25 mg equivalent to 16 mg and 50 mg respectively of *Sceletium tortuosum*—would be entirely safe and have future potential for inclusion in functional food and dietary supplement products.

To date, there have been no formal safety or efficacy studies in humans of *Sceletium tortuosum* or the investigational product extract. No pharmacokinetic or metabolic studies are known. The primary objective of the study was to evaluate the safety and tolerability of 8 mg and 25 mg once daily of extract *Sceletium tortuosum* (Zembrin®), compared to placebo, in healthy adult volunteers through the measurement of safety assessments.

Materials and Methods

Investigational product

The investigational product, Zembrin®, was an extract of the South African plant *Sceletium tortuosum* (L.) N.E. Br., family Mesembryathemaceae, known as *kanna* in Nama, *kougoed* in Afrikaans, and *Sceletium* in English. The extract Zembrin® lot number was 8587 and was manufactured according to good manufacturing practice (GMP) by the company Gehrlicher GmbH in Eurasburg, Germany. The extract was in the form of a fine dry powder with the dry plant material : extract ratio of 2:1, produced from the dry aerial parts of cultivated plant material extracted in a solvent solution of purified water 30% (V/V) and 70% ethanol, spray-dried, with lactose monohydrate (Eu. Ph.) and colloidal anhydrous silica (Eu. Ph.) as excipients. The raw material for the production of extract Zembrin® Lot 8587 was supplied to the manufacturer in five separate bags respectively numbered 24003B3, 24003B5, 24003B7, 24003B12, and 24003B22.

The identity of representative samples from each bag of raw material was confirmed as *Sceletium tortuosum* by Professor Alvaro Viljoen (Department of Pharmaceutical Sciences, Tshwane University of Technology, Pretoria, South Africa) by examination of representative samples of the raw material organoleptically, by thin layer chromatography (TLC), and by HPLC analysis against validated analytical reference standards for the four main *Sceletium* alkaloids—mesembrenol, mesembrenone, mesembrine, and mesembranol. The extract was standardized to 0.4% W/W total for the four alkaloids mesembrenol, mesembrenone, mesembrine, and mesembranol, with the relative amounts of the three mesembrine-alkaloids conforming to the profile (as quantified by HPLC): mesembrenone + mesembrenol >70%, mesembrine <20%; mesembranol is present in the profile. Figure 1 shows the chemical structures of the four main mesembrine-alkaloids that are quantified to define the alkaloid content and composition of extract *Sceletium tortuosum* (Zembrin®).

Each size 1 hard-shell gelatin capsule contained 0 mg, 8 mg or 25 mg of *Sceletium tortuosum* herb dry extract (plant:extract ratio was 2:1; excipient: lactose, silicon dioxide; extraction solvent: purified water 30% V/V, 70% ethanol 95%, equivalent to 16 mg or 50 mg respectively, of crude *Sceletium tortuosum* herb. Placebo capsules contained no

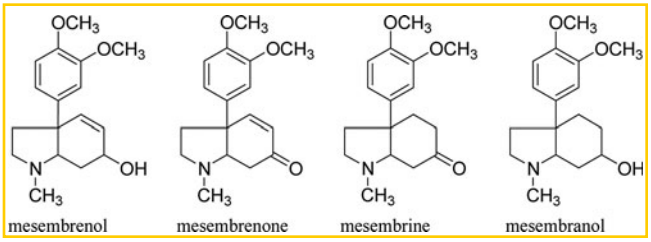

FIG. 1. Four main mesembrine-alkaloids that are quantified to define the alkaloid content and composition of extract *Sceletium tortuosum* (Zembrin®).

herbal extract. The excipients used in the capsules, to give a final capsule weight of 300 mg, were lactose monohydrate, sodium starch glycolate, and magnesium stearate. The capsules were manufactured by Pharmaceutical Contractors (Pty) Ltd., a GMP-certified pharmaceutical manufacturer in Isando, South Africa. A total of one placebo capsule was taken each day for a 2-week run-in period, and one placebo capsule or capsule containing 8 mg or 25 mg of herbal extract for an additional 12 weeks. The placebo and herbal extract capsules were identical in size and were all an identical opaque green color, with no discernible difference in color, odor, or taste between the herbal extract and placebo powders. The individual capsules were not sealed, but because of the large dilution factor with the excipients 8 mg or 25 mg of herbal extract in a total capsule weight of 300 mg, opened placebo capsules and herbal extract capsules appeared identical in color.

Participants

The study was approved by the authors' independent ethics committee and the Medicines Control Council of South Africa, and all subjects provided written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki, guidelines laid down by the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) in clinical trials. The IMP was manufactured according to GMP.

Thirty-seven subjects were screened. All subjects provided written informed consent. There were no screening failures and all subjects were randomized and received IMP. Of the enrolled subjects, 12 were allocated to the extract *Sceletium tortuosum* (Zembrin®) 8-mg group, 12 to the extract *Sceletium tortuosum* (Zembrin®) 25-mg group, and 13 to the placebo treatment group. One subject (placebo group) withdrew from the study at Visit 4 due to an adverse event (AE). Thirty-six subjects completed the study. All randomized subjects were included in the safety analyses. Subjects included were male or nonpregnant females between 18 and 55 years, had a body weight >50 kg and body mass index ranging from 18.5–29.9 kg/m^2, had no clinically significant diseases or clinically significant abnormal laboratory values during pre-study screening, had a 12-lead ECG without significant abnormalities, and were on no regular medical treatment.

Interventions and study design

This was a randomized, double-blind, parallel-group, placebo-controlled single-center study of two doses (8 mg and 25 mg) of extract *Sceletium tortuosum* (Zembrin®) or matching placebo and was performed over a period of 16 weeks per subject. Following written informed consent, subjects were screened for inclusion into the study. The screening visit was followed by a 2-week placebo run-in period during which eligible subjects underwent 2 weeks' placebo treatment and a subject diary. Subjects entered their daily use of placebo medication in the diary in order to assess compliance prior to randomization. Subjects who met all of the inclusion and none of the exclusion criteria were randomized at Visit 3 to one of the three treatment groups for a period of 3 months.

Safety assessments were performed at the screening visit and at Visits 4, 5, and 6 (final visit) and included vital signs, physical examination, laboratory tests (hematology, serum biochemistry, and urinalysis), 12-lead ECG, and recording of AEs.

Visits 3, 4, 5, and 6 were scheduled at monthly intervals (±3 days). Subjects were issued a diary at Visits 2, 3, 4, and 5 and were asked to record the occurrence of AEs, their daily use of study medication, and the intake of concomitant medications.

Sample size

As this was the first formal study in humans, there was no data to perform a formal sample size calculation. It was believed that 12 subjects per treatment group would be sufficient to assess safety and tolerability for this first study in healthy human volunteers. The relatively small sample size is a limitation of this study.

Randomization and blinding

Subjects were assigned a sequential screening number at the screening visit. Eligible subjects were randomized according to a predefined randomization schedule. This was a double-blind study; therefore, investigators, other clinical staff, and subjects were not aware of the treatment schedule allocated to individual subjects, although this information was available in the event of an emergency in a set of sealed emergency code break envelopes.

Statistical Methods

The Full Analysis Set (FAS) comprised of all randomized subjects and was used for all safety analyses. All raw data were listed and sorted by treatment and subject number. For data collected over time, the data were further sorted by visit. Where applicable, variables were summarized by treatment; otherwise, variables were summarized by study visit. Continuous variables were summarized using descriptive statistics: n, mean, standard deviation (SD), median, minimum and maximum, as well as 95% confidence intervals (CIs). Categorical variables were summarized as the number (and percentage) of subjects in each category. Statistical testing was two-sided, and the 5% significance level used in accordance with standard practice. All data were analyzed using SAS® (Version 9.1.3; SAS Institute Inc., Cary, NC).

Data on subject disposition, demography, and other baseline characteristics were summarized descriptively for each treatment. Compliance, determined from the subject's diary data, reflecting each subject's intake of study medication, was listed. Analysis of the safety variables was presented in safety tables that were based on the FAS and summarized by treatment group or study visit.

All AEs were coded to system organ class (SOC) and preferred term, using MedDRA version 12.0. Each AE was analyzed according to the last dose of IMP taken before the onset of the event. Subjects were included only once under each SOC and only once in the overall totals under the most severe event occurrence for each treatment. AE's were also summarized by relationship to IMP, by SOC, and preferred term. A summary of the incidence of serious AEs is presented by event and SOC for each treatment (Table 1).

Table 1. Incidence of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Treatment—Full Analysis Set

	Extract Sceletium tortuosum *(Zembrin)* 8 mg (N = 12)			*Extract* Sceletium tortuosum *(Zembrin)* 25 mg (N = 12)			*Placebo* (N = 13)		
System organ class/preferred term	N	n	(%)	N	n	(%)	N	n	(%)
Subjects with adverse events	4	6	(33.3)	7	14	(58.3)	11	22	(84.6)
Gastrointestinal disorders	1	1	(8.3)	2	2	(16.7)	3	7	(23.1)
Abdominal pain	0	0		0	0		3	5	(23.1)
Constipation	1	1	(8.3)	0	0		0	0	
Diarrhea	0	0		0	0		1	1	(7.7)
Gastroenteritis	0	0		1	1	(8.3)	0	0	
Nausea	0	0		0	0		1	1	(7.7)
Tooth abscess	0	0		1	1	(8.3)	0	0	
General disorders and administration site conditions	0	0		2	2	(16.7)	0	0	
Fatigue	0	0		1	1	(8.3)	0	0	
Irritability	0	0		1	1	(8.3)	0	0	
Immune system disorders	0	0		1	1	(8.3)	0	0	
Rhinitis allergic	0	0		1	1	(8.3)	0	0	
Injury, poisoning, and procedural complications	1	1	(8.3)	0	0		0	0	
Animal bite	1	1	(8.3)	0	0		0	0	
Metabolism and nutrition disorders	0	0		1	1	(8.3)	0	0	
Decreased appetite	0	0		1	1	(8.3)	0	0	
Musculoskeletal and connective tissue disorders	0	0		1	1	(8.3)	1	1	(7.7)
Muscle spasms	0	0		1	1	(8.3)	1	1	(7.7)
Nervous system disorders	2	2	(16.7)	3	5	(25.0)	5	5	(38.5)
Agitation	0	0		1	1	(8.3)	1	1	(7.7)
Headache	1	1	(8.3)	2	3	(16.7)	4	4	(30.8)
Insomnia	1	1	(8.3)	1	1	(8.3)	0	0	
Psychiatric disorders	0	0		1	1	(8.3)	0	0	
Depressed mood	0	0		1	1	(8.3)	0	0	
Renal and urinary disorders	0	0		0	0		1	1	(7.7)
Urinary tract infection	0	0		0	0		1	1	(7.7)
Respiratory, thoracic, and mediastinal disorders	2	2	(16.7)	1	1	(8.3)	7	8	(53.8)
Influenza	1	1	(8.3)	1	1	(8.3)	1	1	(7.7)
Nasopharyngitis	0	0		0	0		2	2	(15.4)
Sinusitis	1	1	(8.3)	0	0		1	1	(7.7)
Upper respiratory tract infection	0	0		0	0		4	4	(30.8)

N = number of subjects; *n* = number of incidences.

Laboratory assessments and results of the pregnancy tests were listed and summarized by treatment and visit. For hematology and biochemistry parameters, values were compared with the respective normal ranges, and those outside the normal range flagged. Shifts from screening to Visit 6 were summarized by treatment. In addition, the observed values at screening, and the observed values and changes from screening at Visit 6 were summarized for all subjects, together with 95% CIs.

For vital signs and body weight, the change from screening to Visits 3, 4, 5, and 6 (body weight) and from screening to Visits 4, 5, and 6 (vital signs) was calculated, listed, and summarized. The change in each of the measured vital signs and body weight from screening to Visit 6 was subjected to an analysis of variance (ANOVA) with a treatment effect. A 95% CI was calculated for the difference in treatment means, for "extract *Sceletium tortuosum* (Zembrin®) 8 mg–Placebo," "extract *Sceletium tortuosum* (Zembrin®) 25 mg–Placebo" and "extract *Sceletium tortuosum* (Zembrin®) 25 mg–extract *Sceletium tortuosum* (Zembrin®) 8 mg." All other safety assessments were listed and summarized appropriately. Shifts in physical examination and laboratory data from screening to Visit 6, and in 12-lead ECG from screening to Visits 4, 5, and 6, were summarized.

Results

Twenty-two (22/37; 59.5%) of the randomized subjects experienced at least one AE during the study. Four (4/12; 33.3%) subjects reported six AEs in the extract *Sceletium tortuosum* (Zembrin®) 8-mg group; seven (7/12; 58.3%) subjects reported 14 AEs in the extract *Sceletium tortuosum* (Zembrin®) 25-mg

Table 2. Results of Statistical Analysis on Change in Vital Signs from Screening to Visit 6: Full Analysis Set

		Least squares mean				
Vital sign (sitting)	*Contrast*	*1st treatment*	*2nd treatment*	*Difference*	*95% CI*	p-*value*
SBP (mmHg)	8 mg–Placebo	0.00	−2.50	2.50	−6.03; 11.03	0.55
	25 mg–Placebo	−5.33	−2.50	−2.83	−11.36; 5.69	0.50
	25 mg–8 mg	−5.33	0.00	−5.33	−13.86; 3.19	0.21
DBP (mmHg)	8 mg–Placebo	1.92	−6.17	8.08	1.51; 14.65	0.02
	25 mg–Placebo	−3.33	−6.17	2.83	−3.74; 9.40	0.39
	25 mg–8 mg	−3.33	1.92	−5.25	−11.82; 1.32	0.11
Pulse rate (bpm)	8 mg–Placebo	2.92	−0.08	3.00	−4.67; 10.67	0.43
	25 mg–Placebo	3.42	−0.08	3.50	−4.17; 11.17	0.36
	25 mg–8 mg	3.42	2.92	0.50	−7.17; 8.17	0.90
Respiratory rate (breaths/min)	8 mg–Placebo	0.17	0.83	−0.67	−2.43; 1.10	0.45
	25 mg–Placebo	1.83	0.83	1.00	−0.77; 2.77	0.26
	25 mg–8 mg	1.83	0.17	1.67	−0.10; 3.43	0.06
Temperature (°C)	8 mg–Placebo	0.08	−0.38	0.47	0.15; 0.78	0.005
	25 mg–Placebo	0.16	−0.38	0.54	0.23; 0.86	0.001
	25 mg–8 mg	0.16	0.08	0.08	−0.24; 0.39	0.63

SBP = systolic blood pressure; DBP = diastolic blood pressure; 8 mg = extract *Sceletium tortuosum* (Zembrin®) 8 mg; 25 mg = extract *Sceletium tortuosum* (Zembrin®) 25 mg.

group; and 11 (11/13; 84.6%) subjects reported 22 AEs in the placebo group (Table 2).

The most commonly reported AE was headache, with eight incidences reported by seven (7/37; 18.9%) subjects. Of these, four incidences occurred in four (4/13; 30.8%) subjects in the placebo group, three incidences occurred in two (2/12; 16.7%) subjects in the extract *Sceletium tortuosum* (Zembrin®) 25-mg group, and one incidence was reported by one (1/12; 8.3%) subject in the extract *Sceletium tortuosum* (Zembrin®) 8-mg group. This was followed by abdominal pain (five incidences in three [3/13; 23.1%] subjects receiving placebo), upper respiratory tract infection (four incidences in four [4/13; 30.8%] subjects receiving placebo), and influenza (three incidences in three subjects, one in each treatment group).

With the exception of two events, all AEs were of mild or moderate intensity. Two (2/13; 15.4%) subjects in the placebo treatment group reported severe AEs: one case of abdominal pain was considered by the investigator as possibly related to IMP, and one case of headache, considered by the investigator as probably related to IMP, led to the withdrawal of the subjects from the study.

Most AEs were considered by the investigator as unrelated to study medication. For the extract *Sceletium tortuosum* (Zembrin®) 8-mg group, one case each of constipation, headache, and insomnia were regarded as possibly related to IMP. For the extract *Sceletium tortuosum* (Zembrin®) 25-mg group, one case each of decreased appetite, muscle spasms, agitation, headache, and depressed mood were considered by the investigator as possibly related to the IMP, with one case of irritability considered as probably related to IMP. In the placebo group, four events (abdominal pain, nausea, agitation, and headache) were regarded as possibly related to study drug administration; one case of headache was assessed as probably related to IMP.

An SAE was reported for one subject during the placebo run-in phase. The subject suffered a rib fracture after a motorcycle accident and was hospitalized. The event was unrelated to study medication and had resolved by the end of the study. One subject in the placebo group withdrew from the study at Visit 4 due to severe intermittent headaches that occurred over a period of 23 days. The event was considered by the investigator as probably related to IMP.

An assessment of the vital signs showed that no trends were apparent for any of the variables for any treatment group. None of the comparisons showed marked differences between the three treatments with regard to the change in vital signs from screening to the end of the study, with the exception of the difference "8 mg–placebo" for diastolic blood pressure (DBP). For the extract *Sceletium tortuosum* (Zembrin®) 8mg group, a mean increase in DBP of 1.92 mmHg occurred from screening to Visit 6, and following placebo, a mean decrease of 6.17 mmHg was observed in mean DBP. This resulted in a mean difference of 8.08 mmHg between these two treatments, with a corresponding 95% CI of 1.51–14.65. This significant difference was not supported by extract *Sceletium tortuosum* (Zembrin®) 25-mg *versus* placebo. Although statistically significant differences were observed for the comparisons "8 mg–placebo" and "25 mg–

Table 3. Positive Effects: Full Analysis Set

Treatment	*Subject*	*Reported*	*Positive effect*
8 mg	S006	Visits 5–6	Subject feels he can cope better with stressful situations
25 mg	S012	Visits 4–6	Subject feels generally in a higher spirit
	S018	Visits 4–6	Better sleeping at night
	S034	Visits 4–6	Subject feels she copes better with depressing situations
Placebo	S005	Visits 4–6	Subject feels better–about 1 level up

8 mg = extract *Sceletium tortuosum* (Zembrin®) 8 mg; 25 mg = extract *Sceletium tortuosum* (Zembrin®) 25 mg.

placebo" for body temperature (p-values < 0.05), these differences (0.47°C and 0.54°C, respectively) were not clinically relevant (Table 2).

Other safety results showed no apparent differences between the three treatments with regard to 12-lead ECG or physical examination findings during the 3-month treatment period, and no significant shifts were observed in laboratory parameters between screening and Visit 6.

There was very little difference between the three treatment groups with regard to the mean change in body weight from screening to Visit 6. None of the comparisons showed any clinically (or statistically) significant differences between either dose of extract *Sceletium tortuosum* (Zembrin®) and placebo with regard to change in body weight over the 3-month study period.

During the course of the study the investigator noted several unsolicited positive comments recorded in the diary cards of five subjects regarding changes in their health. These comments were recorded by one subject (1/12; 8.3%) in the extract *Sceletium tortuosum* (Zembrin®) 8-mg group; three subjects (3/12; 25.0%) in the extract *Sceletium tortuosum* (Zembrin®) 25-mg group; and one subject (1/13; 7.7%) in the placebo group. The comments included sleeping better at night, coping better with stressful situations, and feeling better in general (Table 3).

Discussion

The purpose of this study was to establish the safety and tolerability of 8 mg and 25 mg, once daily, of extract *Sceletium tortuosum* (Zembrin®) in healthy adults through the measurement of safety assessments over a period of 3 months.

It was anticipated that the doses of 8-mg and 25-mg extract used in this study would be safe. These very low daily doses are anticipated to be potentially useful in functional food, beverage, and dietary supplement products. The uses reported for *Sceletium tortuosum* span a very wide range from foodlike uses as simple masticatory and tea and for relief of thirst, hunger, and fatigue; to restorative, mood-elevating, and sedative uses including therapeutic use for treating anxiety and depression. Intoxication and euphoria have also been reported.[13] This spectrum of uses for *Sceletium tortuosum* suggests a dose-response, whereby the lowest doses of active compounds are ingested at the food side of the spectrum of uses, higher doses at the botanical medicine part of the spectrum, 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.

The greatest incidence of AEs reported in the present clinical study occurred in the placebo treatment group, followed by the extract *Sceletium tortuosum* (Zembrin®) 25-mg group, and the extract *Sceletium tortuosum* (Zembrin®) 8-mg group. Headache, abdominal pain, upper respiratory tract infection, and influenza were the most commonly reported AEs. All AEs were of mild or moderate intensity, except one severe case of abdominal pain and one severe headache, both reported in the placebo group. The severe headache led to the withdrawal of the subject from the study. An SAE (rib fracture) was reported for one subject during the placebo run-in phase: this event was unrelated to IMP. There were no apparent differences between the three treatments with regard to vital signs, 12-lead ECG, body weight, and physical examination during the treatment period. No significant shifts were observed in safety laboratory parameters between screening and Visit 6.

Conclusions

For the first time, a randomized, placebo-controlled study has been conducted on the first standardized and characterized extract of the African botanical *Sceletium tortuosum*, extract *Sceletium tortuosum* (Zembrin®), providing an important step toward understanding of the safety of these botanicals in healthy humans.

The results of this study have shown that both extract *Sceletium tortuosum* (Zembrin®) treatments at doses of 8 mg and of 25 mg, once daily for 3 months, were well tolerated. In addition, there were no clinically significant differences between the treatment groups in vital signs, 12-lead ECG, physical examination, and laboratory safety tests.

During the course of the study several unsolicited positive comments were recorded in the diary cards of five subjects regarding changes in their health. The comments were recorded by three subjects in the extract *Sceletium tortuosum* (Zembrin®) 25-mg group, one subject in the extract *Sceletium tortuosum* (Zembrin®) 8-mg group, and one subject in the placebo group. The comments included feeling better in general, coping better with stressful situations, and sleeping better at night. Future clinical studies should be designed to investigate the activity of extract *Sceletium tortuosum* (Zembrin®) on cognitive function, mood, and anxiety.

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Contributors

Drs. H. Nell and N. Gericke made primary contributions to the design and conduct of the study, analysis, and interpretation of results, as well as preparation of the manuscript. Dr. H. Nell, M. Siebert, and Dr. J. Du Bois conducted and controlled the quality of the trial and contributed to the study results. Pashini Chellan contributed to preparation and editing of the manuscript.

Disclosure Statement

Nigel Gericke is the Director, Medical and Scientific Affairs, of HG&H Pharmaceuticals (Pty) Ltd, the company that has developed extract *Sceletium tortuosum* (Zembrin®). The other authors declare that they have no competing interests.

References

1. Smith MT, Crouch NR, Gericke N, et al. Psychoactive constituents of the genus *Sceletium* N.E.Br. and other Mesembryanthemaceae: A review. J Ethnopharmacol 1996;50:119–130.

2. Van Wyk B-E, Gericke N. People's Plants. Useful Plants of Southern Africa. Pretoria: Briza Publications, 2000:351.
3. Rood B. Uit Die Veldapteek. Cape Town: Tafelberg, 1994:115.
4. Smith CA. Common Names of South African Plants. Botanical Survey Memoir No. 35. Republic of South Africa: Botanical Research Institute, Department of Agricultural Technical Services, 1966:642.
5. Watt JM, Breyer-Brandwijk MG. The Medicinal and Poisonous Plants of Southern and Eastern Africa. London: E & S Livingstone Ltd., 1960:1457.
6. Van Wyk B-E, Wink M. Medicinal Plants of the World. Pretoria: Briza Publications, 2004:480.
7. Popelak A, Letterbauer G. The mesembrine alkaloids. In: Manske RHF, ed. The Alkaloids: Chemistry and Physiology, Vol. 9. New York: Academic Press,1967.
8. Herre H. The Genera of the Mesembryanthemaceae. Cape Town: Tafelberg, 1971.
9. Waterhouse G, DeWet GC, Pheiffer RH, eds. Simon van der Stel's Journey to Namaqualand in 1685. Cape Town: Human & Rousseau, 1979.
10. Kolben P. The Present State of the Cape of Good Hope. Vol. 1, 2nd ed. G. Medley (trans.) W. Innys and R. Matiby. London, 1738.
11. Laidler. The magic medicine of the Hottentots. S Afr J Sci 1928;25:433–447.
12. Gericke N. Clinical Application of Selected South African Medicinal Plants. Aust J Med Herbalism 2001;13:3–17.
13. Gericke N and Viljoen AM. *Sceletium*—a review update. J Ethnopharmacol 2008;119:653–663.
14. Gericke N. Plants, products and people: Southern African perspectives. In: Iwu M, Wootton JC, eds. Ethnomedicine and Drug Discovery. Amsterdam: Elsevier, 2002.
15. Gericke N and van Wyk B-E. Pharmaceutical compositions containing mesembrine and related compounds. US Patent 6,288,104, 1999.
16. Alan L, Harvey AL, Young LC, et al. Pharmacological actions of the South African medicinal and functional food plant *Sceletium tortuosum* and its principal alkaloids. J Ethnopharmacol 2011;137:1124–1129.

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