Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Sceletium tortuosum

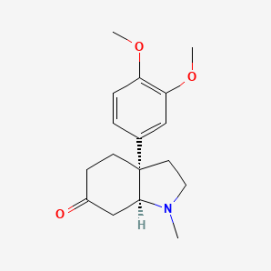
Evidence Summary

Zembrin, a standardized extract of *S. tortuosum*, may improve some complex cognitive functions and mood, though clinical trials to date have been small and short. It is generally well-tolerated.

Neuroprotective Benefit: Small clinical trials suggest Zembrin may improve some complex cognitive functions along with mood/anxiety and sleep in healthy people. To date, there have not been any large or long-term studies or studies in specific diseases.

Aging and related health concerns: No studies have tested the effects of *S. tortuosum* on aging-related diseases that are not associated with the central nervous system.

Safety: Zembrin is generally well-tolerated and adverse event incidence is typically lower than placebo. While *S. tortuosum* has a long history of use in South Africa, no clinical trials have established long-term safety beyond 3 months.

Availability: over the counter	**Dose**: not established; The most commonly tested dose in clinical trials is 25 mg of Zembrin per day, orally.	**Chemical formula:** e.g., Mesembrine: $C_{17}H_{23}NO_3$ **MW**: 289.4 (for mesembrine)  Source: PubChem
Half-life: likely vary across alkaloids; not documented in humans	**BBB**: penetrance not documented	
Clinical trials: The largest clinical trial enrolled 60 healthy men and women.	**Observational studies**: none	

What is it?

Sceletium tortuosum (*S. tortuosum*; also known as *Mesembryanthemum tortuosum* and commonly referred to as "kanna" or "kougoed") is a perennial climbing succulent plant indigenous to South Africa. It has a long history of use in South Africa for spiritual and social purposes with the aim of enhancing sociability, elevating mood, improving general well-being, improving memory, treating alcoholism, improving endurance, reducing fatigue, relieving anxiety and depression, promoting calmness, improving insomnia, quenching thirst and hunger, relieving pain (e.g., headache, toothache), reducing nausea, ameliorating colic, reducing abdominal cramps and constipation, improving asthma, and as a euphoriant or intoxicant at very high doses (Brendler et al., 2021). For example, *S. tortuosum* has been used as a sedative in the form of a tea, decoction, or tincture; local anesthetic or analgesic (e.g., for extracting teeth), or mixed in breast milk to treat colic in infants. The indigenous population used *S. tortuosum* more for recreational purposes than as a therapeutic for a medical condition.

Mesembrine alkaloids are the most studied active ingredients of *S. tortuosum* for their potential psychoactive and other actions. Isolated pure mesembrine is a highly selective inhibitor of the 5-HT transporter (Ki=1.4 nM) and mesembrenone acts as an inhibitor of the 5-HT transporter and phosphodiesterase type 4 (PDE4; IC50s under 1 µM for both)(Harvey et al., 2011). Zembrin, a commercial dry extract of *S. tortuosum*, also potently inhibits the 5-HT transporter (IC50=4.3 µg/ml) and

PDE4 (IC50=8.5 µg/ml). Extracts of *S. tortuosum* also block cannabinoid type 1 receptors (CB1Rs) and the acetylcholinesterase (AChE)(Lubbe et al., 2010), an enzyme that breaks down the neurotransmitter acetylcholine, important for learning and memory.

Neuroprotective Benefit: Small clinical trials suggest Zembrin may improve some complex cognitive functions along with mood/anxiety and sleep in healthy people. To date, there have not been any large or long-term studies or studies in specific diseases.

Types of evidence:

- 5 randomized controlled clinical trials
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

In a randomized placebo-controlled crossover trial of 21 cognitively healthy people aged 45-65, *S. tortuosum* treatment (Zembrin; 25 mg capsule once daily; manufactured according to EU GMP) for 3 weeks improved cognitive set flexibility ($p<0.032$; Cohen's d effect size=1.47) and executive function ($p<0.022$; Cohen's d effect size=1.49) compared with placebo, but did not significantly improve verbal memory, visual memory, processing speed, psychomotor speed, reaction, or complex attention (Chiu et al., 2014). Zembrin treatment did not significantly affect the composite score of the 9 cognitive tests or depression scores (measured by HAM-D). Subjects taking Zembrin reported improvement in the subjective quality of sleep (on the HAM-D subscale) and a positive effect on onset of sleep compared with the placebo group. The *S. tortuosum* extract (Zembrin) was in the form of a fine dry powder with the dry plant material to extract ratio of 2 to 1, standardized to a total alkaloid content for the 4 main sceletium alkaloids (mesembrenone, mesembrenol, mesembrine, and mesembranol) of 0.4%.

In a randomized controlled trial of 60 physically active men and women aged 20-35 (exercised at least 2 days per week), *S. tortuosum* extract treatment (25 mg/day, orally; Zembrin, PLT Health Solutions, Morristown, NJ) for 8 days significantly improved complex reactive performance (which required the subjects to respond to repeated visual stimuli with a cognitive load) compared with placebo (Hoffman et al., 2020). The complex task involved reacting to a moving visual stimulus while saying a 5-digit number (3.63 ± 7.18 hits with Zembrin, 0.23 ± 12.42 hits with placebo). Zembrin treatment was also associated with a significantly higher reactive agility compared to placebo in a task that required decision making

(direction of movement; p<0.001). However, no significant differences between Zembrin and placebo groups were observed for visual tracking performance, motor reaction time, visual reaction time, physical reaction time, anxiety, depression, anger/hostility, vigor, confusion, subjective feelings of alertness, or subjective energy. Overall, Zembrin appeared to improve cognitive functions compared to placebo when a cognitive stress was added to the task, while tasks without cognitive load showed no differences. It is worth noting that in this study, 11 outcomes related to reactive performance and visual tracking, and 9 outcomes related to mood and subjective changes in alertness and energy were assessed, without statistically correcting for multiple comparisons.

In a double-blind randomized placebo-controlled trial of 20 young healthy volunteers with experimentally-induced anxiety, a single dose of *S. tortuosum* (25 mg, orally; Zembrin) ameliorated the anticipatory increase in subjective feelings of anxiety (measured by the State–Trait Anxiety Inventory) prior to a 5-minute simulated public speaking task (Reay et al., 2020). Heart rate showed a treatment x time interaction that indicated a physiological response to the speaking task in the placebo group that was not observed in the Zembrin group. The public speaking task involved a 2-minute preparation period, followed by a 5-minute speech in front of the researcher on why they would be the most suitable applicant for a job of their choosing. Participants were informed that their speech would be recorded and their performance evaluated by a panel of experts. In the same study, a dose of Zembrin had no anxiolytic or cognitive effect on a different kind of experimentally-induced anxiety—a 20-minute multitasking framework (visual warning, mail alert, telephone entry, and math) that is known to elicit cognitive demand, negative affect, and stress. The lack of a treatment effect in the multitasking stressor may be due in part to the low anxiety experienced by the participants with this stressor and the nature of the tasks involved non-executive memory processing.

In a double-blind randomized placebo-controlled trial of 36 healthy adults assessing the safety and tolerability of *S. tortuosum* (8 or 25 mg, once daily, orally; Zembrin, Gehrlicher GmbH, Germany) for 3 months, unsolicited positive effects on well-being were noted in patient diaries by some participants taking Zembrin (Nell et al., 2013). These comments were recorded by 1 subject (8.3%) in the Zembrin 8-mg dose group; 3 subjects (25.0%) in the Zembrin 25-mg dose group; and 1 subject (7.7%) in the placebo group. The comments included sleeping better at night (1 subject receiving the 25-mg dose), coping better with stressful situations (1 subject receiving the 8-mg dose), coping better with depressing situations (1 subject receiving the 25-mg dose), and feeling better in general (1 subject each in the placebo group and the 25-mg dose group).

In a double-blind randomized placebo-controlled crossover study of 16 healthy volunteers, a single dose of Zembrin (25 mg) attenuated amygdala reactivity to fearful faces under low perceptual load conditions (Terburg et al., 2013). Amygdala-hypothalamus coupling was also reduced as measured by a connectivity analysis on the emotion-matching task.

Human research to suggest benefits to patients with dementia:

No clinical trials have tested the efficacy of *S. tortuosum* in people with dementia.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

The primary mechanisms of action of *S. tortuosum* for neuroprotection are inhibition of the 5-HT transporter (IC_{50}=4.3 µg/ml) and PDE4 (IC_{50}=8.5 µg/ml), based on studies of the standardized *S. tortuosum* extract, Zembrin (Harvey et al., 2011). Of the alkaloids, mesembrine showed the strongest inhibition against the 5-HT transporter (K_i=1.4 nM), while mesembrenone was potent against the 5-HT transporter and PDE4 with IC_{50} values under 1 µM for both. Other biological activities of *S. tortuosum* include antioxidant, immunomodulatory, neuroprotective, and neuromodulatory effects (reviewed in Olatunji et al., 2022). The 4 major alkaloids (mesembrine, mesembrenone, mesembrenol, and mesembranol) have been shown in *in vitro* studies to be permeable across porcine intestinal, sublingual, and buccal mucosa (Shikanga et al., 2012).

In a rat model of depression (Flinders Sensitive Line rats), an acute dose of Zembrin (25 and 50 mg/kg, oral gavage) showed significant dose-dependent anti-depressant-like effects, measured by the reversal of immobility in the forced swim test compared to saline treatment (Gericke et al., 2022). The highest Zembrin dose tested (50 mg/kg) was the most effective antidepressant dose, showing equal efficacy to 5 mg/kg escitalopram (oral gavage) in the head-to-head comparison.

In a rat model of stress (repeated restraint stress), *S. tortuosum* extract treatment (5 mg/kg/day, orally) for 17 days reduced stress-induced self-soothing behavior as well as decreased stress-induced corticosterone levels (Smith, 2011). However, these positive effects were also accompanied by increased inflammation, measured by levels of C-reactive protein and prostaglandin E2.

In a rat model of unpredictable chronic mild stress, Zembrin treatment (12.5 mg/kg, orally; HG&H Pharmaceuticals, Johannesburg, South Africa) for 36 days significantly decreased anhedonia- and anxiety-like behavior, decreased cortical and hippocampal PDE4B, and increased plasma IL-10 in male

rats, but did not improve cognitive functions (measured by Barnes maze)(Gericke et al., 2025). The rats were exposed to one stressor per day most days, including cage tilt, removal of bedding, wet cage interior, wet bedding, foreign object exposure, white noise exposure, cage swap with an unknown rat from the same group/sex, pairing with stressed intruder of the same sex, light-dark reversal, restraint stress, and food/water deprivation. The unpredictable chronic mild stress protocol failed to induce depressive and anxiety-like behavioral changes in female rats, and therefore, only the intervention effects in males were presented in the publication. The unpredictable chronic mild stress protocol in male rats increased hippocampal PDE4B concentrations, increased cortical DOPAC (metabolite of dopamine) concentrations, and decreased cortical serotonin concentrations. Mesembrine treatment also transiently decreased anhedonia-like behavior, increased hippocampal serotonergic and cortical dopaminergic activity, and decreased hippocampal PDE4B. Interestingly, a higher dose of Zembrin (25 mg/kg, orally) in stressed male rats increased plasma IL-10 and decreased cortical glutathione (GSH, an antioxidant), suggesting an anti-inflammatory but prooxidant effects.

The effects of Zembrin treatment (5 or 10 mg/kg, daily, orally, for 1 week) in rats were tested *ex vivo* in hippocampal slices and the study found that Zembrin attenuated the AMPA receptor-mediated amplitude of the population spike during electric stimulation as single shock or theta burst stimulation (Dimpfel et al., 2018). Hippocampal slices from Zembrin-pretreated rats showed a lower excitability and lower amplitudes. *In vitro* studies showed that mesembranol and mesembrenol also attenuated AMPA receptor-mediated transmission. The authors speculated that Zembrin may be beneficial as an adjunctive treatment for epilepsy.

In a zebrafish larvae model of Parkinson's disease (exposed to 6-OHDA), neuroprotective and neurorestorative potentials of 3 different *S. tortuosum* extracts were tested: an acid-based extract, methanol extract, and the standardized extract, Zembrin (Lepule et al., 2025). Zembrin showed the most neuroprotective activity by significantly attenuating locomotor deficits and increasing antioxidant activity (measured by total GSH content) when administered concurrently with 6-OHDA. When administered after 6-OHDA insult, the methanol extract showed the most neurorestorative activity by significantly increasing antioxidant activity (total GSH content) and locomotor activity. The methanol extract showed reactive oxygen species-scavenging ability when administered concurrently with 6-OHDA, or 24 hours after 6-OHDA insult. The methanol extract had Δ7-mesembrenone as the major bioactive compound, while the acid-based extract contained higher levels of Δ7-mesembrenone and mesembrine compared to mesembranol and mesembrenone. Zembrin contained mesembrenol, mesembranol, mesembrenone and mesembrine as its major compounds.

In another study of zebrafish larvae, Zembrin at a concentration of 12.5 µg/mL showed the most anxiolytic-like effects and significantly decreased locomotor activity in the light-dark transition test (Gericke et al., 2024). Only the highest concentration of Zembrin (25 µg/mL) showed antidepressant-like properties (measured by the reversal of reserpine-induced effects). Of the different alkaloids tested, only mesembrine showed significant anxiolytic-like effects, while no single alkaloid showed antidepressant-like effects.

In an *in vitro* study, subfractions of *S. tortuosum* scavenged the free radical DPPH and inhibited acetylcholinesterase (AChE), monoamine oxidase type B (MAO-B), and glutamate NMDA receptor-mediated current, suggesting these are possible mechanisms of its neuroprotective effects (Luo et al., 2022). Gene ontology and docking analyses showed that molecular targets of *S. tortuosum* components included AChE, MAO-B, NMDA receptor subunit 2B, adenosine A2A receptor, and cannabinoid receptor 2 (CB2R). Gene ontology terms of biological processes included chemical synaptic transmission, locomotor behavior, memory, learning, response to amphetamine, behavioral response to cocaine, dopaminergic synaptic transmission, and others. Analysis of cellular functions showed that these targets included dopamine binding, dopamine neurotransmitter receptor activity, beta-amyloid binding, and others. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of these targets suggested that *S. tortuosum* components play a role in neuroactive ligand-receptor interaction, serotonergic synapse, dopaminergic synapse, Alzheimer's disease, alcoholism, cAMP signaling pathway, Parkinson's disease, calcium signaling pathway, and amphetamine addiction.

Trimesemine, another proprietary extract of sceletium with a relatively high content of mesembrine (70% stabilized mesembrine w/w, Botanical Resource Holdings [PTY] Ltd), promoted monoamine release (in human astrocytes and mouse hippocampal cells)(Coetzee et al., 2016), downregulated SERT expression similarly to citalopram (Coetzee et al., 2016), exerted cytoprotective, mitoprotective, and anti-inflammatory effects under endotoxin (LPS) exposure (in primary human monocytes) (Bennett and Smith, 2018), and altered glucocorticoid, mineralocorticoid, and androgen production (in human adrenocortical carcinoma cells) (Swart and Smith, 2016).

APOE4 interactions:

Unknown.

Aging and related health concerns: No studies have tested the effects of *S. tortuosum* on aging-related diseases that are not associated with the central nervous system.

Types of evidence:

- 0 clinical trials
- 0 observational studies
- 0 laboratory studies

S. tortuosum has not been studied for peripheral conditions given the mechanisms of action of its active alkaloids.

Safety: Zembrin is generally well-tolerated and adverse event incidence is typically lower than placebo. While *S. tortuosum* has a long history of use in South Africa, no clinical trials have established long-term safety beyond 3 months.

Types of evidence:

- 3 clinical trials
- 1 review
- 1 toxicological study in rats

In a double-blind randomized placebo-controlled trial of 36 healthy adults, *S. tortuosum* (8 or 25 mg, once daily, orally; Zembrin, Gehrlicher GmbH, Germany) for 3 months did not significantly affect vital signs, 12-lead ECG, body weight, physical examination, hematology, or biochemistry parameters compared to baseline or placebo (Nell et al., 2013). Both doses of Zembrin were well-tolerated, and the placebo group had a higher incidence of adverse events than the two Zembrin groups. Four (4/12; 33.3%) subjects reported 6 adverse events Zembrin 8-mg dose group; 7 (7/12; 58.3%) subjects reported 14 adverse events in the Zembrin 25-mg dose group; and 11 (11/13; 84.6%) subjects reported 22 adverse events in the placebo group. The most commonly reported adverse event was headache (30.8% in placebo group, 8.3% in the 8-mg dose group, and 16.7% in the 25-mg dose group), followed by abdominal pain (23.1% in placebo group, 0% with Zembrin), and upper respiratory tract infections (30.8% in placebo group, 0% with Zembrin). With the exception of 2 events, all adverse events were of mild or moderate intensity. Two subjects in the placebo group reported severe adverse events: 1 case of abdominal pain ('possibly related' to the study drug) and 1 case of severe intermittent headache occurring over a period of 23 days ('probably related' to the study drug), led to the withdrawal of the

subjects from the study. For the Zembrin 8-mg dose group, 1 case each of constipation, headache, and insomnia were regarded as 'possibly related' to the study drug. For the Zembrin 25-mg dose group, 1 case each of decreased appetite, muscle spasms, agitation, headache, and depressed mood were considered 'possibly related' to the study drug, with 1 case of irritability considered as 'probably related' to the study drug. In the placebo group, 4 events (abdominal pain, nausea, agitation, and headache) were regarded as 'possibly related' to study drug, and 1 case of headache was assessed as 'probably related' to study drug.

In a randomized placebo-controlled crossover trial of 21 cognitively healthy people aged 45-65 years old, *S. tortuosum* treatment (Zembrin; 25 mg capsule once daily; manufactured according to EU GMP) for 3 weeks was well tolerated and there were no changes in blood pressure, pulse, temperature, or weight (Chiu et al., 2014). Subjects taking Zembrin reported transient gastrointestinal discomfort (9.5%), which was resolved spontaneously and the investigators did not ascribe a direct link to Zembrin. Overall, the placebo group reported more frequent adverse events than the Zembrin group. Common side effects with placebo included mild skin irritation (10%) and weight loss (15%), and interrupted sleep (10%).

In a randomized controlled trial of 60 physically active men and women aged 20-35 (exercised at least 2 days per week), *S. tortuosum* extract treatment (25 mg/day, orally; Zembrin, PLT Health Solutions, Morristown, NJ) for 8 days did not result in any side effects (Hoffman et al., 2020). Compliance for the supplement was 100% among the subjects.

In male and female rats, no mortality or treatment-related adverse effects were observed in the 14- or 90-day oral toxicity studies of Zembrin (Murbach et al., 2014). The 14-day study tested Zembrin doses of 250, 750, 2500, and 5000 mg/kg/day by oral gavage. The 90-day subchronic repeated oral toxicity study tested Zembrin doses of 100, 300, 450, and 600 mg/kg/day by oral gavage. The rats exhibited normal behavior and physical condition with no significant abnormalities in clinical signs. In the 14-day study, slight to moderate transient salivation was observed immediately after administration of Zembrin in all high-dose group female rats, which were regarded as incidental and without toxicological significance because they were of low degree, transient in occurrence, and of short duration (ceasing within a few minutes after administration of Zembrin) and there were no other related findings. The investigators attributed this presentation to a physical or chemical feature of Zembrin, such as taste. There were no observed effects of Zembrin on body weight or food consumption in the 14- or 90-day study. No eye lesions were observed on ophthalmologic examination in any rats (across the 14- and 90-day studies) before or after the treatment period. There were also no remarkable alterations in hematologic or

clinical chemistry measures. The no-observed adverse event levels (NOAELs) for the 14- and 90-day studies were concluded as 5000 and 600 mg/kg/day, respectively, which were the highest doses tested.

Drug interactions:

There are no reports to date of herb-drug interactions with *S. tortuosum* (Brendler et al., 2021). However, based on its mechanisms of action, it should not be used with drugs known to alter serotonin uptake or release, including SSRIs and SNRIs. Other drugs that may interact with *S. tortuosum* based on its mechanism of action include luteolin (a phytochemical) and roflumilast (approved in the US and EU for treating severe chronic obstructive pulmonary disease), both of which inhibit PDE4.

Sources and dosing:

S. tortuosum extract is available over-the-counter as an oral supplement in the forms of tablets, capsules, and tincture. The total crude alkaloid content of *S. tortuosum* is variable, ranging from 0.05 to 3.0% in outliers (Brendler et al., 2021). In South Africa, aerial parts of the plant are masticated or chewed, taken as tea or tincture, and occasionally smoked (reviewed in Olatunji et al., 2022).

Zembrin is a standardized water and ethanol (purified water 30% v/v and ethanol 70% v/v) extract of *S. tortuosum* that contains a total alkaloid content (mesembrenone, mesembrenol, mesembranol, and mesembrine) of around 0.4%. The alkaloid composition should contain greater or equal to 60% of mesembrenone plus mesembrenol and 20% or less of mesembrine (Olatunji et al., 2022). Most clinical trials have tested a Zembrin dose of 25 mg, daily, orally (Nell et al., 2013; Chiu et al., 2014; Hoffman et al., 2020), which is equivalent to 50 mg of dry raw *S. tortuosum* and 100-200 µg of total alkaloids. Zembrin has been investigated in clinical trials for its potential benefits on mood, cognition, and well-being.

Trimesemine is another proprietary extract of sceletium with a relatively high content of mesembrine (70% stabilized mesembrine w/w, Botanical Resource Holdings [PTY] Ltd)(Brendler et al., 2021). Due to the high mesembrine content, it is thought to be more potently antioxidant and anti-inflammatory than Zembrin (Olatunji et al., 2022).

Research underway:

There are no ongoing clinical trials testing *Sceletium tortuosum* based on ClinicalTrials.gov.

Search terms:

Pubmed, Google: zembrin, Sceletium tortuosum

Websites visited for zembrin, Sceletium tortuosum:

- Clinicaltrials.gov
- NIH RePORTER (0)
- Examine.com
- DrugAge (0)
- Drugs.com
- WebMD.com (0)
- PubChem
- DrugBank.ca (0)
- Labdoor.com (0)
- ConsumerLab.com (0)