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Review

Sceletium Tortuosum: Effects on Central Nervous System and Related Disease

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Core tip: *Sceletium tortuosum*, a medicinal plant in South Africa, is used as dietary supplements, natural medicines and health food, which has been confirmed to be active to central nervous system by inhibiting phosphodiesterase isozyme 4, serotonin uptake and acetylcholinesterase. It is a useful therapeutic agent in clinical use.

Abstract:

Sceletium tortuosum is a well-known medicinal plant in South Africa with potential applications. Its raw material, extracts and isolated alkaloids are used as dietary supplements, natural medicines and health food. In this paper, methods of planting, extraction, isolation and identification of *Sceletium tortuosum*, as well as its chemical structure of main extracted alkaloids, their related pharmacological effects and mechanisms for treating the disease are reviewed. In general, *Sceletium tortuosum* is active to central nervous system (CNS) by inhibiting phosphodiesterase isozyme 4 (PDE4), serotonin (5-HT) uptake and acetylcholinesterase (AChE). It also acts as a monoamine releasing agent for antidepressant effects. Therefore, it is a useful therapeutic agent in clinical use.

Key words *Sceletium tortuosum*, alkaloids, phosphodiesterase isozyme 4, 5-hydroxytryptamine, central nervous system.

Dedication: The article is dedicated to summarize the research development of *Sceletium tortuosum* for researchers, who would be interested in the exploitation of its pharmaceutical value.

INTRODUCTION

Sceletium tortuosum (L.) N.E. Br. (abbreviated as *Sceletium tortuosum*), a succulent medical plant in South Africa, is commonly known as *Sceletium* (family Aizoaceae) or by its indigenous name, Kanna. The alkaloids from its extract have medicinal value in clinic use.

In the early days, *Sceletium tortuosum* was found to have anesthesia, sedation and analgesic properties, and widely used by local populace in South Africa. It was also used as a chew for hunter-gatherers and herders to cope with life stress ¹. Later, Japanese veterinary research showed that in the case of clinical diagnosis of dementia, *Sceletium tortuosum* reduced the cage pressure of companion animal cats and the night call of older cats ². The first clinical case report on *Sceletium tortuosum* described its rapid onset of resistance to anxiety and depression ³. Then more and more plant supplements, healthy teas and beverages containing *Sceletium tortuosum* were available through farm stalls, health food stores, pharmacies and internet sales. These products are often used to promote calm and health, relieve stress, boost mood and reduce anxiety. In recent years, study found that it may delay chronic disease progression *via* alkaloid-dependent antioxidant or anti-inflammatory action ⁴. In general, exploring the pharmacological effects and medicinal value of *Sceletium tortuosum* are under way.

PLANTING

Wild type of *Sceletium tortuosum* grew up naturally in the Western, Eastern and Northern Cape provinces of South Africa which generally hidden under other bushes, and a few will grow in the open air. The seeds of the previous generation floated behind and grew moist with rain during the winter, while in the summer, its leaves slowly turned yellow, withered and finally died. When the leaves are green, they are very juicy and can be dried, while the roots can be crushed with rocks, placed in plastic bags, and then mixed and dried. But wild *Sceletium tortuosum* is almost extinct due to excessive picking, and its commercial value prompts people to plant. The commercially available *Sceletium tortuosum* is grown organically in the greenhouse and grown in moist parts of farm ⁵. In addition, Smith ¹ described a rapid *Sceletium tortuosum* planting method in which firewood ash was produced on a small fire, placed on the bottom of the sand hollow, and the freshly picked whole plant was placed in it and covered with hot sand.

EXTRACTION, ISOLATION AND IDENTIFICATION OF ALKALOIDS

Many researchers had tried to extract the alkaloids from the herbal material. The methods could be summarized as follows: The plant material was extracted with ethanol. After filtration and concentration, the extract was acidified with acid solution. The extract was also obtained by using acid solution to extract the plant material straightly.

The acid extract was neutralized with basic solution and then extracted with organic solvents such as ethyl acetate, acetone, acetonitrile, chloroform or dichloromethane. Then the organic layer was evaporated to give a crude alkaloid ⁶.

In general, most studies so far have used Soxhlet extraction to extract alkaloids from plant materials. However, the methods of alkaloid separation are constantly updated with advances in instrumentation and software. Chromatography is an excellent tool for the rapid and effective separation of these alkaloid, including solid-phase supported chromatography, high performance liquid chromatography (HPLC), gas chromatography (GC) and so on ^{7, 8}. In addition, Shikanga developed a more sensitive reversed phase-ultra high performance liquid chromatography-photodiode array (RP-UHPLC-PDA) method which was useful for raw plant materials and commercial products containing *Sceletium tortuosum* alkaloids ⁹. Based on these, Meyers developed a new liquid chromatography-linear ion trap high-resolution mass spectrometry (LC-HR-MSn) method. In addition to the separation and identification of alkaloids in *Sceletium tortuosum*, this method can be used to separate and identify its metabolic components ¹⁰.

Besides chromatographic separation methods, capillary zone electrophoresis analysis was also a tool for analyzing alkaloids in *Sceletium tortuosum*. In the research by Patnala and Kanfer, the mesembrine in *Sceletium tortuosum* products were analyzed by this method ¹¹. Later, Roscher's research proposed a new nonaqueous capillary electrophoresis mass spectrometry (NACE-MS) method which is a powerful tool for separating complex alkaloid mixtures in difficult matrices for forensic analysis of *Sceletium*-containing products ¹².

Currently, the main methods for alkaloid identification include mass spectrometry (MS)¹² and nuclear magnetic resonance (NMR) spectroscopy^{10,13,14}. Most studies have used the separation methods in combination with identification methods, like Gas chromatography-mass spectrometry (GC-MS)¹⁰, liquid chromatography-ultraviolet/mass spectrometry (LC-UV/MS)⁹, liquid chromatography-linear ion trap high-resolution mass spectrometry (LC-HR-MSn)¹⁰ and nonaqueous capillary electrophoresis mass spectrometry¹².

STRUCTURES OF MAJOR ALKALOIDS

The structures of main alkaloids^{3,15} which have been isolated from *Sceletium tortuosum* (Fig. 1). It was reported that they play a major pharmacological role and widely studied.

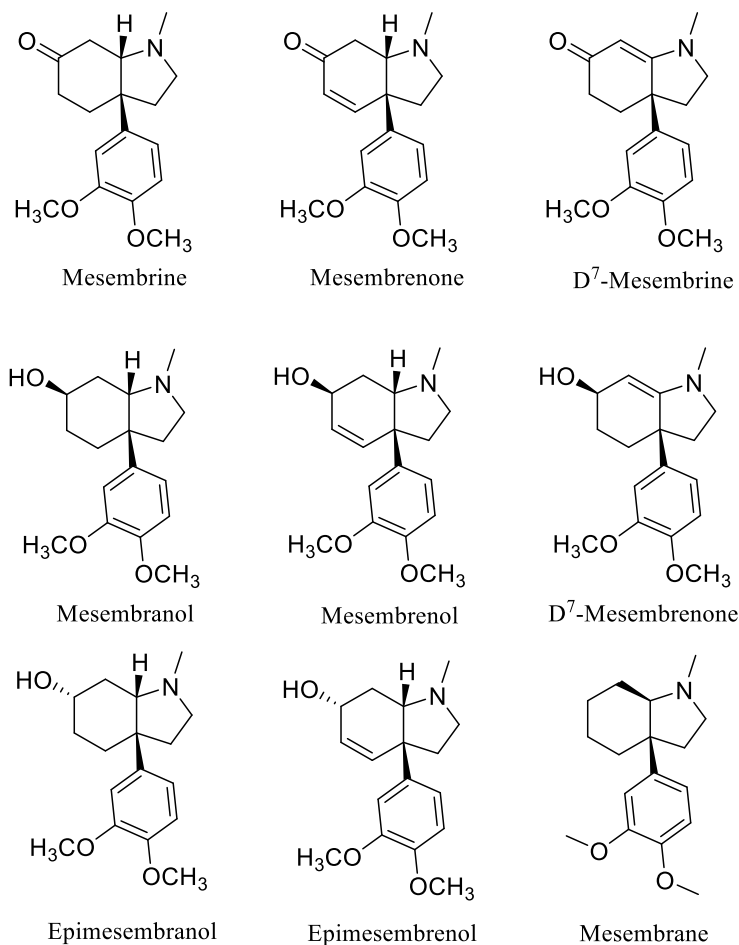


Figure 1 Main alkaloids of the *Sceletium tortuosum*.

Pharmacological Function and Clinical Use

IMPROVE MEMORY AND ENHANCE COGNITIVE FUNCTION

In previous studies, it was determined that *Sceletium tortuosum* was a PDE4 inhibitor with an IC_{50} of 8.5 μ g/mL. The extract, Mesembrenone, was the main alkaloid and also had the activity of inhibiting PDE4 with an IC_{50} value $<1 \mu$ M^{16,17}. It showed *Sceletium tortuosum* has the efficacy of inhibiting PDE4 *in vitro*. A new phenomenon was discovered in the PDE4 knockout animal experiment, that was the extract of *Sceletium tortuosum* improved the memory of rodent species compared with the control¹⁸. Then in nine cognitive domain test experiments, *Sceletium tortuosum* was examined in healthy subjects with composite memory, speech memory, visual memory, processing speed, executive function, psychomotor speed, response, complex attention and cognitive flexibility, which, for the first time, proved that *Sceletium tortuosum* enhances cognition in the field of executive function and cognitive flexibility¹⁹. In fact, there had been reported of the cognitive benefits of PDE4-cAMP-CREB (cAMP-response element binding

protein) signalling ^{20, 21}, therefore *Sceletium tortuosum* had been well-proven for improving cognition.

On the other hand, *Sceletium tortuosum* was also a serotonin inhibitor ^{22, 23}. It was not only effective for memory improvement ²⁴, but may also coordinate with PDE to coordinate age-related cognitive changes ²⁵.

In the quantitative electroencephalogram (EEG) source density combined with eye movement test experiments, it was found that in the presence of *Sceletium tortuosum* in the positive brain, the arithmetic calculation and the resolution of the $\alpha 2$ spectral power of cerebral palsy were increased ²⁶. The $\alpha 2$ power had been used to differentiate patients with mild cognitive impairment during memory tasks, while $\alpha 2$ power was associated with stored procedures, which increased memory storage and improved cognitive impairment ²⁷⁻²⁹. Therefore, *Sceletium tortuosum* improved memory and enhances cognition by increasing the $\alpha 2$ spectral power. Because Alzheimer's disease also has significant barriers to memory and cognition, whether *Sceletium tortuosum* can delay or reverse age-related cognitive decline and Alzheimer's disease process will be a new research direction.

ANALGESIC EFFECT

Sceletium tortuosum was used by South African people for anesthesia, sedation and analgesia very early ³⁰, but it was not studied in depth at that time until the extraction of alkaloids-mesembrine from *Sceletium tortuosum* had been found to have analgesic effects in the hot plate experiments in which compared with the reference compound morphine, the alkaloid components of *Sceletium tortuosum*, Mesembrine could increase hot plate delay, appeared to have analgesic properties without abuse liabilities or ataxia ³¹.

Saura and Valero *et al.* observed the changes in the electroencephalogram (local field potential) after alkaloids-mesembrine administration, and found that the reduction of θ waves associated with the attenuation of δ , $\alpha 2$ and $\beta 1$ ²¹ further proved its analgesic effect. Then the results of using the quantitative EEG source density combined with eye tracking on the psychophysiological effects of 60 healthy subjects showed that the data of *Sceletium tortuosum* was projected into the vicinity of another sedative and Ginkgo ginseng mixture ³², proved that *Sceletium tortuosum* had a certain analgesic effect.

The analgesic effect of *Sceletium tortuosum* naturally raised concerns about addiction, but surprisingly, unlike cocaine, the role of *Sceletium tortuosum* did not seem to cause addiction or hallucinations ³³, hence it had a good medicinal significance. Then the scientists immediately conducted research, and the results were exhilarating. The high extract of *Sceletium tortuosum* was not only a selective serotonin reuptake inhibitor (SSRI), but also a monoamine releasing agent ³⁴. It played a role as a monoamine releasing agent (MRAs), like other MRAs, for example, cocaine and sertraline could exert analgesic effects by blocking the serotonin transporter (SERT) ³⁵. Interestingly, the addiction effect of cocaine and its dual inhibition of SERT and dopamine transporter (DAT) were not applicable in *Sceletium* extracts ³⁶. *Sceletium* extract and the pharmacological studies of the key alkaloids mesembrine, mesembrenone and mesembrenol reported that it only blocked the SERT but had no significant inhibitory effect on the DAT ¹⁷. The role of *Sceletium tortuosum* did not cause addiction, so mesembrine product may have the potential to be developed as a therapeutic adjuvant for the treatment of cocaine addiction.

ANTI-STRESS EFFECT

Long-term life stress can translate into chronic physical and mental illness. Over the past 15 years, more and more healthy individuals were using *Sceletium* products, including teas, tinctures, tablets, capsules, and raw powdered plant material to promote well-being and relieve stress. In the peripheral compartment, Bennett *et al.* had shown the *Sceletium tortuosum* extract to inhibit adrenal steroidogenesis *via* inhibition of CYP17, 3 β HSD and 17 β HSD, suggesting beneficial therapeutic potential in conditions of stress ³⁷.

SLEEP FUNCTION

Studies had shown that the extract of *Sceletium tortuosum* had a good safety and tolerance to sleep quality ³⁸. Emerging evidence suggested that the PDE4-cAMP-CREB signaling cascade played a crucial role in regulating sleep-wake cycles and affective regulation, and *Sceletium tortuosum* had been found improve sleep by acting as a PDE4 inhibitor in this signaling cascade¹⁹. In the sleep deprivation model, sleep deprivation for 5 hours in C57BL/6J mice showed selective damage to cAMP/phosphokinase A-dependent synaptic plasticity, resulting in long-term potentiation (LTP) in the hippocampus ³⁹, while taking *Sceletium tortuosum* improved subjective quality of sleep on the Hamilton Rating Scale for Depression (HAM-D) subscale compared with model group mice and it was safe and well tolerated ²⁰.

ANTI-ANXIETY EFFECT

Sceletium tortuosum was used as medicine and health care product in South Africa, in part because people had always recognized its anti-anxiety effect. People had long known that gamma-aminobutyric acid (GABA) and δ -opioid receptor agonists have an anxiolytic effect ⁴⁰⁻⁴³, while *Sceletium tortuosum* appeared to affect γ -aminobutyric acid and opioid receptors at higher doses to produce anxiolytic effects ¹⁷. In addition, the chick anxiety depression model and the psychological stress model ^{44,45} had verified that it did have the effect of relieving anxiety, but might have some side effects.

In a pharmacological functional study, a single dose of 25 mg of *Sceletium tortuosum* was found to reduce the amygdala's reactivity to fearful faces under low perceptual load conditions. Subsequent connectivity analysis of the emotional matching task showed that the amygdala-hypothalamus coupling was also reduced. These results firstly demonstrated that *Sceletium tortuosum* could play an anti-anxiety role by attenuating the threat circuitry of the human brain, and this effect may be related to its dual 5-HT reuptake inhibition and PDE4 inhibition ⁴⁶.

In experiments using quantitative EEG source density combined with eye tracking of the psychophysiological effects of healthy subjects, the results reflected an increase in $\alpha 1$ spectral power with the treatment of *Sceletium tortuosum*. Higher spectral $\alpha 1$ power indicated relaxation and a higher degree of calm to slow the effects of anxiety, hence *Sceletium tortuosum* seemed to have the effect of anti-anxiety ³².

It has been known that when we feel anxious and stressed, the hormones in our body will change accordingly. Similarly, disorders of hormones in the body (such as glucocorticoids and sterols) can also affect our emotions. Anxiety is a form of realizing emotions. Recently, it has been discovered that extract of high mesembrine in *Sceletium tortuosum* can exert anxiolytic effects by affecting related hormone levels. Studies have shown that alkaloids can regulate glucocorticoid and aldosterone production under simulated stress conditions and can be used to treat stress and anxiety ⁴⁷.

ANTI-DEPRESSANT EFFECT

Early on, the prototype PDE4 inhibitor rolipram showed antidepressant activity in animals ⁴⁸ and clinical patients ⁴⁹. More and more animal studies have also confirmed that PDE4 inhibitors may be used to treat depression ⁵⁰ while 5-HT reuptake inhibitors are also widely used in depression ⁵¹. Therefore, *Sceletium tortuosum*, a SSRI and PDE4 inhibitor, produce synergistic therapeutic potential in CNS disorders while providing greater symptomatic efficacy and broader therapeutic utility than the drug itself? The answer is: yes. Since studies had shown that repeated treatment with SSRIs can upregulate PDE4 ⁵², which in turn reduced sensitivity to long-term treatment of SSRIs, allowing both SSRIs and PDE4 to perform better and reduce side effects. This result suggests that dual treatment with SSRIs and PDE4 inhibitors may be a promising approach ⁵³. Then this assumption was verified by Perrine *et al.* in their experiments. In two separate functional magnetic resonance imaging design experiments, *Sceletium tortuosum* was used as a dual inhibitor of SSRI and PDE4, showing reduced anxiety-related amygdala reactivity and amygdala-hypothalamic coupling compared with placebo which supported the further study of the clinical application of dual PDE4 and 5-HT reuptake inhibitors in the treatment of anxiety and depression ⁴⁰.

In the spectral local field power electron map of *Sceletium tortuosum* acting on rats, it was found that *Sceletium tortuosum* dose-dependently induced attenuation of all frequency ranges to varying degrees and produced antidepressant activity at higher doses ²¹. However, in another experimental study, the extract of *Sceletium tortuosum* did have antidepressant properties, but it produced ataxia, which would affect its development as an antidepressant drug ²⁴. It is also worth noting that *Sceletium tortuosum* dose-dependently induces attenuation in all frequency ranges, with a significant statistically significant decrease in the $\alpha 2$ and $\beta 1a$ waves, which are associated with activation of dopaminergic and glutamatergic emission systems, respectively. The strong influence is a reduction in the frequency range of δ and θ , which are associated with changes in cholinergic and norepinephrine systems, respectively, which are associated with neurodegenerative diseases and may warrant further investigation.

Recent study found that the high membrane extract of *Sceletium tortuosum* up-regulated the vesicular monoamine transporter-2 (VMAT-2) ³⁴ to promote monoamine release and slightly inhibit the activity of type A monoamine oxidase (MAO-A). Its slight inhibition not only produced antidepressant effects, but also reduced chronic lung toxicity, excessive side effects associated with monoamine releasing agent-methylene dioxymethamphetamine (MDMA) leading to death and other side effects. Therefore, it has good medicinal value ⁵⁴⁻⁵⁶. In addition, MAO-A inhibition reduced intracellular monoamine breakdown and has been shown to be effective in the treatment of neurodegenerative diseases such as depression, Alzheimer's disease and Parkinson's disease ^{37,57}. Recent reports indicated that the potential therapeutic efficacy of *Sceletium tortuosum* for depression treatment depends at least in part on the down-regulation of pro-inflammatory signals associated with increased mitochondrial activity, and studies have also found that it up-regulated interleukin 10 (IL-10) release, reduced inflammation, down-regulated lipopolysaccharide (LPS) and promoted mitochondrial survival, which helps to attenuate cytokine-induced depression, as well as systemic low-grade inflammation. Since LPS levels are elevated not only in pathogenic infections, but also in chronic diseases such as Alzheimer's disease, *Sceletium tortuosum* may play an important role in chronic diseases by regulating LPS levels ⁵⁸.

ANTI-EPILEPSY EFFECT

Study have found that alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA) receptors have a glutamate binding site and mediate glutamate-related signals and AMPA-mediated attenuation is associated with successful adjuvant therapy in patients with epilepsy ⁵⁹. In the latest study on the effects of *Sceletium tortuosum* and its four alkaloids on hippocampal electrical excitability, it was found that *Sceletium tortuosum* and its alkaloids acted on AMPA-mediated transmission to prevent seizures ⁶⁰.

SUMMARY

Natural products are a rich source of new therapeutic agents. Based on the extraction, isolation, identification, and pharmacological research on the alkaloids from *Sceletium tortuosum*, suggestion is given to more animal preclinical and clinical researches on it. *Sceletium tortuosum* and its alkaloids can act as PDE4 and 5-HT inhibitors to improve memory and improve cognition. It acts as an anti-anxiety and anti-depressant synergist as a PDE4 and serotonin reuptake inhibitor, and also acts as a monoamine releasing agent to slightly inhibit monoamine oxidase type A activity. It regulates anxiety by regulating related hormones and produces antidepressant activity. At high doses combined with GABA and opioid receptors, it can relieve anxiety symptoms.

Sceletium tortuosum improves sleep quality by regulating the sleep-wake cycle by regulating the PDE4-cAMP-CREB signaling cascade. It also reduces pain-related δ , $\alpha 2$ and $\beta 1$ attenuation associated θ waves to exert analgesic effects and does not produce addiction due to non-inhibition of dopamine transporter. In addition, it has a certain potential for epilepsy treatment because of its action on AMPA-mediated transmission.

Sceletium tortuosum may be involved in a variety of neurodegenerative diseases, chronic diseases, for the targeting of the central nervous system. The related pharmacological effects have been demonstrated by experiments. It has played a certain role in neurological diseases.

The alkaloids of *Sceletium tortuosum* exerted cellular protective and anti-inflammatory effects and exhibited effective antioxidant effects to maintain the integrity of the central nervous system, which may be employed as either a preventative supplement or complimentary treatment in the context of obesity and diabetes ⁴.

Nowadays, people face increasing levels of stress, anxiety, insomnia and depression. Particularly, the aging people are susceptible to have diseases such as cognitive memory disorders, Alzheimer's disease, vascular dementia, Parkinson's disease and so on. Excitingly, animal and human studies of *Sceletium tortuosum* have showed an excellent safety profile. At the same time, preliminary human studies and clinical experience have shown its therapeutic efficacy in anxiety, depression, cognitive impairment and so on. Therefore, *Sceletium tortuosum* will be a potential drug candidate which is worthy of further research and development in pre-clinical and clinical trials.

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Abbreviations:

CNS: central nervous system; PDE4: phosphodiesterase isozyme 4; 5-HT: serotonin; AChE: acetylcholinesterase; HPLC: high performance liquid chromatography; GC: gas chromatography; RP-UHPLC-PDA: reversed phase-ultra high performance liquid chromatography-photodiode array; LC-HR-MSn: liquid chromatography-linear ion trap high-resolution mass spectrometry; NACE-MS: nonaqueous capillary electrophoresis mass spectrometry; MS: mass spectrometry; NMR: nuclear magnetic resonance; LC-UV/MS: liquid chromatography-ultraviolet/mass spectrometry; CREB: cAMP-response element binding protein; EEG: electroencephalogram; SSRI: selective serotonin reuptake inhibitor; MRAs: monoamine releasing agent; SERT: serotonin transporter; DAT: dopamine transporter; LTP: long-term potentiation ; HAM-D: Hamilton Rating Scale for Depression; GABA: gamma-aminobutyric acid; VMAT-2: vesicular monoamine transporter-2; MAO-A: type A monoamine oxidase; MDMA: methylene dioxymetham-phetamine; IL-10: interleukin 10; LPS: lipopolysaccharide; AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid.