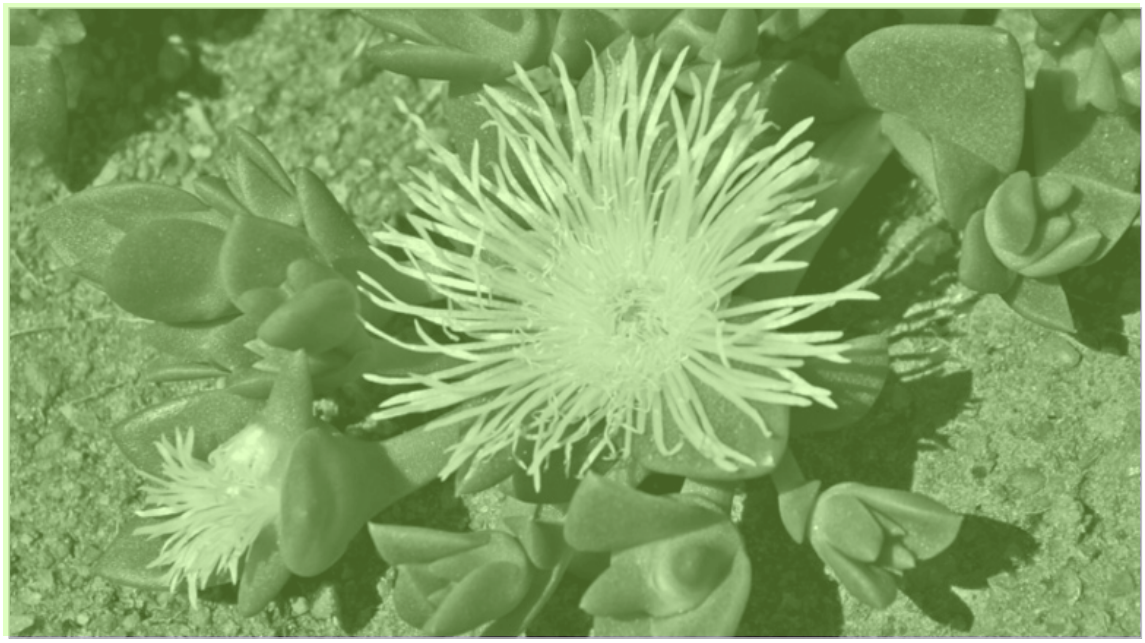
Kabbo's !Kwaiń: The Past, Present and Possible Future of *Kanna*

Nigel Gericke, MD

Founding Director of HG&H Pharmaceuticals (Pty), Ltd., Bryanston, South Africa

Gericke, N. Kabbo's !Kwaiń: The Past, Present and Possible Future of Kanna, pp. 122-150, in McKenna, D. et al. (Eds.) 2018. The Ethnopharmacological Search for Psychoactive Drugs. Synergetic Press, Santa Fe. ISBN-13: 978-0907791683



Flower of a low-mesembrine Sceletium cultivar.

ABSTRACT

PART I

The history of the use of *kanna*, the traditionally used plant material derived from a number of Sceletium species, is given from 1610-1971. This overview includes fragments of history documenting European ships docking in the Cape to search for *kanna* roots as a "ginseng" to trade in the Far East, and an ethnographic record from the 1700s transcribed directly from //Kabbo, a /Xam San "Bushman" from the Breakwater Convict Station in Cape Town, who gave us the name *!k"wai* for *kaauwgoed*, the Dutch name for *kanna*, and his own account of the uses of the plant.

Part II

The recent ethnobotany, ethnopharmacology and pre-clinical research on a commercialized standardized extract of Sceletium (trademarked Zembrin®) is given for the period 1995 to 2017. *In vitro* studies have demonstrated that the major alkaloids of *kanna*, including mesembrine, mesembrenone and mesembrenol, are responsible for the psychoactivity of Sceletium, and have dual serotonin reuptake inhibitory (SRI) activity and phosphodiesterase-4 (PDE4) inhibitory activity. The effect of the extract of *Sceletium tortuosum*, Zembrin®, on brain electrical activity has been studied *in vivo*, demonstrating by discriminant analyses that the quantitative EEG electropharmacogram of the extract plots in close proximity to the plots for *Ginkgo biloba*, *Rhodiola rosea*, and also to the first-generation pharmaceutical PDE4 inhibitor Rolipram, indicating the potential of this extract for managing anxiety and depression and enhancing cognitive function.

Part III

Clinical experience with Sceletium is summarized and the results of pilot randomized, double-blind, placebo-controlled clinical studies on the extract of *Sceletium tortuosum*, Zembrin®, are presented, including:

- A safety and tolerability study.
- A pharmaco-Magnetic Resonance Imaging study.
- A study on cognitive function domains using CNS Vital Signs, a computerized neurocognitive test battery.
- A study looking at changes in brain electrical activity in response to cognitive and emotional challenges; changes in psychometric tests; and changes in the Hamilton Anxiety Scale (HAM-A).

Part IV

Scenarios on the future of *kanna* and alkaloids derived from *kanna* are considered.

Folk names for traditionally used Sceletium species

kanna	Nama-speaking Khoikhoi people. Sometimes also written *canna* and *channa*.
kougoed	Afrikaans-speaking people of European or mixed descent, derived from the earlier Dutch *kaauwgoed* or *kauwgoed*, meaning “chewing stuff.”
!k”waï	Also *!k”wai:n.* /Xam-speaking San people. This language is now extinct.

BOTANY

The genus Sceletium of the Family Aizoaceae, Mesembryanthemoideae, is characterized by the distinctly skeletonized leaf venation visible in dried older leaves. Sceletium is a genus with a climbing, or decumbent, habit and succulent leaves that sometimes have prominent idioblasts, or bladder-like cells. The flowers range from white or yellow to pale pink. The fruit capsules contain numerous very small kidney-shaped seeds, brown to black in color.

The genus is distributed in the arid southwestern parts of South Africa, including parts of three provinces: Northern Cape Province, Western Cape Province, and Eastern Cape Province. The plant populations and individual plants are typically widely scattered, but in the *Kougoedvlakte* (literally translated as “Chewing Stuff Plains”) of Namaqualand in the Northern Cape Province, and in the *Kannaland* district (literally, “The Land of Kanna”) in the Western Cape Province, the plants were once locally abundant and traded widely.

Klak et al. (2007) proposed a single genus, Mesembryanthemum, that includes members of the genus Sceletium. However, for the purpose of this paper, the use of the genus Sceletium is retained, and the genus Mesembryanthemum (sometimes spelled Mesembrianthemum in former times) is used when quoting historical texts.

The taxonomy of Sceletium is complex, and will hopefully become clearer when species based on standard plant morphological features can be interpreted in the light of DNA-bar coding and plant chemistry. Eight Sceletium species are recognized in the revision by Gerbaulet (1996):

Sceletium tortuosum (L.) N.E. Br.
Sceletium crassicaule (Haw.) L. Bolus
Sceletium emarcidum (Thunb.) L. Bolus ex H.J. Jacobson
Sceletium exalatum Gerbaulet
Sceletium expansum (L.) L. Bolus
Sceletium rigidum, L. Bolus
Sceletium strictum L. Bolus
Sceletium varians (Haw.) Gerbaulet.

To illustrate the taxonomic complexity at the species level, the following synonyms have been used for *Sceletium tortuosum* (L.) N.E.: (Nortje, 2011).

Mesembryanthemum aridum Moench
Mesembryanthemum concavum Haw.
Mesembryanthemum tortuosum L.
Pentacoilanthus tortuosus (L.) Rappa and Camorrone
Phyllobolus tortuosus (L.)Bittrich
Sceletium boreale L. Bolus
Sceletium compactum L. Bolus
Sceletium concavum (Haw.) Schwantes
Sceletium framesii L. Bolus
Sceletium gracile L. Bolus
Sceletium joubertii L. Bolus
Sceletium namaquense L. Bolus var. *namaquense*
Sceletium namaquense L. Bolus var. *subglobosum* L. Bolus
Sceletium ovatum L. Bolus
Sceletium tugwelliae L. Bolus

Part I

Historical reports, 1610 - 1971

Early visitors to the Cape of Good Hope in the 17th century frequently emphasized the value attached to *kanna*. The captains of trading ships en route to the East Indies thought of the roots of *kanna* as a Cape ginseng, and also called it *ningin* root or *ningimm* root, a corruption of vernacular names used for the ginseng root they had seen in Japan and China. Ships of the East India Company, stopping off at the Cape en route to Japan to stock up on fresh water, fruit and vegetables, were instructed to search for the roots as a valued item for trade.

1610

The English East Indiaman *The Globe*, under the command of Captain Hippon, stopped to replenish water supplies at the Cape of Good Hope en route to the East Indies. Captain Hippon's lieutenant, Peter Floris, reported:

> Being by Gods grace here arrived, wee presently fell to the ordering of the shippe, and hooping of our caske to fill freshe water, for much refreshing was not here to bee had att this tyme of the yeare, by the greate quantitie of rayne, being now in the chiefeste of winter so that the mountains laye covered with snowe : during which tyme wee used great diligence in seeking of the roote Ningimm according to our instruction, the aforesaid 2 Holland shipps being expressly come thether for the same purpose, being one of Japan that first discovered the secret; butt, being winter tyme, there was for this tyme no more to bee done but to go awaye as wyse as wee came, for the olde roote

being decayed and rotten, the new leaf began onely to come foorth, so that had it not bene by reason of some information that was gotten of one who here shalbee nameles for dyvers considerations sake, wee shoulde have bene fayne to have departed without notice thereof, the right time of gathering the same being in December, January, and February, being called by the inhabitants Canna. (Moreland, 1934)

1615

Purchas 1625: Saldanha Bay, approximately 130 kilometers north of the Cape of Good Hope: "The Countrey people brought vs downe of the Root Ningin, whereof wee bought one handful for a piece of Copper an inch and halfe broad, and two inches and halfe in length. Our men got [some], but not [so] full, nor ripe, this being not the [season], which in the full perfection is as tender and [sweet] as [anise seeds]. On the twentieth wee [set sail]." "Ningin, a medicinable root much prized in Japan" .

1660

"It was the control over fields of canna that made the Inqua king Hijkon "chief lord of all kings and potentates", for he was one of the patrons whose power flowed from the precious canna that grew in the desert" (Gordon, 1996, quoting from Jan van Riebeeck's journal, 21-22 Sep. 1660, from the Archives of the Nederlandsche Oost-Indische Compagnie).

1662

In 1652, the Vereenigde Oost-Indische Compagnie or VOC (the Dutch East India Company), founded a refreshment and recuperation station at the Cape of Good Hope for the benefit of the crews of its fleets trading between Europe and Asia. The station was to supply fresh fruit and vegetables, meat and clean water to the VOC ships whose crews were decimated by scurvy during the long ocean voyages. In 1662, the first commander of this station, Jan van Riebeeck, received *kanna* and sheep from the indigenous people in exchange for gifts, and pronounced that *kanna* is similar to Chinese ginseng (Smith, 1966).

1685

Dutch expedition to Namaqualand (Gericke, 2014)

In 1657, the first commander of the VOC's refreshment station at the Cape, Jan van Riebeeck, heard from an indigenous interpreter that the copper in indigenous tribal earrings and beads came from the Namaqua, a tribe of pastoralists who lived to the north of the Cape. Between 1659 and 1663, seven expeditions were dispatched north to the land of the Namaquas to look for copper and any other riches, but they all failed, unable to penetrate through the mountainous and difficult terrain. In 1679, Simon van der Stel was appointed commander of the settlement at the Cape of Good Hope by the VOC, and concerned himself with the development of agriculture and viticulture and the improvement of the company's botanical and herbal garden. In April 1682, some Namaqua people visited the VOC fort at Table Bay with pieces of good quality copper ore. Expeditions sent north to find the source of the copper ore failed, unable to cross the mountainous terrain.

In 1685, Hendrik van Rheede tot Drakenstein, a VOC commissioner, arrived at the Cape and gave Commander van der Stel permission to personally lead an expedition to find the Copper Mountains. In addition to the search for copper, the expedition was charged with cultivating friendly relations with the Namaquas, describing the country, and documenting useful plants. The expedition, which left the Cape of Good Hope on 25 August 1685, was a major undertaking. The party included van der Stel as commander, his three slaves, fifty-six people of mainly European extraction, a prince from Makassar (now within Indonesia), forty-six local people of mixed ancestry as drivers and leaders for the wagon train and accompanying stock animals, and a number of Khoikhoi translators. The expedition included a carriage, seven wagons, eight carts, a boat for river crossings, and two small cannon. Technical specialists accompanying the expedition included a navigator, a mineralogist, and the apothecary and artist Heinrich Claudius, who also served as the expedition's cartographer. Claudius had been sent to the Cape from Batavia in the East Indies to collect botanical specimens for a private collector, and was then retained at the Cape by the VOC on account of his exceptional abilities as naturalist and artist.

It is not known what became of the original journal of the 1685 expedition, or of Claudius' original drawings, but copies of excerpts from the expedition journal and accompanying drawings were made shortly after the expedition. One of the copies of the journal is in the collection of Trinity

College Library, Trinity College MS. 984 (TCMS), and is thought to have been removed from the Archives of the Dutch East India Company in 1691 or 1692. TCMS includes seventy-one pages of coloured drawings believed to be the work of Heinrich Claudius, with descriptive text on alternate folios. The drawings include two landscapes within the Copper Mountains, a Namaqua man and woman, forty-three plants, eleven birds, nine reptiles, one fish and eight insects. Watercolor copies of Claudius' drawings are in the collection of the Iziko South African Museum in Cape Town, known as the Codex Witsenii (CW). These copies were made in 1692 for Nicolaas Witsen, a prominent citizen of Amsterdam and a director of the Amsterdam Chamber of the VOC. A third manuscript on the expedition, written by Jan Commelin (JCMS) about 1687, is held by the Staatsbibliothek Kuturbesitz, Berlin, as ms. germ. qu. 238.

The journal entry in TCMS, which accompanies a fine painting easily recognized as Sceletium and including the flower and skeletonized lower leaves, states:

> This plant is found with the Namaquaas and then only on some of their mountains. It is gathered in October and is called Canna. It is held by them and the surrounding tribes in as great esteem as the betel or areca with the Indians. They chew the stem as well as the roots, mostly all day, and become intoxicated by it, so that on account of this effect and its fragrance and hearty taste one can expect some profit from its cultivation. Found on the 20th October. (Waterhouse et al., 1979)

The journal entry in Codex Witsenii, accompanying a copy of the painting of Sceletium, states:

> This is from the Namaquas and also other nations the famous *kanna*, which they carry in the mouth daily and chew, as the Indians do with Areca, and who do it often can easily get drunk from it, it is held in great esteem by them, like all things that corrupt the mind, and make drunk. And that there is something particular in these plants is seen not only from the activity, but also the pleasant and cordial taste, are found nowhere but on certain mountains in the country of the Namaqua and collected in October; found 20 October 1685.

1686

Guy Tachard (1651–1712), also known as Père Tachard, was a French Jesuit missionary and mathematician of the 17th century who was sent on two occasions to the Kingdom of Siam by Louis XIV, and en route spent time at the Cape of Good Hope. Translated from the original French,

> This captain, pleased with his gifts, sent us in gratitude two fat tail sheep, each tail weighing more than twenty pounds, with a large vessel full of milk, and a certain herb which they call Kanna, it is apparently this famous plant that the Chinese call Ginseng; for Monsieur Claudius, who has seen it in China, asserts that he had found two plants at the Cape, and shows us the whole figure which he had painted in nature." (Tachard, 1686)

1726

François Valentijn was a Dutch minister, naturalist and author. In his Beschryvinge van de Kaap der Goede (Descriptions of the Cape of Good Hope), he noted that the "Canna of the Hottentots closely resembles the Chinese root Nisi or Ginseng" (Serton, 1971).

1731

Peter Kolben was sent to the Cape of Good Hope with letters of introduction from the mayor of Amsterdam, with a mandate to compile a comprehensive description of South Africa for geographical research and surveying. He wrote detailed accounts of the geography, climate, flora and fauna, followed by a study of the indigenous Khoi people (called Hottentots at that time), covering their language, religion, lifestyle and customs:

> There is a Root, gather'd in the *Hottentot* Countries, called Kanna; which is in [such Esteem] among the *Hottentots* for its great vertues that they almost adore it. What greatly enflames the Value of this Root, is its Scarcity; for 'tis very rarely found. They look upon

> it as the [greatest] Chearer of the Spirits, and the [noblest] Restorative in the world. They will give [almost] any Thing in Exchange for it; and will, any of 'em, run Twenty Miles upon an Errand, or perform a hard Day's Work, for a very small Bit of it. With a piece of Kanna you may manage 'em [almost] in any Manner you [please]. You win their hearts Forever by [presenting] them with the smallest Chip of it; and they will run, fetch and carry for you like your Slaves, under [so] charming an Obligation…I have often [seen] the Effects of *Kanna* upon *Hottentots*. They chew and retain it a [considerable] Time in their Mouths. But taking generally too much of it at a Time, it drowns 'em in Intoxications. They chew it not long, before their Spirits [visibly] [rise], their Eyes brighten, their Faces take a jovial Air, and they [Sport] and wanton under a [thousand] Gaieties of Imagination. But in the End it [Strips] 'em of their [Senses], and throws 'em into the [wildest] *Deliria* (Kolben, 1731).

1763

De la Caille (1763): "The Canna of the Hottentots is entirely different from [Ginseng]. I have seen both, they are entirely different. They harvest the root in the months of November and December, add water and put some honey in it, and leave it in the rocks to ferment. They drink it while it lasts, abruptly unable to do anything. When the supply is exhausted, they are long sick; eating orca restores them."

1772-1775

Carl Peter Thunberg was a Swedish botanist and physician who had been a student of Linnaeus. He made two journeys to the Eastern Cape region of South Africa between 1772 and 1774, and reported that valuable narcotic plants were found in the vicinity of the present-day town of Oudtshoorn in the Little Karoo, in an area formerly occupied by the Attaqua Khoikhoi. This area of South Africa is still known as Kannaland. According to Thunberg (Forbes, 1986),

> Kon, was a name given by the Hottentots to a shrub that grew here (*Mesembryanthemum emarcidum*) and was famous all over the country. The Hottentots came far and near to fetch this shrub with the root, stalk and leaves which they stamp together, and afterwards twist them up like pig-tail tobacco; after which they let the mass ferment, and keep it by them for chewing, especially when they are thirsty. If it be chewed immediately after fermentation, it intoxicates. The word kon is said to signify a quid; the colonists call it canna root. It is found in the driest fields only, and is gathered chiefly by the Hottentots, who live near this spot. These afterwards hawk it about, frequently to a great distance, and exchange it for cattle and other commodities."

1851

The Great London Exhibition of 1851 may have been a pivotal moment in the history of Sceletium, where the plant was exposed to international visitors that would have included physicians, chemists and pharmacists. A collection of the most important Cape botanical medicines was sent to the exhibition from Cape Town by Messrs S.H. Scheuble & Co. (Gunn and Codd, 1981). Karl Wilhelm Ludwig Pappe, a German-born physician and botanist who moved to Cape Town to practice as a physician, wrote a small book as a commentary to accompany the exhibited medicinal plants. In the entry for *Sceletium tortuosum* (as *Mesembryanthemum tortuosum*. Lin.), Pappe wrote, "This species, a native of the Karroo, appears to possess narcotic properties. The Hottentots, who know it by the name *Kauw-goed*, are in the habit of chewing it, and become intoxicated, while the farmers use it in the form of decoction or tincture, as a good sedative" (Pappe, 1868).

1856

Confusion between *kanna* and ginseng seems to have persisted well into the 19th century, with a French-English Dictionary of the time describing *kanna* as a species of ginseng (Collot, 1856).

1858

The distinction between processed and unprocessed plant material, and differences in the activity of different Sceletium species, is made by Tully: "*Mesembryanthemum emarcidum*, like *Nicotiana*

tobacum, is not narcotic until it has undergone a certain change in consequence of it being treated in a peculiar manner. *Mesembryanthemum tortuosum* is considered narcotic without any such change" (Tully, 1858).

1873

The Bleek and Lloyd Archive of the University of Cape Town is a remarkable collection of /Xam San oral literature, language and ethnography documented in Cape Town by W. H. I. Bleek and Lucy C. Lloyd between 1870 and the early 1880s. They became aware of a group of /Xam San prisoners at the Breakwater Convict Station in Cape Town and received permission for //Kabbo to stay in their Mowbray home as a research participant. Later, other San prisoners were also allowed to stay in the house, including ≠Kasiŋ. //Kabbo, meaning "Dream", stayed with Bleek and Lloyd between February 1871 and October 1873. He was sent from the Breakwater Convict Station, where he had been imprisoned for two years for stock theft or sharing in the spoils of theft, as prisoner Number 4628. ≠Kasiŋ arrived at Bleek and Lloyd for the first time from November 1873 until March 1874, after //Kabbo had left. He had been imprisoned at the Breakwater Convict Station for culpable homicide and served four years of a five-year sentence as prisoner Number 4435 (Digital Bleek & Lloyd, 2017).

//Kabbo and ≠Kasiŋ were shown a number of "Bushman medicines" that had been found in the hut of a "Bushman sorcerer", and their comments on these medicinal plants were transcribed into English by Wilhelm Bleek and Lucy Lloyd (MSS BC151 006; Prader-Samper, 2007). I was surprised to find that none of the botanical names of these plant medicines was known. Two informants, //Kabo and ≠Kasin independently identified the same plant sample as *kaauwgoed*, and on this basis the botanical identity was established as Sceletium sp. since no other South African plant has before or since been given this Dutch vernacular name. Indeed, the Afrikaans name for Sceletium to this day is *kougoed*, derived from the older Dutch *kaauwgoed*, meaning "chewing stuff." We finally have the first reports on the uses of Sceletium from indigenous people, in their own words, as well as the original /Xam San name for the plant as *!k"wa:ï* or *!k"wai:n*.

> Bleek's notes documented from //Kabbo *!k"wa:ï* singular and plural. *Kaauwgoed*

> A small plant found on the great mountains growing out of crevices in the rocks. It is chewed by Bushmen, and gives strength to their limbs; and takes away pain and makes their memory strong. The two Bushmen from Stuurmansfontein had some with them to enable them to walk till they met the wagon. Is found around the Berg Bushmen.

> Lloyd's notes documented from ≠Kasiŋ *!k"wai:n Kaauwgoed*

> If a little child that is still being suckled is ill inside, they take a little piece of it, & put it into a spoon of cold water, & rub it about in it, the water becomes yellow (like tobacco water), and they give it to the child to drink. Men and women chew it; and swallow their saliva. The plant is in some cases short, but in others long, like a pumpkin in growth. It grows on the ground. It grows in ≠Kasiŋ's place.

1874

The botanical identity of a sample of *kougoed* was confirmed to be *Mesembryanthemum tortuosum* and the uses of it were described: "The Koegoed [sic], besides being used as stated by Mr. Keyworth as a sedative for cattle, is chewed by the Hottentots as an intoxicating agent, and appears to possess narcotic properties which deserve further attention" (Holmes, 1874).

1876

Twenty-five years after the Great London Exhibition, Sceletium may have become available as a botanical medicine in the United States, evidenced by the inclusion of *Mesembryanthemum tortuosum* in C.E. Hobbs' *Botanical Hand-Book* (Hobbs, 1876) and in J.M. Nicholl's *Botanical Ready Reference* (Nicholl, 1895). These books were lists of botanicals apparently in common use in the United States, and written for apothecaries and pharmacists. In both books, the plant was classified as a narcotic.

1896

The first pharmacological research on Sceletium was reported by Isaac Meiring in the Transactions of the South African Philosophical Society. In this paper, Meiring gives the locality the plant

material came from, the vernacular name as "*Hottentot's Kauwgoed*" and had the plant material used in his experiments botanically identified as *Mesembrianthemum tortuosum* L.:

> Like so many Cape plants, it has great medicinal virtues ascribed to it, chief of which are its soporific influence on young children and its curative and quieting effect on them when suffering from acidity. It is alleged that for these purposes the plant is very widely used, the method of procedure being one or two drops of the juice of the green plant is given to the child, who then enjoys a deep, quiet rest for several hours.

Meiring made a crude alkaloid extract from the plant, and noted that when injected into a frog it had a marked hypnotic effect. He then went on to do some "clinical experiments" with a tincture of dry plant material, and found it had marked pain-relieving activity "without concomitant bad effects." Meiring then gave his remaining plant material to a Dr. Rubenstein to take to Germany, where a Dr. Fromm in Freiburg found it contained a compound capable of being crystallised, and which resembled morphine in its action (Meiring, 1896).

1898

In his book Die Heilpflanzen Der Verschiedenen Völker Und Zeiten[1] , Dragendorff lists two species of Sceletium: "*Mesembryanthemum anatomicum* Hav. (*Mesembryanthemum emarcidum* Thbg). Herb is used as a light narcotic (and smoked). Also *Mesembryanthemum tortuosum* L." (Dragendorff, 1898).

1905

Juritz stated that Mesembryantheum tortuosum is soporific, causes dilatation of the pupil, and decreases sensation (Juritz, 1905).

1913

Zwicky isolated a crude alkaloid extract from *Mesembryanthemum tortuosum*, which he called mesembrine, and on testing with various chemical reagents concluded that there was no similarity between cocaine and mesembrine; he further concluded that this active principle, mesembrine, was also found in *Mesembryanthemum expansum*. In the first detailed documentation on self-ingestion of Sceletium plant material and alkaloid extract, Zwicky reported the following observations (Zwicky, 1913):

> I. After chewing 5g of Sceletium:
>
> The taste was bitter, astringent, unpleasant, irritating to the mouth. During the chewing, tingling was noticed on his tongue, later weak anaesthesia in the mouth, which lasted for some time. The pulse remained normal, while the temperature was weakly increased from 36.9 ° to 37.1 °. I noticed nausea, headache, loss of appetite.
>
> II. After taking a decoction of 15g of Sceletium at 14:00:
>
> Half an hour after taking the decoction I felt blood pressure in the head and slight headache, but it did not last long. I had the feeling that the food was not digested and only at 10:30 in the evening appetite returned. In general, the effects were not very different from the 1st experiment. ; in any case, they were not 3 times as strong as the first.
>
> III. After taking 0.15g of an alkaloid concentrate extracted from Sceletium at 15:00:
>
> Congestion of the head, noises in the ears, tiredness accompanied by slight tremors in the arms and legs, headache, general depression; loss of appetite until 10 in the evening.

1928

The Khoikhoi chew the leaf for the relief of toothache and pain in the abdomen, "the effect apparently being narcotic" (Laidler, 1928).

---

1 Rough translation: The Medicinal Plants of Different Peoples and Times.

1937

Crystalline pure alkaloid was isolated from Sceletium plant material obtained from Namaqualand (Rimington and Roets, 1937), identified as mesembrine, and assigned the formula $C_{17}H_{23}O_3N$. It was concluded that this formula is identical to hyocyamine and atropine, suggesting that mesembrine is a tropane alkaloid.

1960

All Sceletium species "contain the poisonous principle "mesembrine" a relative of cocaine and other principles" (Jacobsen, 1960). Jacobsen noted that *kougoed* was still being made traditionally and sold, and concluded "perhaps it may give a valuable medicine."

1962

Sceletium tortuosum "is used as a narcotic by the African in the Queenstown district" (Watt & Breyer-Brandwijk, 1962). A geologist and mining engineer observed that "the Nama have a universal addiction to *kougoed*", and it "is also used by the Nama for the relief of all types of pain, and to relieve hunger...A Nama mother chews the root and ejects her saliva into the mouth of her child from an early age" (Watt & Breyer-Brandwijk, 1962).

1971

Herre (1971) stated that while other members of the Aizioaceae also contain mesembrine, it is present in lower concentrations than in Sceletium, which produces mesembrine when grown in North Carolina, but not in Europe and northern countries. He noted that the German pharmaceutical company C.F. Boehringer & Söhne of Mannheim was investigating Sceletium, and also the company S.B. Penick in New York.

Table 1. Summary of historical reports on preparation and uses of *Sceletium* species

SUBJECT	NOTES	REFERENCES
Species	*Mesembryanthemum tortuosum*	Tully, 1858; Pappe, 1868 ; Hobbs, 1876; Nicholl, 1895 ; Meiring, 1896; Juritz, 1905; Zwicky, 1913; Tully, 1858;
	Mesembryanthemum emarcidum	Forbes, 1986; Holmes, 1874
	Mesembryanthemum anatomicum	Dragendorff, 1898
	Mesembryanthemum expansum	Zwicky, 1913
Folk names	Ningin, Ningimm	Purchas 1625; Moreland, 1934
	Kanna, Canna	Tachard, 1686; Kolben, 1731; Moreland, 1934; Serton, 1971; Smith, 1966; Wilson, 2002; Forbes, 1986
	Kauw-goed; *Kaauwgoed*; *Kauwgoed*; Koegoed, *kougoed*	Holmes, 1874; Meiring, 1896; Marloth, 1917; Smith, 1966; Forbes, 1986
	!k"wa:ï ; !k"wai:n	Prader-Samper, 2007
Preparation	Roots fermented with honey	De La Caille, 1763
	Whole plant fermented	Forbes, 1986
	Tincture	Pappe, 1868
	Cold water infusion	Prader-Samper, 2007
	Drops of freshly squeezed plant	Meiring, 1896
	Smoked	Forbes, 1986; Dragendorff, 1898
	Roots chewed, saliva given to infant	Watt & Breyer-Brandwijk, 1962

SUBJECT	NOTES	REFERENCES
Activities	Intoxicant	Waterhouse et al, 1979; Kolben, 1731; Tully, 1858; Pappe, 1868; Holmes, 1874
	Narcotic, Sedative, Hypnotic	Kolben, 1731; Tully, 1858; Pappe, 1868; Holmes, 1874; Hobbs, 1876; Nicholl, 1895; Meiring, 1896; Dragendorff, 1898; Juritz, 1905; Laidler, 1928; Watt & Breyer-Brandwijk, 1962
	Decrease sensation, local anaesthesia	Juritz, 1905; Zwicky, 1913; Watt & Breyer-Brandwijk, 1962
	Nausea, loss of appetite, decrease hunger	Zwicky, 1913; Laidler, 1928
	Toothache	Laidler, 1928
	Elevate mood	Kolben, 1731
	Analgesic	Meiring, 1896; Laidler, 1928; Watt & Breyer-Brandwijk, 1962
	Pain	Prader-Samper, 2007; Laidler, 1928
	Endurance	Prader-Samper, 2007
	Memory	Prader-Samper, 2007

Part II

Ethnobotany, Ethnopharmacology & Pre-clinical Research 1995-2017

Ethnobotany

In late 1991, I was given a sample of *kanna* by the ethnobotanist Fiona Archer, who had been documenting local plant uses in Namaqualand for an MSc degree in anthropology at University of Cape Town. At the time, I was searching for South African plants with psychedelic activity. On inquiring if she had encountered possible psychoactive plants from Namaqualand, Fiona told me about a plant called *kougoed*, traditionally used by locals, and that when she had tried some it felt as if her perceptions of time and space had been altered. Fiona gave me a brown paper bag containing about 500g of stringy, brown, traditionally fermented and dried *Sceletium*. I chewed a few grams of the plant material, and after about fifteen minutes, the plant caused a rather sudden rush of euphoria. Over the following hour, this gradually changed to a feeling of deep calm that persisted for some four or five hours. Following from this intriguing initial experience, my wife Olga, myself and Fiona began a period of self-experimentation and gave samples of *kanna* to friends, fellow doctors and psychiatrists, anthropologists, botanists and an African traditional healer. I wrote up some of this early experimentation in Smith et al., 1996:

> Additional information on the effect of *kougoed* has been documented from a dozen individuals who self-experimented with the traditionally prepared plant material, and provided oral anecdotes of these experiences. Most users found that *kougoed* induced a marked anxiolytic effect. One informant used about 5ml of powdered *kougoed* orally before giving a lecture he was anxious about. He reported feeling relaxed throughout the lecture with no cognitive impairment. Many users felt that *kougoed*, on its own or with alcohol, enhanced social intercourse at parties and functions. Users felt considerably less inhibited and self-conscious, and more open than usual in conversation with strangers. One user claimed she felt that *kougoed* was a "truth drug". Of *kougoed*, some claimed there was a synergistic effect with alcohol, and with smoked *dagga* (*Cannabis*

sativa). One experimenter, a polysubstance abuser, used *kougoed* in addition to alcohol (whiskey) and smoked *dagga*. He experienced a traumatic flashback to a violent event he had participated in during a regional armed conflict. 1

A polysubstance abuser, addicted to nicotine and a frequent abuser of alcohol and dagga, reported that after a single dose of *kougoed* he felt no craving for alcohol, dagga or nicotine for 4 days. Some reported euphoria as well as a feeling of meditative tranquility. Several users felt that the relaxation induced by *kougoed* enabled one to focus on inner thoughts and feelings, if one wished, or to concentrate on the beauty of Nature. Some informants reported heightened sensation of skin to fine touch, as well as sexual arousal. A senior traditional healer, not previously exposed to *kougoed*, tried it and announced that it "relaxes the mind" and makes one's body feel "light" the following day. 2

From 1995 to 1999, I undertook detailed ethnobotanical studies on *Sceletium* in the field to document the local uses of the plant, and to determine whether the plant had addictive potential. The focus of this field work was in the rural hamlets of Paulshoek and Nourivier in the Kamiesberg mountains of Namaqualand, not far from the 1685 trail of the Dutch expedition led by Simon van der Stel. Fieldwork was also undertaken in the vicinity of *Kougoedvlakte* (the area named after the once-abundant wild *Sceletium tortuosum* resource of this arid plain), and interviews and discussions were held with shepherds and goatherds in the western area of what is now the Riemvasmaak Community Conservancy. In rural hamlets, elderly male and female members of the local community, who had themselves used *Sceletium* for many decades, were interviewed. Three key informants, recognized by the communities for their specialist knowledge on medicinal plants, were selected for more detailed interviews: the renowned traditional healer Gert Dirkse or "Oom Gert" (meaning Uncle Gert) living near Paulshoek; a younger healer, Jap-Jap Klaase, living in Nourivier; and the shepherd Lodewyk Mories, living near the farm Ratelkraal situated between the towns Springbok and Pofadder. 3

Some of this ethnobotanical research has been published in Smith et al., 1996, Gericke & van Wyk, 2000, and in Gericke & Viljoen, 2008. *Sceletium tortuosum* is typically harvested by local people during the dry-season months from October through to January, when the plants have partly died back and become yellowish in colour. The plants are often found growing under woody shrubs, partially shaded and sheltered from the wind and from foraging by animals. The died-back yellowing plants are regarded as having more "power" than the vigorously growing green plants of the June to August winter rainy season. The plant is cut above the ground, leaving the roots and a small portion of stem behind to resprout. While some collectors gather the entire uprooted plant, older healers claim this is not following tradition and will prevent the plants from regenerating. The collected succulent plant material is crushed with a large stone on a flat rock and the resulting dripping wet fibrous pulp is put into a plastic bag. According to local people, traditional sheepskin bags were used in former times. The plastic bag is tied to exclude air, and the material is allowed to macerate in the hot sun for eight days with intermittent mixing. On the eighth or ninth day, the plant material is spread on a flat rock to dry in the sun, resulting in dry clumps of amorphous, light brown plant material with a characteristic musty "old socks" smell. This is the traditional *kougoed* or *kanna* of the Namaqualanders. 4

ADDICTION POTENTIAL 5

The following excerpt is taken verbatim from a field report (Gericke, 1995). In order to assess the potential for addiction, I had asked my friend Dr. Greg McCarthy, an academic addictionologist, to accompany me on a field trip to Namaqualand and give me an independent opinion on this. Sadly, Greg passed away in 2016, still working as an academic psychiatrist and addictionologist. 6

"In order to assess whether *Sceletium* use leads to addiction or dependence, a consultant psychiatrist from the Cape Town Drug Rehabilitation Centre, Dr. Greg McCarthy, accompanied Dr. Gericke on a field trip to Namaqualand to investigate the use of *kougoed* by traditional healers and members of rural communities. Dr. McCarthy is a consultant psychiatrist at Valkenberg Hospital Community Service, and was recently a consultant at Avalon, an alcohol treatment centre. He serves on the Western Cape Alcohol and Drug Forum. 7

"The DSM-IV criteria for dependence were translated into a questionnaire appropriate to the rural population. Three well-respected traditional healers, and eight long-term regular users of *kougoed* were interviewed. All were cooperative and open. There was clear convergence of the anecdotes and all denied any hallucinogenic or psychotomimetic effects of *kougoed*. 8

"While *kougoed* is used as a euphoriant or intoxicant, almost solely by elderly men, its medicinal qualities are highly regarded by the entire community. The recognized medicinal uses include use as an hypnotic or sedative, as a mild laxative, as a gripe-water, for abdominal cramps, and for alcohol rehabilitation. All research participants were adamant that *kougoed* was less habit-forming than alcohol, tobacco or *dagga* [*Cannabis sativa*].

"Tolerance was denied by all users except one, who reported "*jy raak gewoond daaraan*" ["you get used to it"]. It was not clear whether he was referring to true tolerance, where increasing doses are required to bring about the same effect, or whether he was referring to the fact that one gets accustomed to the use of *kougoed*, as the naïve user can experience nausea.

"Withdrawal signs or symptoms were not reported by anyone. This significant finding is reliable, because even regular users run out of supplies of *kougoed* due to decreased availability of the material. Mr. Mories (pers. comm.) reported there were no signs or symptoms of withdrawal even if a person ran out of *kougoed* after six months of habitual use. Some regular users would perhaps have a slight feeling as if something was missing, and some would make an effort to contact friends who may have some *kougoed*, but would not run into any difficulties if no more was obtained. All confirmed it would be far easier to give up *kougoed* than alcohol, tobacco or *dagga* [*Cannabis sativa*].

"An idea of the social and occupational functioning of the informants was easy to gauge although formal employment is scarce. The local environment is harsh, and daily living requires hard work, including walking long distances to collect brushwood for firewood, shepherding sheep and goats, and ploughing wheat-fields using donkey-drawn ploughs. There were no reports of "social dropouts" from habitual *kougoed* use, and use in this rural context can be viewed as a socially sanctioned activity. It is not possible to extrapolate what effect habitual use of *kougoed* as an euphoriant would have outside of this context.

"The medicinal use of *kougoed*, administered for specific indications, in lower doses, taken less frequently and for a finite duration must be seen as entirely separate from use as an euphoriant." (Gericke, 1995).

WELL-BEING

Kanna was commonly used by elderly men and women for a sense of calm and well-being. Elderly research participants, some in their eighth and ninth decade of life, were interviewed who had chewed quids of *kanna* daily throughout their adult lives. A small quid of fermented Sceletium is kept in the cheek and sucked, and the resulting saliva is swallowed. For a sense of calm and well-being, the quid is removed about fifteen minutes later. Men in the community then place the wet quid in their hatband to dry out so it can be sucked on or chewed later, a sequence repeated a number of times during the day. The author was cautioned "*Doktor, jy moet leer hoe om dit te gebruik*" – "Doctor, you must learn how to use it" – because once one begins feeling intoxicated by it, one has already chewed far too much. The intention of these users is to enjoy a pleasant sense of well-being, not to get intoxicated.

INTOXICATION

There were convergent reports that some people, invariably older males rather than females, did indeed use *kanna* on occasion as an intoxicant or euphoriant. No visual or auditory hallucinations were associated with the intoxication, and the state was described as being similar to being intoxicated with alcohol: "*dis onse droë drank*" – "it is our dry liquor" (Lodwewyk Mories, pers. comm., 1995). Plants from particular areas are regarded as being more potent intoxicants, and through the traditional "fermenting" process, the *kanna* would give a better "trek" – euphoria or a high. Younger men in the community were not using *kanna* at this time, and it seemed the use of tobacco, alcohol and possibly also *dagga* (marijuana) had displaced the former use of *kanna* by younger people in these rural communities.

INSOMNIA

Kanna is used as a hypnotic, with a small quid kept in the cheek by some users when going to bed. Paradoxically, some participants reported that if too much *kanna* was used, it would in fact cause insomnia.

ALCOHOLISM

Both of the healers, Gert Dirkse and Jap-Jap Klaase, maintained that *kanna* was used to wean alcoholics off of alcohol, but only if the alcoholic was committed to stop drinking. Alcohol was replaced

The late Gert Dirkse, right, the last great healer of the Kamiesberg Mountains, with *Sceletium tortuosum*, and Jap-Jap Klaase, left.

Gert Dirkse with Dr. Nigel Gericke, Paulshoek, Namaqualand, 1995.

by the chewing of *kanna*, and it was not considered to be a problem for the person to subsequently stop using the *kanna*. In some cases, a strong decoction of *kanna* would be added to a bottle of wine, so that if the alcoholic drank this wine it would cause vomiting and an aversion to wine.

CONSCIOUSNESS

The healer Gert Dirkse maintained that using *kanna* "opened the mind", and he used both hands expanding out from his temples to demonstrate this (pers. comm., 1999). He denied that the plant could cause any visions.

PREGNANCY

A quid of *kanna* is commonly chewed by women during pregnancy for treating nausea, indigestion, or for treating constipation in pregnancy. It was noted that if one took too much it had a sedating effect. The plant was not known to cause abortion or congenital defects.

PARTURITION

Infusions of *kanna* are taken to help expel any remaining afterbirth, to help contract the uterus, for abdominal pain after giving birth and for indigestion.

INFANTS

Kanna is commonly administered to infants to treat colic, excessive crying and stomach cramps. A small amount of dried herb (the samples demonstrated were estimated to be ~200-500 mg) or fermented dried herb is wrapped in cloth and dipped in breast milk in a teaspoon until the liquid has turned slightly brown. A few drops of this liquid are given orally to make the infant sleep restfully. Dried fermented herb is also lightly fried in sheep fat taken from the tail of a fat-tail sheep; this is strained through a cloth and kept in a small bottle. One to two drops of this medicated liquid fat are given to an infant with colic. The baby usually falls asleep soon after the administration of the drops. None of the mothers had ever heard of an infant needing to be taken to a doctor after too much *kanna* had been administered; they acknowledged that sometimes too high a dose is inadvertently given, but all that happens is that the baby will sleep for some hours.

CHILDREN

Hot-water infusions or decoctions of *kanna* are given to children for constipation, abdominal pain, winds and also as a "*kalmeermiddel*" or calming medicine. A child suffering from abdominal pain will fall asleep soon after the *kanna* is administered.

OTHER

Kanna is also used in Namaqualand to treat asthma, abdominal cramps, constipation and headache.

RAW MATERIAL SUPPLY

Elderly Namaqualanders confirmed that *kanna* had once been plentiful, but was now very scarce as it had been overharvested for sale to local trading stores and shops in the local towns, including the town of Springbok. Lodewyk Mories (pers. comm., 1995) recalled a time when as a young boy in the 1940s, he had seen wagonloads of *kanna* being transported from Namaqualand, presumably destined for Cape Town. Some local farmers maintained that wild stocks of Sceletium had been eaten by overgrazing sheep; however, indigenous shepherds with more intimate knowledge of the eating habits of stock maintained that sheep would only nibble on Sceletium and then move on, and that it was not the sheep that had depleted wild stocks of Sceletium, but people who had overharvested the plant, who had "run after the money."

It was clear that for the development of a product (at that time, for the South African pharmaceutical company Pharmacare Limited, as I was the Phytomedicines Development Manager), wild-harvesting of plants would not be ecologically sustainable, and that selections of Sceletium would need to be cultivated from scratch as a new crop. For this purpose, plant chemotype studies were started by Professor Ben-Erik van Wyk, and plant propagation and production studies were started by the late Professor Earle Graven and Myke Scott of Grassroots Natural Products. This work was on contract to Pharmacare Ltd., and directed by myself. From 1999 onward, the propagation and production of Sceletium work was continued by Du Roi Nurseries, and in 2004 by Niche Botanicals

(Pty) Ltd., in cooperation with Hannes de Lange, PhD. The first successful large-scale commercial production of a select chemotype of *Sceletium tortuosum*, both under shade-house conditions and open-field conditions, was achieved in 2008 by Du Roi Nurseries and H.L. Hall and Sons Ltd., growing the plants on contract to the South African company HG&H Pharmaceuticals (Pty) Ltd. It had taken more than a decade of investment in research into plant selection, propagation and production studies to demonstrate that Sceletium could be grown successfully on a large scale as a new commercial South African crop. The reliable supply of raw material with a defined alkaloid content and composition finally allowed the development of a standardized and characterized spray-dried extract of the plant, suitable for all subsequent pre-clinical and clinical research.

CHEMISTRY

The literature on the Sceletium alkaloids has recently been thoroughly reviewed (Krstenansky, 2017), and validated analytical methods have been described for quantifying the major mesembrine-type alkaloids including mesembrine, mesembrenol, mesembrenone, mesembranol, Δ7mesembrenone, and epimesembranol (Patnala & Kanfer, 2010; Shikanga et al., 2012).

Based on the alkaloid skeleton, Jeffs et al. (1982) separate Sceletium alkaloids into four structural groups:

I the 3aaryl-*cis*-octahydroindole class (e.g., mesembrine)

II the C-seco mesembrine alkaloids (e.g., joubertiamine)

III alkaloids containing a 2,3-disubstituted pyridine moiety and two nitrogen atoms (e.g., Sceletium alkaloid A4)

IV a ring C-seco Sceletium alkaloid A4 group (e.g., tortuosamine).

The revision of Gerbaulet (1996) recognizes eight species of Sceletium, of which the alkaloids in *Sceletium strictum*, *Sceletium subvelutum* (=*Sceletium varians*), *Sceletium tortuosum*, *Sceletium joubertii* and *Sceletium namaquense* have been studied in great detail. The latter two species are now considered synonyms of *Sceletium tortuosum*. The local utilization of Sceletium as *kanna*, *kaauwgoed* or *kougoed* has included a number of Sceletium species and a wide range of Sceletium alkaloids. Compounds that have been isolated from the genus Sceletium are presented in Fig 5.

EXTRACT SCELETIUM TORTUOSUM, ZEMBRIN®

The first standardized extract of *Sceletium tortuosum* was made by the German company Gehrlicher GmbH in 1999 on contract to my consulting company, African Natural Health Close Corporation. The first fully standardized and characterized extract of *Sceletium tortuosum*, Zembrin®, was produced to EU-GMP standards by the Spanish company Polifenoles Naturales SL. The company is now renamed Nektium Pharma SL, and continues to manufacture the extract Zembrin® on contract to the company I co-founded, HG&H Pharmaceuticals (Pty) Ltd. This extract was developed and commercialized from a cultivated special selection of plants that are relatively rich in mesembrenol and mesembrenone as the major compounds, and relatively low in mesembrine and mesembranol. Zembrin® is standardized to contain 0.4% total alkaloids by weight, with the relative alkaloid composition of mesembrenone + mesembrenol ≥60%, mesembrine <20%, and mesembranol must be present in the UPLC profile. The structures of these four compounds are given in Figure 6.

PRIOR INFORMED CONSENT BENEFIT-SHARING AGREEMENT

The development of a product from a medicinal plant used by indigenous people has to take into consideration the contribution that indigenous knowledge – past and present – makes to the foundational ethnobotanical research that gives a preliminary indication of safety, therapeutic indications, and in the case of Sceletium, the apparent lack of potential for dependence. Local participants were able to point out plants that they considered mild in effect in terms of euphoria or intoxication (called *mak* or "tame" plants), and plants which they considered a *trek* variety, which were considered to me far more potent plants than the *mak* variety and which could cause euphoria or intoxication, especially after fermentation.

Two years before the launch on the South African market of the standardized Sceletium extract Zembrin®, a prior informed consent benefit-sharing agreement was negotiated and signed between the South African San Council (SASC) and HG&H Pharmaceuticals (Pty) Ltd. (HG&H). The agreement was signed on 21 February 2008, and must be one of the first such agreements entered into with indigenous knowledge holders. This agreement was the result of many months of meetings and discussions with the South African San Council, who were supported in their negotiations by the internationally recognized human rights attorney Roger Chennels, ensuring that the SASC were well informed and that the agreement reached by the two parties was aligned with international best practices. 1

This benefit-sharing agreement recognized that the San were the primary indigenous knowledge holders of the South African endemic plant *Sceletium tortuosum*. The SASC in turn recognized that the original ethnobotanical research conducted by myself in the Namaqualand communities of Nourivier and Paulshoek contributed important information on the uses of *Sceletium*. In recognition of this contribution to the project, the SASC agreed to share 50% of royalty payments made to SASC with these two communities in an agreement signed on 30 June 2008 (Gericke, 2011). Royalty payments have been made to the SASC by HG&H from 2008 to the present time, at a rate of 5% of royalties on all sales of the extract *Sceletium tortuosum*, Zembrin®, and an additional 1% royalty on the use of the SASC logo on products containing Zembrin®. The payments are based on total invoiced sales, not on "profit" (revenues after costs). The SASC in turn have paid 50% of the royalties to the two communities of Paulshoek and Nourivier, represented by local community organizations established for this purpose. All payments are made into a South African Government trust fund established for this purpose, and are then paid out in full to the SASC, who in turn pay the two Namaqualand community groups. This prior informed consent benefit-sharing agreement has been cited as a positive case study in the commercialization of a product derived from indigenous knowledge (Iatridis and Schroeder, 2016). 2

PHARMACOLOGY 3

SEROTONIN REUPTAKE INHIBITION (SRI) 4

On 25 July 1989, President George Bush, in response to reports by the National Advisory Council of the National Institute of Neurological Disorders and Stroke and the National Institute for Mental Health (NIMH), and the urging of Congress, signed a presidential declaration designating the 1990s as the Decade of the Brain, a national research endeavor to better understand how the brain and nervous system is organized, how it functions, why it fails to function and what can be done to prevent and treat dysfunction. As part of this research, NIMH screened large numbers of compounds through a research agreement with the company Novascreen. In November 1995, I was working as a Visiting Scholar at the US Pharmacopoeia (USP), and not far from USP was the NIMH. I was introduced to Dr. Linda Brady, who was then the chief of the Neuropharmacology and Drug Discovery Program. Dr. Brady kindly agreed to screen an extract of Sceletium as well as isolated pure mesembrine. Both the extract and mesembrine turned out to be exceedingly potent 5-HT uptake inhibitors in the radioligand binding screening and in a subsequent functional assay. This work formed the basis for US Patent 6,288,104 (Gericke and Van Wyk, 1999), which disclosed the use of mesembrine and related compounds, and extracts of Sceletium standardized to these compounds, as serotonin-uptake inhibitors (SRIs), and the use of these compounds in pharmaceutical formulations for the management of depression, anxiety, drug dependence, bulimia and obsessive-compulsive disorder. 5

Subsequently, the standardized Sceletium extract Zembrin® was confirmed to be an SRI with an IC50 of 4.3µg/ml, and mesembrine was found to be the most active alkaloid against the 5-HT transporter (SERT), with a Ki of 1.4nM (Harvey et al , 2011). See Table 2 below. In fact, mesembrine is a more potent inhibitor on SERT than fluoxetine (Prozac). 6

PHOSPHODIESTERASE-4 INHIBITION (PDE4 INHIBITION) 7

I self-experimented with isolated pure mesembrine on a number of occasions from 1996 to 1999, on some occasions with a friend and fellow natural products enthusiast, Dr. George Davidson. Isolated pure mesembrine, taken sublingually in tincture form or on a blotter, resulted in a tangible entactogenic effect with an onset of action some ten to fifteen minutes after taking 100µg. Higher doses at about 500µg gave an experience not dissimilar to MDMA but far more tranquil. It was clear that there had to be additional CNS mechanism/s of action in addition to the SRI activity. 8

Table 2. The inhibitory constants (Ki in nM) for three mesembrine alkaloids on the serotonin transporter. 2

Compound	Inhibition of SERT Ki nM
mesembrenone	27
mesembrine	1.4
mesembrenol	63

3

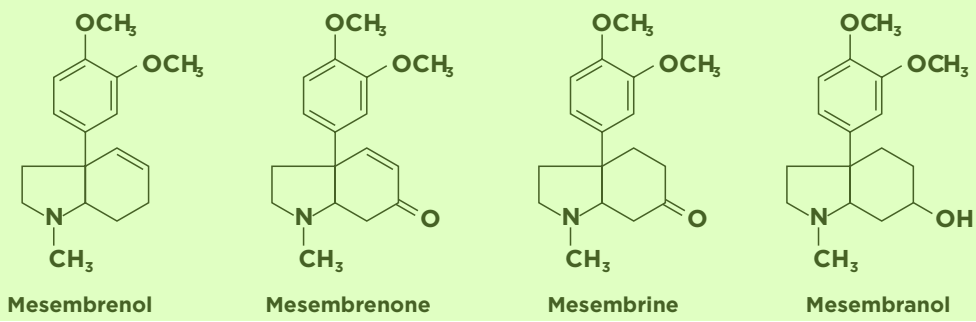
4

Cultivated Sceletium for the production of the standardized extract Zembrin®. 5

Table 3. PDE4 inhibition of the prototypical PDE4 inhibitor Rolipram and the Sceletium alkaloids mesembrenone, mesembrine and mesembrenol. 6

Compound	PDE4B Inhibition IC_{50} µM
Rolipram	0.13
mesembrenone	0.47
mesembrine	7.8
mesembrenol	16

7



8

Fig. 1 The four alkaloids quantified in the standardized Sceletium extract Zembrin. 9

The results of the broad *in vitro* screening of the Sceletium extract Zembrin® and some isolated alkaloids is reported in Harvey et al., 2011. Zembrin® was found to be an inhibitor of the phosphodiesterase-4 (PDE4) enzyme in addition to being an SRI (Harvey et al., 2011). The three isolated mesembrine alkaloids tested were all found to be PDE4B inhibitors, with the most potent of the three being mesembrenone, which is about one third as potent as the prototypical research PDE4 inhibitor Rolipram (Harvey et al., 2011; MacKenzie and Houslay, 2000). See Table 3 below. US Patent 8,552, 051 (Harvey et al., 2013) discloses the use of mesembrenone as a dual SRI and PDE4 inhibitor. 1

While SRIs and selective SRIs (SSRIs) are widely used for the treatment of anxiety disorders and depression, the combination of an SSRI with a PDE4 inhibitor has been argued to have synergistic therapeutic potential. Repeated treatment with SSRIs can upregulate PDE4 (Ye et al., 2000), which in turn reduces sensitivity to SSRIs in response to long-term treatment. The treatment with a dual SSRI and PDE4 inhibitors may thus have a therapeutic advantage (Cashman et al., 2009). Enzymes in the PDE4 family catalyze the hydrolysis of cyclic AMP (cAMP) and have a critical role in controlling the intracellular concentration of cAMP and increasing phosphorylation of cAMP-response element-binding protein. PDE4s are found throughout the brain but their levels are decreased in depressed individuals not on medication, reflecting a downregulation of the cAMP cascade that can potentially be restored using PDE4 inhibitors. The prototypical PDE4 inhibitor Rolipram has been shown in both animal and clinical studies to have antidepressant activity (Terburg et al., 2013). 2

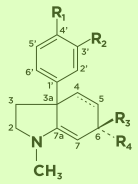
PRE-CLINICAL RESEARCH 3

Prior to the development of a standardized extract, I sent samples of milled *Sceletium tortuosum* plant material to colleagues in Japan who were interested in studying the effect of Sceletium in a veterinary clinic setting. The veterinarians reported that the Sceletium reduced cage stress and travel stress in cats, and decreased the excessive nocturnal crying and barking of aged cats and dogs with a clinical diagnosis of dementia. These results have been published in Japanese (Hirabayashi et al., 2002; Hirabayashi et al., 2004; Hirabayashi et al., 2005). 4

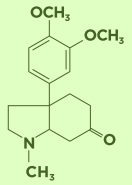
Sceletium extract Zembrin® was studied in a 14-day repeated oral toxicity study conducted at 0, 250, 750, 2500, and 5000 mg/kg body weight/day (equivalent to total mesembrine alkaloids of 0, 1, 3, 10, and 20 mg/kg bw/day). A 90-day subchronic repeated oral toxicity study was conducted on Sceletium extract Zembrin® at 0, 100, 300, 450, and 600 mg/kg bw/day (equivalent to total mesembrine alkaloids of 0, 0.4, 1.2, 1.8, and 2.4 mg/kg bw/day). Since Sceletium species were known to be psychoactive, a functional observation battery, including spontaneous locomotor activity measured using the LabMaster ActiMot light-beam frames system, was employed. Parameters such as locomotion, rearing behavior, spatial parameters and turning behavior were investigated. No mortality or treatment-related adverse effects were observed in the rats in the 14- or 90-day studies. In the 14- and 90-day studies, the No Observed Adverse Effect Levels (NOAEL) for Zembrin® were 5000 and 600 mg/kg bw/d, respectively, the highest dose groups tested (Murbach et al., 2014), equivalent to the NOAEL for total mesembrine alkaloids of 20 and 2.4mg/kg bw/day. 5

In a model of restraint-induced psychological stress it was found that a dose of only 5mg/kg of Sceletium extract (although not stated in the paper, this was Lot #8587 of Zembrin®) given by gavage reduced restraint stress-induced self-soothing behavior, as well as decreased stress-induced corticosterone levels (Smith, 2011). This dose is equivalent to a total alkaloid dose of only 20 µg/kg bw/day. 6

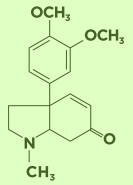
The effect of single doses of Sceletium extract Zembrin® on rat brain electrical activity was studied using wireless EEG recordings in free-living rats. 3 doses of the Sceletium extract Zembrin® and vehicle (0, 2.5, 5.0 and 10.0 mg/kg, equivalent to total mesembrine alkaloids of 0, 10, 20 and 40 µg/kg) were given by gavage. The resulting electropharmacograms (plotted from Fast Fourier Transformation of the analogue EEG recording for each frequency range) of Zembrin® were compared to the databased electropharmacograms of reference herbal extracts, dietary ingredients and the pharmaceutical PDE4-inhibitor Rolipram. Zembrin® had a similar electropharmacogram to the electropharmacograms for extracts of *Ginkgo biloba* and *Rhodiola*. A discriminant analysis confirmed these similarities and also demonstrated that Zembrin® had a similar electropharmacogram to citicoline, a compound originally developed for cognitive enhancement, and to the PDE4-inhibitor Rolipram. These results provide support for future translational clinical studies on Zembrin® to investigate the activity of the extract on cognitive function in Mild Cognitive Impairment, for treating depression and as an analgesic (Dimpfel et al., 2016). 7



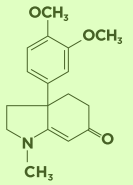
The 3a-aryl-cis-octahydroindole skeleton



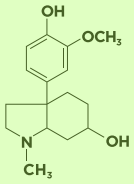
mesembrine



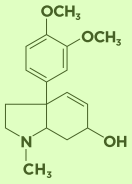
mesembrenone



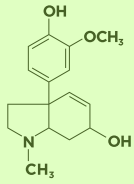
Δ7mesembrenone



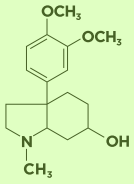
4'-O-demethylmesembranol



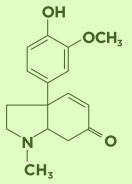
mesembrenol



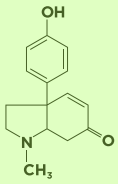
4'-O-demethylmesembrenol



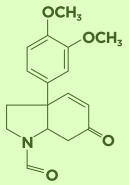
mesembranol



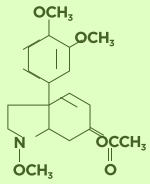
4'-O-demethylmesembrenone



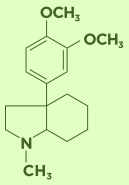
sceletenone



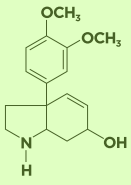
N-demethyl-N-formylmesembrenone



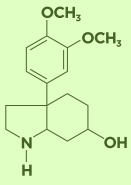
O-acetylmesembrenol



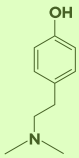
mesembrane



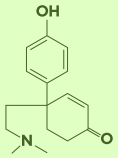
N-demethylmesembrenol



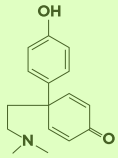
N-demethylmesembranol



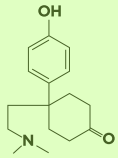
hordenine



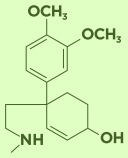
joubertiamine



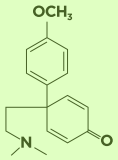
dehydrojoubertiamine



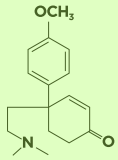
dihydrojoubertiamine



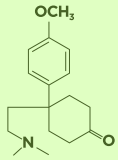
joubertinamine



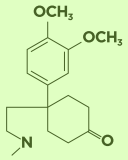
O-methyldehydrojoubertiamine



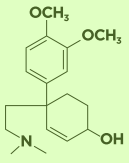
O-methyljoubertiamine



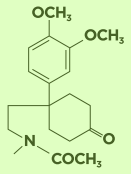
O-methyldihydrojoubertiamine



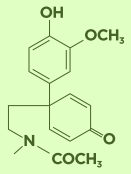
3'-methoxy-4'-O-methyljoubertiamine



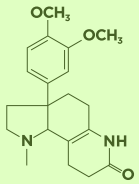
3'-methoxy-4'-O-methyl joubertiaminol



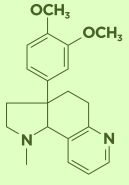
4-(3,4-dimethoxyphenyl)-4-[2-acetylmethylamino)ethyl] cyclohexanone



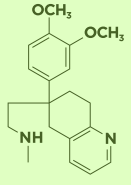
4-(3-methoxy-4-hydroxy-phenyl)-4-[2-acetylmethylamino) ethyl]cyclohexadienone



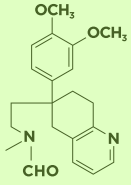
"unnamed alkaloid"



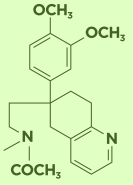
sceletium alkaloid A4



tortuosamine



N-formyltortuosamine



N-acetyltortuosamine

Fig. 2 Structures of alkaloids isolated from the genus Sceletium (Gericke & Viljoen, 2008). 2

Part III

Clinical Studies on Sceletium Extract Zembrin®

Introduction

The following three case reports on the clinical use of Sceletium, presented at the 4th International Conference on Phytotherapeutics on 23-25 February 2001, Kurrajong, NSW Australia, are the first clinical case reports for this plant and demonstrate that the plant has therapeutic potential for anxiety and depression. These historical case reports are given in full from Gericke (2001).

1. Patient with a first episode of severe depression with marked anxiety

Reported by the author

H.M., a 29-year-old female doctor, presented at my practice asking for a natural treatment for severe depression. She had had no previous psychiatric history, no history of epilepsy, head injury or substance abuse, and had a past medical history of atopic eczema and occasional asthma, not presently on any medication.

Main complaint

A four-month period of depressed mood with diurnal variation: the depression was far worse in mornings, improving somewhat as the day progressed. There was an obvious physiological shift with decrease in appetite, weight loss and insomnia with difficulty initiating sleep and early morning waking. Markedly decreased energy and drive were a significant problem for the patient. The symptoms were accompanied by feelings of anxiety and somatic symptoms of anxiety including palpitations and epigastric discomfort. Other symptoms of note included suicidal ideation, feelings of worthlessness, lack of concentration and motivation, tearfulness, emotional lability and general loss of interest in life.

Treatment

The patient requested to be put on *Sceletium*, having heard about it from a colleague who is a psychiatrist, and was started on a low dose of 50mg [milled plant material] as a tablet taken in the mornings.

The patient initially reported a transient increase in anxiety after taking medication, which would last up to three hours. This effect was no longer apparent after a week of continual use. No changes in libido were noted, and libido had not been affected by the depression either. A sustained improvement in mood was reported from somewhere between 1-2 weeks of continual use of 50mg Sceletium taken daily, with a marked decrease in the generalized anxiety. The patient's insomnia improved at the onset of treatment. There was a marked improvement in drive and energy, accompanied with a return of interest in the mundane activities that constitute much of everyday living.

The only side effects elicited were the initial transient increase in anxiety and some initial appetite suppression, neither of which was severe enough to warrant discontinuation of treatment, and both of which were no longer apparent after the first two weeks of treatment.

Conclusion

A low dose of *Sceletium* (50mg daily) taken orally as a tablet proved to be a very effective anxiolytic and mood elevator in a first episode of a major depression. The *Sceletium* was discontinued after 4 months of continual use with no signs or symptoms of withdrawal, and there has so far (about 6 months) been no return of symptoms of anxiety or depression.

2. PATIENT WITH POSTNATAL MAJOR DEPRESSIVE DISORDER.

Reported by Dr Olga Gericke MUDR (Vienna) FC Psych. (SA)

A 28-year-old married housewife with two children, aged three and a half and two months old respectively, presented with depressive symptoms that she had had since the seventh month of her second pregnancy. Complaining of depressed mood, increased sleep, overeating, low energy, increased anxiety to the point of perceptual illusions and depersonalization, feelings of worthlessness, psychomotor agitation, thoughts of death, decreased ability to concentrate and forgetfulness. She also complained of inability to bond with her newborn and felt very irritable and aggressive towards her three-year-old. The patient had self-medicated with St John's Wort (*Hypericum perforatum*) over the last two weeks, with minimal effect.

PAST PSYCHIATRIC HISTORY

Severe postnatal depression after her first child, needed hospitalization, was on Aurorix (Moclobemide) for two years with limited success and discontinued it due to side effects. Her first onset of depression was at age 16, which was treated with Amitryptyline and therapy.

PAST MEDICAL HISTORY

Pre-eclampsia with first pregnancy and currently hypertension, obesity.

HABITS: nil.

PRESENT MEDICATION: ACE inhibitor for hypertension.

FAMILY AND SOCIAL: Disruptive upbringing, mother suffered from severe depression and was hospitalized frequently, both sisters suffer from panic disorder.

DIAGNOSIS

- Major depressive disorder, recurrent, severe, postnatal onset
- Borderline personality traits
- Hypertension

TREATMENT

The patient was started on *Sceletium* 50 mg [milled plant material] in the morning and at lunchtime. The immediate effect (the first day of treatment) was mood elevation, significantly decreased sleep (from 14 hours a day to eight hours a day) and increased energy. The patient voluntarily started doing housework again. After four weeks of treatment, symptoms of mild depression and anxiety were present again. After six weeks of treatment with *Sceletium*, and supportive therapy and group sessions with a postnatal depression support group, the patient appeared to be fully recovered and is presently well on a maintenance dose of 50 mg *Sceletium* twice a day.

COMMENT

To date, I have successfully used *Sceletium* in 10 patients with a diagnosis of Major Depressive Disorder according to DSM-IV criteria. My patients are usually more severely depressed or anxious than the clients of psychologists and patients of general practitioners, and most of them have been on various pharmaceutical antidepressants before. Most of the patients had a strong anxiety component to the depression. *Sceletium* alleviates anxiety very quickly, though in sensitive individuals the first dose can actually increase the anxiety for about half an hour, after which it is relaxing. My starting dose is usually 50mg in the morning and most patients increase it to an additional 50mg at lunchtime or early afternoon. If taken later, it can cause insomnia in some patients. In some patients I have had to increase the dose to 100mg/12 hours.

3. CASE REPORT BY CHERYL INGGS 1

B.A. Honours, MA(Clin. Psych.) Rhodes 2

The client is a 19-year-old university student who started therapy (once a week) towards the end of her second year (1999). She completed her bachelor's degree at the end of 2000 and has just entered her Honours degree. 3

THE CLIENT PRESENTED WITH THE FOLLOWING: 4

Axis I : Dysthymia. She felt despondent and "trapped inside", she isolated herself and "couldn't see a way out", was sometimes tearful, alternating with an emptiness inside and a pervasive sense of sadness; she had low self-esteem, a loss of interest in activities with social withdrawal, loss of motivation, some distractability and short-term memory loss, tiredness, lethargy, hypersomnia and loss of appetite with occasional "comfort eating" mostly of junk food. There was no suicidal ideation. 5

Axis II : Borderline Personality. Described feeling "out of touch" and depersonalized, with some self-mutilation (scratching her upper arm and wrist). Some impulse binge-drinking when socializing. She had tried "ecstasy" (MDMA) and indulges in marijuana very occasionally. A baseline mood of depression alternating with anxiety and a feeling of tension particularly around her studies and exam performance (sweaty palms, constipation and hair loss). Feelings of emptiness and fear of abandonment. Inappropriate and intense anger. Battling with a sense of self and identity, feeling unsure of who she is, feeling distant, isolated and lonely. 6

THERAPEUTIC ISSUES 7

The client clearly presented with long-standing dysthymia and some anxiety. She had also been sexually abused from age 12-15. She is the middle child and only daughter of an emotionally absent father and a career-oriented mother on whom the client is emotionally dependent. She vacillates between idealizing her mother when she is available and feeling abandoned by her when she is unavailable. The client carries a great deal of anger, and has body-image problems coupled with a fear of sexual intimacy. 8

TREATMENT 9

The therapeutic approach was from a self-psychology model providing a containing environment with careful intervention and gentle interpretation. The client was able to be very insightful but lacked the capacity to process the insight in any meaningful way. She presented with an ongoing sense of emptiness and depersonalization, with a deep despondency and hopelessness. *Sceletium* was administered as a 50mg tablet daily from October 2000. Within ten days, the patient said that her mood had lifted and that she felt slightly less depersonalized. She was able to feel more focused, more engaged and not so socially "distant." She doubled her dose to two 50-mg tablets daily just prior to her examination (November 2000) and described feeling less anxious and more able to cope with her usual examination anxiety. An interesting development on *Sceletium* was that she described feeling less inclined to overindulge in alcohol (she said that it didn't taste as good). 10

CONCLUSION 11

The client clearly has personality problems that require ongoing therapy. However, what is significant is that the *Sceletium* certainly helped her feel more contained, lifted her mood and also helped with anxiety. There is a sense in which the *Sceletium* has stabilized her to the point where we were able to actively engage in some of the more pressing therapeutic issues. 12

The rapid improvements in mood and anxiety in these initial three patients provided the impetus for the development of the proprietary standardized and characterized *Sceletium* extract Zembrin® for formal clinical research. 13

SAFETY & TOLERABILITY (Nell et al., 2013) 14

The safety and tolerability of Sceletium extract Zembrin® was studied in the first formal clinical study of a Sceletium extract. In this randomized, double-blind, placebo-controlled clinical study, two doses of Zembrin® (8mg and 25mg, equivalent to total mesembrine alkaloids of 32µg and 100µg 15

respectively) were taken orally once daily for three months by healthy adult volunteers. No efficacy variables were assessed. The extract was found to be safe and well tolerated. An interesting aspect of the study was unsolicited positive effects on well-being noted in patients' side-effect diaries by some participants taking the extract, including improved coping with stress and improved sleep at night.

PHARMACO-FMRI STUDY (Terburg et al., 2013)

The acute effects of extract Zembrin® were investigated in a pharmaco-fMRI study focused on anxiety-related activity in the amygdala and the connected neuro-circuitry. In a double-blind, placebo-controlled cross-over design, 16 healthy university student participants were scanned during performance of an emotion-matching task under low and high perceptual loads. Amygdala reactivity to fearful faces under low perceptual load conditions was attenuated, with a decreased blood oxygenation level-dependent (BOLD) signal for Zembrin® compared to placebo on low-load exposure to fearful faces compared with neutral challenges in the bilateral amygdala ($P<0.01$) after a single 25mg (equivalent to 100µg total mesembrine alkaloids) dose of Zembrin®. Follow-up connectivity analysis on the emotion-matching task demonstrated that amygdala–hypothalamus coupling was also reduced. These results demonstrated, for the first time, the attenuating effects of an extract of Sceletium on the threat circuitry of the human brain and provided supporting evidence that this extract may have anxiolytic potential by attenuating subcortical threat responsivity. These results are consistent with the *in vitro* dual serotonin reuptake inhibition and PDE4 inhibition reported by Harvey et al., 2011.

COGNITION-ENHANCING ACTIVITY (Chiu et al., 2014).

In a randomized double-blind placebo-controlled cross-over clinical study normal healthy older subjects (total n=21) (mean age: 54.6 years ± 6.0 yrs; male/female ratio: 9/12) received either a 25 mg capsule of Sceletium extract Zembrin® (equivalent to 100mg total mesembrine-alkaloids) or placebo capsule once daily for 3 weeks. The primary endpoint was to examine the neurocognitive effects of the extract using the CNS Vital Signs battery of tests. Zembrin® at 25 mg daily dosage significantly improved executive function ($p<0.022$) and cognitive set flexibility ($p<0.032$) compared with the placebo group. Positive changes in mood and sleep were also found, and the extract was well tolerated. It was concluded that PDE-4 inhibition with the resulting cAMP-CREB cascade may play a role in these cognitive enhancing effects of Zembrin®.

ACTIVITY ON EEG, PSYCHOMETRY, AND ANXIETY (Dimpfel et al., 2017).

In a randomized, double-blind, placebo-controlled clinical study, the effect of 25mg or 50mg of Zembrin® (equivalent to 100µg and 200µg of total mesembrine alkaloids, respectively) was studied in comparison to placebo after daily repetitive intake for 6 weeks. Sixty healthy male (n = 32) and female (n = 28) subjects between 50 and 80 years old (59.7 ± 5.43 and 56.7 ± 5.88 years, respectively) were recruited. The EEG was recorded bipolarly from 17 surface electrodes. Six cognitive tests were performed: d2-test, memory test, calculation performance test, reaction time test, number identifying test and number connection test. Three questionnaires were included: Profile of Mood States, Hamilton Anxiety Rating Scale (HAM-A) and a sleep questionnaire. Quantitative EEG revealed increases of delta activity during performance of the d2-test, the number identification and number connection tests in the fronto-temporal brain region. Higher theta activity was seen during relaxation and performance of the d2-test after intake of 50mg of Zembrin®. Statistically conspicuous increases of alpha1 spectral power were seen in the relaxed state. With respect to alpha2 spectral power, larger increases were observed in the centro-occipital region. Discriminant analysis of the EEG data revealed a projection of the Zembrin® data into the vicinity of the EEG data plot for a ginkgo-ginseng combination. Statistically significant improvement during performance of the arithmetic calculation test and number connection test was documented. The HAM-A anxiety score revealed a statistically significant decrease ($p = 0.03$) after six weeks intake within the 50mg Zembrin® group. The results indicate that Zembrin® improves some aspects of cognitive function, and decreases anxiety in healthy older adults.

Part IV
kanna and mesembrine-alkaloids: possible futures 1

Legal highs 2

Legal highs are typically sold by online Smart Shops and may be broadly defined psychoactive substances which have not (in some cases not yet) been proscribed by laws or regulations, and are used to elicit a desired state of mind which may be stimulated, euphoric, empathogenic or entactogenic, entheogenic, sedated or a combination. The substances may be isolated natural compounds, synthetic or semi-synthetic compounds, extracts of plants or fungi, or whole or minimally processed plant or fungal material. The first online sales of Sceletium plant material, originally from 40kg of plant material cultivated by Grassroots Natural Products for Pharmacare Ltd., began in 1999 by Om-Chi Herbs in Eugene, Oregon in the USA, and by Conscious Dreams in Amsterdam in the Netherlands, later to be followed by Botanic Art in the Netherlands. These online stores played a major role in introducing *kanna* to a wide international audience. It is now eighteen years later, and there are many online Legal Highs and botanical supply stores selling fermented and unprocessed *kanna* as milled plant material and extracts. From about 2004, there seems to have been a marked increase in the use of *kanna* in the South African trance scene, where powdered *kanna* is used as a snuff, or mixed with marijuana for smoking to induce a "chilled" state of mind and to decrease anxiety in people who get more anxious while smoking marijuana. *Kanna* is used instead of MDMA by some people in the South African trance scene, and to reduce the come-down after an MDMA session by others. By 2017, *kanna* use had become part of the international trance and party scene, with use of *kanna* apparently being well known in Ibiza, Spain. 3

A recent development of serious concern is the online sale of concentrated to highly concentrated extracts sold as *kanna* which are of uncertain botanical origin, unknown total alkaloid content, unknown relative alkaloid composition and unknown stability. A search of Sceletium extracts on Alibaba.com shows a wide variety of "Sceletium" extracts, many produced in China (some accompanied by photographs of flowers that are definitely not Sceletium flowers). This includes some touted as "100:1" extracts (presumably a raw material to extract ratio, weight/weight) and some purporting to be "98% mesembrine" (Alibaba.com, 2017). There is already nascent legal and regulatory flagging of *kanna*, and overconcentrated extracts carry a potential for serious adverse events. The analysis of Sceletium alkaloids for future forensic toxicology and legislation purposes has already been described (Roscher et al., 2012), and the United Nations Office on Drugs and Crime (UNODC) issued a list of 20 plant-based substances of concern in 2013, including Sceletium. The metabolism of Sceletium alkaloids was investigated in rat urine and pooled human liver preparations (Meyer et al., 2015) because of the increasing popularity of *kanna* as a legal high, and the metabolites, especially in the urine, would be good analytical targets for forensic and legal purposes. Sceletium has already attracted the attention of the Drug Enforcement Agency (DEA) of the United States, featuring in a presentation by a forensic chemist at the DEA Special Testing and Research Laboratory with the title, "Novel Plant Hallucinogens and Plant-Derived Highs" (Dye, undated presentation). Surprisingly, Amazon.com has prohibited the sale of *kanna* and cited it as an example of a plant-derived product that simulates the effect of illegal drugs (Amazon.com, 2017). An additional legal and regulatory threat is the potential for adverse reactions from adulterated *kanna*. During an investigation into the wide phytochemical variability of *kanna* available from online stores, the alarming discovery was made that one of the samples of *kanna* had been adulterated with the stimulant ephedrine (Lesiak et al., 2016). 4

Notwithstanding the forensic and regulatory flagging, the use of isolated pure mesembrine alkaloids may ultimately become more widely available to the general public via the rapidly growing vaping and electronic cigarettes industries, evidenced by two recent US Patent Applications for electronically heated aerosol systems filed by Philip Morris Products S.A., Neuchatel, Switzerland, with mesembrine given as one of the examples of active ingredients to be vaporized (Schneider J-C. et al., 2016; Thorens and Cochand, 2016). 5

Supplement 6

The first commercial supplement product containing Sceletium was put on the South African market in 2001 by a South African company I founded, Phyto Nova (Pty) Ltd. This product consisted simply of a low dose of 50mg tablets of milled cultivated *Sceletium tortuosum*, with the traditional 7

uses stated as stress relief and mood elevation. The recommended dose was specified as one to two tablets daily. Tablets containing 25mg of the standardized Sceletium extract Zembrin® were first launched on the South African market in 2010. The recommended dose is 25-50mg taken once a day (containing 100-200 µg total mesembrine alkaloids). The tablets are used for stress, anxiety and mild to moderate depression. In South Africa, these tablets are popular during exam time, used by university students and matriculated school children for improving concentration and reducing stress while studying for exams. The South African National Defence Force has included tablets containing Zembrin® in its code of products that can be prescribed by military psychiatrists and physicians.

A highlight of the Sceletium project was the marketing authorization given to Zembrin® in 2014 by the Natural and Non-Prescription Health Products Directorate of Health Canada, issued as Product Licence number 80052770 on 29 July 2014, for capsules containing 25mg extract, a daily dose of 100µg mesembrine alkaloids.

There are now many brands of tablets, capsules, tinctures and teas of functional food and dietary supplement products containing Sceletium plant material, Zembrin®, and other extracts on the market, mainly in the United States, with lesser sales in much smaller markets including Canada, South Africa, Malaysia and Japan. The cost of formally addressing the diverse national regulatory requirements has limited the international penetration of Sceletium supplements, and it is not clear if companies will be willing to invest in addressing these requirements in the face of increasing competition from what has essentially become a generic botanical dominated by internet sales of these products directly to consumers.

We are living in a fast-paced, highly stressed and uncertain world, challenged with electronic media competing for mindspace, and assaulted daily with news of dramatic geopolitical, economic, social, climatic and environmental changes. Simultaneously, we are on the threshold of the Fourth Industrial Revolution, which is fundamentally changing our lives, our work, our relationships and blurring the boundary between ourselves and our technologies. Low doses of mesembrine alkaloids, probably in the range of only 200µg-400µg and perhaps best in a sustained-release dosage form, have great potential to safely enhance the daily quality of people's lives. More than twenty years of work on this plant has shown me that we have not yet begun to realize the potential that supplements of Sceletium or Sceletium alkaloids hold for:

- reducing stress and situational anxiety
- enhancing well-being
- elevating mood in mild to moderate depression
- enhancing cognitive function
- reducing alcohol and drug abuse
- facilitating psychotherapy
- facilitating meditative and spiritual states

MEDICINE

To date there have been no clinical trials on extracts of Sceletium in a clinical population. Two recent clinical case reports are presented here, where extract *Sceletium tortuosum* Zembrin® was used by my wife Dr. Olga Gericke in her integrative psychiatric practice in Cape Town (Gericke et al., 2017).

CASE REPORT 1

A 40-year-old married housewife with two children, aged 6 and 9, was referred to Dr. Olga Gericke for medication review. Her history included recurrent major depressive disorder since age 17, postpartum depression and social anxiety disorder. For the previous eight years, she had been on citalopram 20mg per day, which had adequately treated her depression and social anxiety. However, the patient found the side effects difficult to tolerate: loss of libido, emotional blunting and weight gain. Two attempts to discontinue citalopram resulted in recurrence of her depressive symptoms within four months, necessitating resumption of the medication. During consultation, the patient stated she was determined to wean herself off citalopram. After being coun-

seled on pharmaceutical and botanical treatment options, the patient opted for a trial of 25mg extract of *Sceletium tortuosum* (Zembrin®). Citalopram was reduced to 10mg daily for one week and then discontinued while starting 50mg of Sceletium, which was increased to a daily maintenance dose of 75mg. At one-month follow-up, she reported no anxiety/depressive symptoms, though she experienced occasional mild episodes of social anxiety, which she found easy to tolerate. Her libido had returned to normal, she felt much more in touch with her feelings and had lost two kilograms of weight. During the following month, her mood had slightly lowered, but this responded well to an increase of the Sceletium extract to 100mg per day. Eight months after initial assessment, she remained in remission on 100mg per day Sceletium extract Zembrin® with no side effects.

CASE REPORT 2

A 45-year-old married man, visiting South Africa from Europe, was referred to Dr. Olga Gericke by a general practitioner for assessment of depressive symptoms which developed after the birth of the patient's child eighteen months previously. Two prior episodes of depression five years and seven years before were clearly associated with stressors and had resolved without treatment. He had seen a psychotherapist for two years in his country of origin. There was no history of medical illness and routine blood tests were normal. There was a family history of depression but no history of substance abuse. The patient had recently tried self-medicating with a combination product of *Sceletium tortuosum* and *Avena sativa*, but found it too sedating. Treatment was initiated with 50mg per day *Sceletium tortuosum* extract and increased to 100mg a day. In addition, the patient was seen for weekly supportive psychotherapy sessions. Within four weeks, his depressive symptoms remitted and he was discharged from the practice after six weeks when he was returned to his country of origin. He was advised to continue the 100mg *Sceletium tortuosum* extract daily and to seek psychiatric follow-up on his return home.

Standardized and characterized Sceletium extracts clearly have great potential as safe, effective botanical medicines for treating clinical anxiety and depression, and integrating extracts of Sceletium into psychiatric clinical practice has been described based on Olga's fifteen years of experience with Sceletium in her practice in Cape Town, and the clinical experience of Dr. Richard P. Brown, a psychopharmacologist and integrative psychiatrist in New York who has prescribed Sceletium in more than 30 patients during the past 4 years (Gericke et al., 2017).

While standardized Sceletium extracts have great potential to be used as botanical medicine to treat clinical anxiety and depressive states, it is not clear if this potential will ever be realized. The cost of developing the clinical evidence of safety and efficacy to achieve marketing authorization for a botanical medicine is prohibitive, the quality issues of polymolecular botanical medicines continue to be a major challenge, and the regulatory pathway to achieve registration as a botanical medicine is not as clear or as harmonized internationally as for single chemical entities. In the last two decades, the US Food and Drug Administration has only approved two botanical drugs; the first botanical drug approved by the FDA was Veregen®, a treatment for genital and perianal warts that is derived from a green tea extract (*Camellia sinensis* Kuntze), and a number of years later the FDA approved Fulyzaq™, a drug for HIV-associated diarrhea, extracted from the latex of the South American tree (*Croton lechlerii* Müll. Arg) (Ahn, 2017).

Future approved medicines derived from Sceletium are more likely to be developed from isolated pure alkaloids, their metabolites, or from semi-synthetic derivatives. Pathways for the synthesis of mesembrine and related alkaloids have been described from the early 1960s. A review of the synthesis of mesembrine, for example, includes more than thirty described pathways, including isomer-selective synthesis (Zhao et al., 2010). While there is a fairly extensive literature on the chemistry and synthesis of these compounds, the pharmacology of isolated compounds has hardly been explored. The pharmacology of metabolites of these compounds presents a rich field for psychoactive new drug discovery.

Distillation of two decades of experience of indigenous uses, *in vitro* pharmacology, pre-clinical studies, anecdotal reports, clinical case studies and pilot randomized controlled clinical trials

suggest that isolated Sceletium alkaloids (and their metabolites and analogues) have enormous potential for the development of rapidly acting psychoactive drugs with a low side-effect profile for: 1

- Major Depressive Disorder
- Generalised Anxiety Disorder
- Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder
- Post-Traumatic Stress Disorder
- Mild Cognitive Impairment
- Neuroprotection
- Controlling appetite and craving in weight management programs
- Addiction management, including opioid addiction
- Chronic pain
- Schizophrenia

2

My hope is that this paper will stimulate further academic and pharmaceutical research to realize the potential of Sceletium extracts and mesembrine-type alkaloids for preventing, treating and ameliorating diverse mental health diseases, and for enhancing the quality of life of all people. 3

ACKNOWLEDGMENTS 4

Family, friends and colleagues are thanked for their contribution to this Sceletium odyssey: Aaron Santana, Abdulgaseeb Jacobs, Abraham van Rooyen, Alan Gray, Alan Harvey, Alex Schauss, Alison Dyer, Alvaro Viljoen, Andrew Tully, *Mark Tully, *Andries Steenkamp, Antonio Bianchi, Ashley Mashigo, Bani Isaac Mayeng, Barbara Davis, Beatrice Molac, Beatriz Ercilla, Ben-Erik van Wyk, Bruce Gordan, C.C. Kennedy, Carine Smith, Carl Albrecht, Cheryl Inggs, Chris Watson, Christine Tomcheck, Credo Mutwa, Dan Stein, David Terburg, Dennis McKenna, Deon Hofmeyr, Diana-Lee Simon, Dick Doorn, Dierdre Allen, Dorris Schroeder, *Earle Graven, Edda Fiegert, Emmanuel Shikanga, Eric Anderson, Eric Gericke, Fabio Ravanello, Fabio Soldati, Fiona Archer, George Davidson, *Gert Dirkse, *Greg McCarthy, Guy Wertheim-Aymes, Hans van den Hurk, Hannes de Lange, Haylene Nell, *Hibiki Kurono, Holly Bayne, Ingrid Keplinger-Dimpfel, Iris Freie, Isadore Kanfer, Jack van Honk, Jap-Jap Klaasse, Jerry Cott, John Endres, *John Winslow, Julia Wiebe, Kenjiro Shimada, Kenzi Loke, Kia Gericke, Laubi Walters, *Lawrence Penkler, Leana Cloete, Leana Bronkhorst, Linda Brady, Lisa Garson, Lisa Meserole, Lita Cole, Lodewyk Mories, Manuel Lopez-Romero, Marena Manley, Marion Weston, Mark Blumenthal, Maryna Swart, Matt Tripp, Michel Woodbury, Michelle Gericke, Miguel Jimenez del Rio, Myke Scott, Ncindani Maswanganyi, Neal Craft, Nicky Gericke, Nuri Fraile Lopez, Olga Gericke, Patricia Garberg, Paul Flowerman, Paul Jonker, Pete Backwell, Peter Williams-Ashman, Pippa Skotnes, Richard Brown, Roberto Jimenez del Rio, Robb Snaddon, Roger Chennels, Roger Stewart, Roy van Brummelen, Rudi Giger, *Ryo Yonemoto, Satoru Furukawa, Seth Flowerman, Simon Chiu, Sinobu Kurono, Srinivas Patnala, Tanausú Vega, Timothy Murbach, Ulrich Feiter, Veronica Napier, Vladimir Badmaev, Wilfried Dimpfel, William Emboden.
*Deceased. 5

REFERENCES 6

Ahn, K., 2017. The worldwide trend of using botanical drugs and strategies for developing global drugs. *BMB reports* 50(3): 111-116.

Alibaba.com, 2017. https://www.alibaba.com/trade/search?fsb=y&IndexArea=product_en&CatId=&SearchText=sceletium+extracts&isGalleryList=G Accessed 20th April 2017.

Amazon.com, 2017. Drugs and drug paraphernalia. Examples of prohibited listings. https://www.amazon.com/gp/help/customer/display.html/ref=hp_rel_topic?ie=UTF8&nodeId=200277220 Accessed 7th April 2017.

Archer, F.M., 1994. *Ethnobotany of Namaqualand: The Richtersveld* (Master of Arts dissertation, University of Cape Town).

Cashman, J.R., et al., 2009. Stereoselective inhibition of serotonin reuptake and phosphodiesterase by dual inhibitors as potential agents for depression. *Bioorganic & Medicinal Chemistry* 17(1), 337-343.

Chiu, S., et al., 2014. Proof-of-concept randomized controlled study of cognition effects of the proprietary extract *Sceletium tortuosum* (Zembrin) targeting phosphodiesterase-4 in cognitively healthy subjects: implications for Alzheimer's Dementia. *Evidence-Based Complementary and Alternative Medicine* Vol. 2014,1-10.

Collot, A.G., 1856. *A New and Improved Standard French and English and English and French Dictionary*. C.G. Henderson and Company, Philadelphia. 7

De La Caille, M. l'Abbé., 1763. *Journal Historique Du Voyage Fait Au Cap De Bonne Esperance.* Academie Des Sciences, Paris.
Digby, A., 2005. Self-medication and the trade in medicine within a multi-ethnic context: a case study of South Africa from the mid-nineteenth to mid-twentieth centuries. *Social History of Medicine* 18, 439–457.
Digital Bleek & Lloyd. http://lloydbleekcollection.cs.uct.ac.za/xam.html. Accessed 21 June 2017.
Dimpfel, W., et al., 2016. Electropharmacogram of *Sceletium tortuosum* extract based on spectral local field power in conscious freely moving rats. *Journal of Ethnopharmacology* 177, 140-147.
Dimpfel, W., et al., 2017. Effect of Zembrin® on Brain Electrical Activity in 60 Older Subjects after 6 Weeks of Daily Intake. A Prospective, Randomized, Double-Blind, Placebo-Controlled, 3-Armed Study in a Parallel Design. *World Journal of Neuroscience* 7, 140-171.
Dragendorff, G., 1898. *Die Heilpflanzen Der Verschiedenen Völker Und Zeiten*. Verlag Von Ferdinand Enke, Stuttgart.
Dye, E. Undated presentation. Novel hallucinogens and plant-derived highs. Drug Enforcement Agency. https://www.nist.gov/sites/default/files/documents/oles/NIST-Novel-Hallucinogens-and-Plant-Derived-Highs-Final.pdf Accessed 15 April 2017.
Forbes, E.S. (Ed.)., 1986. *Carl Peter Thunberg. Travels at the Cape of Good Hope 1772–1775.* Second Series No. 17, Van Riebeeck Society, Cape Town.
Gerbaulet, M., 1996. Revision of the genus Sceletium N.E. Br. (Aizoaceae). *Botanische Jahrbücher* 118, 9–24.
Gericke, N., 1995. Sceletium Project. Investigation of a Traditional Herbal Sedative. Unpublished research report for South African Druggists Ltd., 30 May 1995.
Gericke, N., 2001. Clinical application of selected South African medicinal plants. *Australian Journal of Medical Herbalism* 13, 3–17.
Gericke, N., 2002. Plants, products and people: southern African perspectives, in: *Advances In Phytomedicine* Volume 1. *Ethnomedicine And Drug Discovery*. Iwu, M.M., Wootton, J.C. (Eds.), Elsevier, Amsterdam.
Gericke, N., 2011. Muthi to medicine. *South African Journal of Botany* 77(4), 850-856.
Gericke, N., 2014. Ethnobotanical records from a corporate expedition in South Africa in 1685. Herbalgram. *Journal of the American Botanical Council* 102, 48-61.
Gericke, N., Van Wyk, B.-E., 1999. Pharmaceutical compositions containing mesembrine and related compounds. US Patent 6,288,104.
Gericke, N., and van Wyk, B.-E., 2000. *People's Plants. A Guide To Useful Plants Of Southern Africa.* Briza, Pretoria.
Gericke, N., and Viljoen, A.M., 2008. Sceletium—a review update. *Journal of Ethnopharmacology* 119(3), 653-663.
Gericke, O., et al., 2017. *Sceletium tortuosum*, in: *Complementary and Integrative Treatments in Psychiatric Practice.* Gerbarg, PL, Muskin PR, Brown RP (Eds.), American Psychiatric Association Publishing, Arlington, VA.
Gordon, D., 1996. From rituals of rapture to dependence: the political economy of khoikhoi narcotic consumption, c.1487–1870. *South African Historical Journal* 35, 62–88.
Gunn, M., Codd, L.E., 1981. *Botanical Exploration of Southern Africa.* A.A. Balkema, Cape Town.
Harvey, A.L., et al., 2011. Pharmacological actions of the South African medicinal and functional food plant *Sceletium tortuosum* and its principal alkaloids. *Journal of Ethnopharmacology* 137(3), 1124-1129.
Harvey, A., et al., 2013. Pharmaceutical compositions containing mesembrenone. U.S. Patent 8,552,051.
Herre, H., 1971. *The Genera Of The Mesembryanthemaceae.* Tafelberg, Cape Town.
Hirabayashi M., et al., 2002. Clinical application of South African tea on dementia dog. *Japanese Journal of Small Animal Practice* 21, 109–113. [Japanese]
Hirabayashi M., et al., 2004. Clinical effects of South African tea for cat. *Japanese Journal of Small Animal* Practice 23, 85–89. [Japanese]
Hirabayashi M., et al., 2005. Clinical effects of South African Tea for dementia animal. *Japanese Journal of Small Animal Practice* 24, 27–31. [Japanese]
Hobbs, C.E., 1876. C.E. Hobbs' *Botanical Hand-Book*. C.E. Hobbs, Boston.
Holmes, E.M., 1874. Materia Medica Notes. *American Journal of Pharmacy* Vol. XlVI (1), 286.
Iatridis, K., Schroeder, D., 2016. *Responsible Research and Innovation in Industry. The Case for Corporate Responsibility Tools.* Springer, Cham, Heidelberg, New York, London.
Jacobsen, H., 1960. *Handbook of Succulent Plants. Vol. III. Mesembryanthemums (Ficoidaceae).* Blandford Press, London.
Jeffs, P.W., et al., 1982. Sceletium alkaloids. Structures of five new bases from Sceletium namaquense. *Journal of Organic Chemistry* 47, 3611–3617.
Juritz, C.F., 1905. *Report of the joint meeting of the British Association for the Advancement of Science and the South African Association for the Advancement of Science* 1, 231.
Klak, C., Bruyns, P.V., 2013. A new infrageneric classification for Mesembryanthemum (Aizoaceae: Mesembryanthemoideae). *Bothalia* 43 (2), 197-206.
Kolben, P., 1731. *The Present State of the Cape of Good Hope.* Translated from German by Mr. Medley. W. Innys, London, 210-213.
Krstenansky, J.L., 2017. Mesembrine Alkaloids: review of their occurrence, chemistry, and pharmacology. *Journal of Ethnopharmacology* 195, 10-19.
Laidler, P.W., 1928. The magic medicine of the Hottentots. *South African Journal of Science* 25, 433–447.
Lesiak, A.D., et al., 2016. Direct analysis in real-time high-resolution mass spectrometry as a tool for rapid characterization of mind-altering plant materials and revelation of supplement adulteration–the case of Kanna. *Forensic science international* 260, 66-73.
MacKenzie, S.J., Houslay, MD, 2000. Action of Rolipram on specific PDE4 cAMP phosphodiesterase isoforms and on the phosphorylation of cAMP-response-element binding protein (CREB) and p38 mitogen-activated protein (MAP) kinase in U937 monocytic cells. *Biochem J.* 347 (Pt 2), 571–578.
Marloth, R., 1917. *The Flora Of South Africa. Dictionary of The Common Names Of Plants.* Specialty Press of South Africa, Cape Town, 105.

Meiring, I., 1896. Notes on some experiments with the active principle of Mesembrianthemum tortuosum, L. *Transactions of the South African Philosophical Society* Volume IX, 48–50.
Meyer, G.M., et al., 2015. GC-MS, LC-MSn, LC-high resolution-MSn, and NMR studies on the metabolism and toxicological detection of mesembrine and mesembrenone, the main alkaloids of the legal high "Kanna" isolated from *Sceletium tortuosum*. *Analytical and bioanalytical chemistry* 407 (3), 761-778.
Moreland, W.H. (Ed.), 1934. *Peter Floris, His Voyage to the East Indies in the Globe, 1611-1615. The Contemporary Translation of His Journal*. Hakluyt Society, London, 4-5.
MSS BC151 006, Manuscript and Archives Department of the Libraries, University of Cape Town.
Murbach, T.S., et al., 2014. A toxicological safety assessment of a standardized extract of Sceletium tortuosum (Zembrin®) in rats. *Food and Chemical Toxicology* 74, 190-199.
Nell, H., et al., 2013. A randomized, double-blind, parallel-group, placebo-controlled trial of extract *Sceletium tortuosum* (Zembrin) in healthy adults. *The Journal of Alternative and Complementary Medicine* 19(11), 898-904.
Nicholl, J.M., 1895. *Botanical Ready Reference*. Murray & Nicholl Manufacturing Company, Chicago.
Nortje, J., 2011. *Medicinal Ethnobotany of the Kamiesberg*, Namaqualand, Northern Cape Province (Doctoral dissertation, MSc thesis), University of Johannesburg.
Nortje, J.M., Van Wyk, B.-E., 2015. Medicinal plants of the Kamiesberg, Namaqualand, *South Africa. Journal of Ethnopharmacology* 171, 205-222.
Pappe, L., 1868. *Florae Capensis Medicae, 3rd ed., Prodromus. An Enumeration of South African Plants used as Remedies by the Colonists of the Cape of Good Hope*. W. Brittain, Cape Town.
Patnala, S., Kanfer, I., 2010. HPLC analysis of mesembrine-type alkaloids in Sceletium plant material used as an African traditional medicine. *Journal of Pharmacy & Pharmaceutical Sciences* 13(4), 558-570.
Prader-Samper, José M. de., 2007. The plant lore of the /Xam San: //Kabbo and ≠Kasin's identification of "Bushman" medicines. Culturas Populares. *Revista Electrónica* 4, 1-17. http://www.culturaspopulares.org/textos4/articulos/deprada.pdf ISSN: 1886-5623.
Purchas, S., 1625. *Purchas His Pilgrimes. In Five Bookes*. Printed by William Stansby for Henrie Fetherstone, London. Book One, 528.
Rimington, C., Roets, C.G.S., 1937. Notes upon the isolation of the alkaloidal constituent of the drug "channa" or "*kougoed*". *Onderstepoort Journal of Veterinary Science and Animal Industry* 9, 187-191.
Roscher, J., et al., 2012. Forensic analysis of mesembrine alkaloids in *Sceletium tortuosum* by nonaqueous capillary electrophoresis mass spectrometry. *Electrophoresis* 33(11), 1567-1570.
Schneider, J-C, Poljoux, J., Fernando,F., Greim, O. 28 September 2016. Heating assembly for an aerosol generating system. European Patent Application EP20130821804
Scott, G., Hewett, M.L., 2008. Pioneers in ethnopharmacology: the Dutch East India Company (VOC) at the Cape from 1650 to 1800. *Journal of Ethnopharmacology* 115(3), 339-360.
Serton, P., Raven-Hart, W.J. de Kock en E.H. Raidt (Eds.), 1971. *François Valentijn, Beschryvinge van de Kaap der Goede Hoope*. Deel I. Van Riebeeck Society, Cape Town.
Shikanga, E.A., et al., 2012. Validated RP-UHPLC PDA and GC–MS methods for the analysis of psychoactive alkaloids in *Sceletium tortuosum*. *South African Journal of Botany* 82, 99-107.
Smith, C., 2011. The effects of *Sceletium tortuosum* in an *in vivo* model of psychological stress. *Journal of Ethnopharmacology* 133(1), 31-36.
Smith, C.A., 1966. *Common Names of South African Plants*. Botanical Survey Memoir 35. Government Printer, Pretoria.
Smith, M.T., et al., 1996. Psychoactive constituents of the genus Sceletium NE Br. and other Mesembryanthemaceae: a review. *Journal of Ethnopharmacology* 50(3), 119-130.
Tachard, G., 1686. *Voyage de Siam, Des Pères Jesuites, Envoyez par le Roy aux Indes & à la Chine*. Arnold Seneuze and Daniel Horthemels, Paris, 102.
Terburg, D., et al., 2013. Acute effects of *Sceletium tortuosum* (Zembrin®), a dual 5-HT reuptake and PDE4 inhibitor, in the human amygdala and its connection to the hypothalamus. *Neuropsychopharmacology* 38(13), 2708-2716.
Thorens, M., Cochand, O., 24 March 2016. Electronically heated aerosol delivery system. United States Patent Application 20160081395.
Tully, W., 1858. *Materia Medica or Pharmacology And Therapeutics*. Jefferson Church MD, Springfield, 823.
UNODC, 2013. *The Challenge of New Psychoactive Substances. List of Plant-based Substances, 101-102.*
Waterhouse, G., et al., 1979. *Simon van der Stel's Journey to Namaqualand in 1685*. Human & Rousseau, Cape Town.
Watt, J.M., and Breyer-Brandwijk, M.G., 1962. *The Medicinal and Poisonous Plants of Southern and Eastern Africa*, 2nd ed. Livingstone, London.
Wilson, M.L., 1993. Early records of some flora and fauna used by the Khoisan of the Western Cape. *Southern African Field Archeology* 2, 67-73.
Ye, Y., et al., 2000. Effects of repeated antidepressant treatment of type 4A phosphodiesterase (PDE4A) in rat brain. J *Neurochem* 74, 1257–1262.
Zhao, Y., et al., 2010. *Review of total synthesis of mesembrine*. Youji Huaxue 30 (1), 47–59.
Zwicky, E., 1913. Über Channa, ein Genussmittel der Hottentotten. *Vierteljahrsschr. Naturforsch. Gesell. Zürich* 58, 371-430.