Chapter 4

Sceletium Plant Species: Alkaloidal Components, Chemistry and Ethnopharmacology

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Additional information is available at the end of the chapter

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Abstract

The genus *Sceletium,* classified under the Aizoaceae family, is indigenous to the Western, Eastern and Northern Cape province of South Africa. There are currently eight reported species divided into two main "types" with five species in the *tortuosum* and three in the *emarcidum* type. It has been observed that, in general, mesembrine-type alkaloids such as mesembrenol, Δ^7mesembrenone, mesembranol, mesembrenone, mesembrine and epimesembranol as well as some non-mesembrine type such as Sceletium A4, tortuosamine and joubertiamine occur in the *tortuosum* type; the *emarcidum* type is devoid of alkaloids. Morphological identification of species type presents a formidable challenge, where subtle differences are found in the secondary veins that branch off from the middle vein toward the leaf margin. In view of the fact that the plant contains a complex mixture of closely related compounds, in particular alkaloidal components, separation techniques and their application to evaluate specific chemical components are an important aspect which permits accurate characterization and quantification. In addition, the development of appropriate analytical methods for chemotaxonomic studies has provided valuable information to confirm specific plant identity. Importantly, these methods are also required for the quality control of plant material used to manufacture complementary and traditional medicines containing *Sceletium*.

Keywords: *Sceletium tortuosum*, *Sceletium emarcidum*, alkaloids, mesembrine, chemotaxonomy, HPLC-MS

1. Introduction and background

Sceletium alkaloids have been studied over a century when their presence was first reported in1896 and later by Zwicky in 1914. In a detailed study by Zwicky on about 40 species of the genus *Mesembryanthemum,* more than 50% of the plants tested positive for alkaloids. Due to

this large number of species, the genus *Mesembryanthemum* was abandoned and some of the species were reassigned to genus *Sceletium*, family Aizoaceae [1].

These alkaloids, originating from *Sceletium* plants species, were widely found in the Western and Karoo regions of South Africa. The name *Sceletium* is derived from the Latin word *Sceletus* meaning skeleton. The derivation of the name is due to the prominent lignified leaf vein structure that is observed in dried leaves of this genus which give a skeletal appearance. Anecdotal evidence suggests that this plant is highly revered and held in great esteem by the tribes who collected and bartered it frequently in exchange for cattle and other commodities. Subsequently, the early Dutch colonists further showed commercial interest in this plant, and many plants of this family were also introduced to European cultivation [2].

The *Sceletium* plants can readily be identified by its persistent dry "skeletonized" leaves which enclose the young leaves during the dry season (**Figure 1a**), to protect them from adverse environmental conditions [3]. The specimens of two main types of Sceletium plants: *Sceletium tortuosum* and *Sceletium emarcidum* are depicted in **Figure 1b** and **c**, respectively.

Figure 1. (a) Skeletonized leaves of *S. tortuosum*. (b) *Sceletium tortuosum*. (c) *Sceletium emarcidum* (with skeletonized leaves).

2. *Sceletium* species

Sceletium species occurs in the Eastern, Northern, Western Cape provinces of South Africa and the genus *Sceletium*, belongs to the family, Aizoaceae [1].

2.1. Identification of *Sceletium* plant species

The specimens were studied and identified using the identification key of Gerbaulet [1]. Based on the identification key, the venation pattern which differs between species is one of the important taxonomic identification features.

There are currently eight reported species [3] of this genus, divided into two "types" with five species in the *tortuosum* type and three in *emarcidum* type as follows:

Tortuosum type: *Sceletium tortuosum; Sceletium crassicaule; Sceletium strictum; Sceletium expansum and Sceletium varians.*

Emarcidum type*: Sceletium emarcidum; Sceletium exalatum and Sceletium rigidum.*

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The main differences are found in the secondary veins that branch off from the middle vein toward the leaf margin. Based on the venation type, the species is mainly classified as either *emarcidum* or *tortuosum* types (**Figure 2**). In the *emarcidum* type, the leaf is more flat and the dried leaf venation pattern shows a central main vein with the curved secondary vein which branches off the main vein, reaching the leaf margins.

In plants of the *tortuosum* type (**Figure 2**), the dry leaves are more concave and usually show about three to five or sometimes up to seven major parallel veins. The secondary veins run straight up to the apex on both sides of the middle vein.

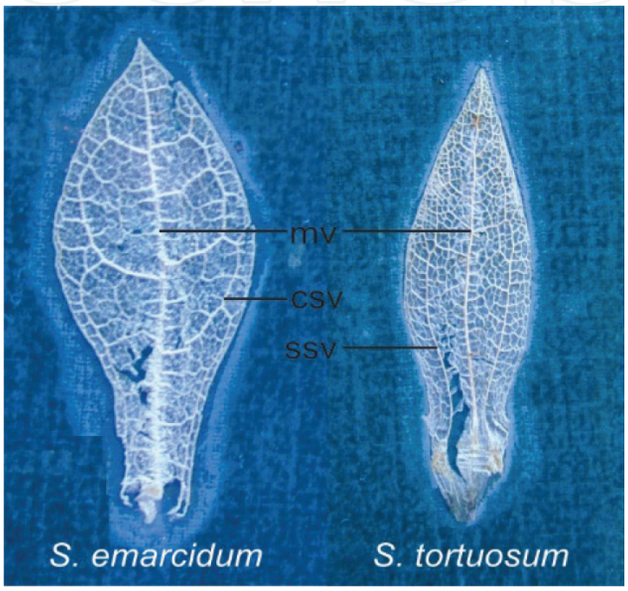

Figure 2. Venation pattern of skeletonized leaves in *Sceletium* species. mv = middle vein, csv = curved secondary vein, ssv = straight secondary vein.

3. Chemistry of *Sceletium* alkaloids

Preliminary studies on *Sceletium* were done by Meiring in 1896, suggesting that the presence of alkaloids and this was confirmed by Zwicky in 1914. Further studies on *S. expansum* and *S. tortuosum* reported by Zwicky in 1914, yielded a noncrystalline alkaloid which was named "mesembrin" with the reported molecular formula, $C_{16}H_{19}NO_4$ [4]. Rimington and Roets [5] reinvestigated this plant in 1937, and attempts to crystallize the alkaloid as a free base or hydrochloride salt were unsuccessful. In their experiments, they managed to obtain a crystalline picrate and platinichloride from the methylated free base and the molecular formula was deduced based on combustion analysis. The molecular formula for "mesembrin" was reassigned as $C_{17}H_{23}NO_3$ and is presently known as mesembrine, suggesting that the molecule belonged to the tropane ester alkaloid group.

Bodendorf and Krieger [6], in their work in 1957, revisited the molecule and successfully crystallized the mesembrine base to its hydrochloride salt, along with isolation of two more bases, namely "mesembrinine," presently known as mesembrenone, which has two hydrogen atoms less, and the structure is closely related to mesembrine. The other base was called

"channaine," which was described as a phenolic base, and it was also reported that all these three compounds were purported to be optically inactive.

Popelak and Lettenbauer [7] in 1967 reported the incidence of *Sceletium* alkaloids in the plants they studied as 1 to 1.5%, which consisted of approximately 0.7% mesembrine and 0.2% "mesembrinine." The structure of mesembrine, deduced from their study, was reported as *N*-methyl-3a-(3′,4′-dimethoxyphenyl)-6-oxo-*cis*octahydroindole, which provided the foundation for continued studies on this group of alkaloids [4].

Jeffs *et al* in 1974 [8] worked further on *S. namaquense* and *S. strictum* and reported five new alkaloids, namely *Sceletium* alkaloid A4, N-formyltortuosamine, 4′-O-demethylmesembrenone, Δ^7mesembrenone and sceletenone. It was also reported that in a concurrent study by Wiechers *et al* on *S. tortuosum*, another base, tortuosamine, was isolated and had a close structural relation to *Sceletium* alkaloid A4.

Arndt and Kruger in 1970 [9] reported three new alkaloids, joubertiamine, dihydrojoubertiamine and dehydrojoubertiamine from *S. joubertii*, where their basic skeletons were biogenetically closely related to mesembrane (**Figure 3**) and not related to the mesembrine—like of alkaloids. The above alkaloids were also isolated and reported in another *Sceletium* species, *S. subvelutinum*, by Herbert and Kattah 1990 [10].

Whereas the phytochemical content of *Sceletium* species has been studied since 1896 [4], the reported alkaloidal content has been constrained to tortuosum-type species only, and related information on the emarcidum species has been conspicuously absent from the literature. However in 2013, Patnala and Kanfer reported the complete absence of mesembrine as well as other alkaloids usually found in the tortuosum type in their investigations involving three emarcidum species: *S. emarcidum, S. exalatum* and *S. rigidum* [11].

The alkaloids which have been isolated from *Sceletium* species are broadly classified into four structural classes. The major subgroup being the 3a-aryl-cis-octahydroindole skeleton which is referred to as the mesembrine group (**Table 1**) which includes Δ^4 series and Δ^7 series based on the double bond at position 4–5 (**Table 2**) and 7–7a (**Table 3**), respectively. *Sceletium* alkaloid A4 (**Table 4**) constitutes the lone member of the second subgroup. The third subgroup is closely related to the second, which is the alkaloid, tortuosamine type (**Table 5**), and the fourth group is the joubertiamine type (**Table 6**), which is closely related to the mesembrine series [10].

Of the above subgroups, the mesembrine type is the largest, consisting of about 15 alkaloids. The class derives its name from mesembrine, which was the first structurally characterized alkaloid molecule [4].

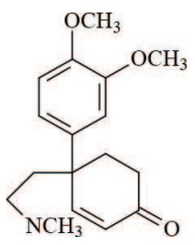

Figure 3. Mesembrane.

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The major alkaloid in mesembrine type is (–)-mesembrine, reported to be present in up to 1% in *S. namaquence* and occurs as a partial racemate in *S. strictum* and *S. tortuosum* in smaller amounts [8]. The reported alkaloids in this subgroup are listed in **Tables 1–3** [12].

3.1. Mesembrine-type (I)

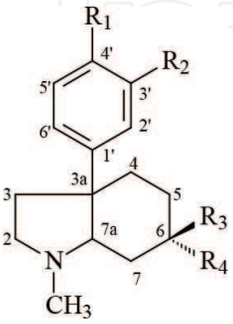
	No.	R1	R2	R3, R4	R3	R4	Compound
	1	OMe	OMe	O	–	–	Mesembrine
	2	OMe	OMe	–	OH	H	Mesembranol
	3	OMe	OMe	–	H	OH	Epimesembranol
	4	OMe	OMe	–	OAc	H	Mesembranol acetate
	5	OH	OMe	–	OH	H	4′Demethyl mesembranol
	6	OMe	OMe	–	OMe	H	Mesembranol methyl ether
	7	OMe	OMe	H	–	–	Mesembrane

Table 1. Mesembrine-type (I) *Sceletium* alkaloids.

3.2. Δ⁴ Mesembrine-type (II)

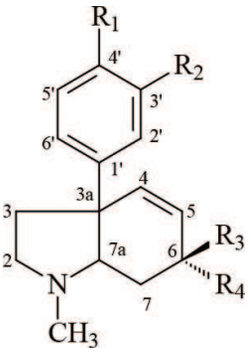
	No.	R1	R2	R3,R4	R3	R4	Compound
	8	OMe	OMe	O	–	–	Mesembrenone
	9	OMe	OMe	–	OH	H	Mesembrenol
	10	OMe	OMe	–	H	OH	6-Epimesembrenol
	11	OMe	OMe	–	OAc	H	Mesembrenol acetate
	12	OH	OMe	–	OMe	H	–
	13	OMe	H	O	–	–	4′-O-methyl sceletenone
	14	OH	H	O	–	–	Sceletenone

Table 2. Δ⁴Mesembrine-type (II) *Sceletium* alkaloids.

3.3. Δ⁷ Mesembrine-type (III)

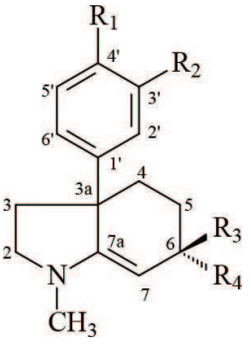
	No.	R1	R2	R3,R4	R3	R4	Compound
	15	OMe	OMe	O	–	–	Δ⁷ Mesembrenone

Table 3. Δ⁷Mesembrine-type (III) *Sceletium* alkaloid.

3.4. *Sceletium* A4 types (IV)

Table 4 depicts *Sceletium* A4 alkaloid (16) and is reported to occur in *S. namaquense* as an optically active crystalline base. The other reported alkaloid [8] which is closely related to this structure is a noncrystalline optically active compound mentioned as dihydropyridone base (17).

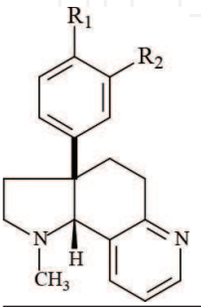
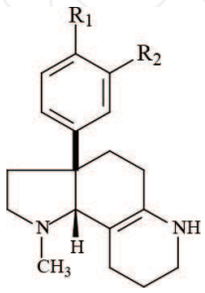
	No.	R1	R2	Compound
	16	OMe	OMe	*Sceletium* A4
	17	OMe	OMe	Dihydropyridone base

Table 4. *Sceletium* A4 type (IV) alkaloids.

3.5. Tortuosamine type (V)

The reported alkaloids (**Table 5**) in this subclass are tortuosamine (18), N-formyltortuosamine (19) and N-acetyltortuosamine (20). Tortuosamine, a noncrystalline optically active base, was isolated from *S. tortuosum* [8].

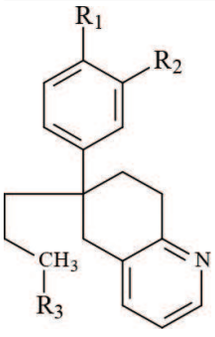
	No.	R1	R2	R3	Compound
	18	OMe	OMe	H	Tortuosamine
	19	OMe	OMe	CHO	N-formyltortuosamine
	20	OMe	OMe	COMe	N-acetyltortuosamine

Table 5. Tortuosamine-type (V) *Sceletium* alkaloids.

3.6. Joubertiamine types

These alkaloids are reported to occur principally in *S. joubertii* and have also been reported to occur in *S. subvelutinum*. These alkaloids are further classified as depicted in **Tables 6–8** [8].

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3.6.1. Dihydrojoubertiamine (VI)

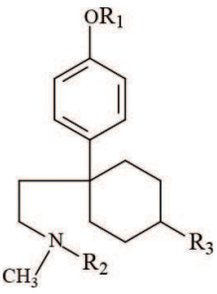
	No.	R1	R2	R3	Compound
	21	H	Me	O	dihydrojoubertiamine
	22	H	Me	Me	O-methyldihydrojoubertiamine

Table 6. Dihydrojoubertiamine-type (VI) *Sceletium* alkaloids.

3.6.2. Dehydrojoubertiamine (VII)

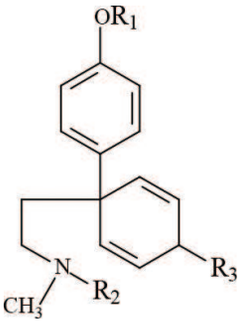
	No.	R1	R2	R3	Compound
	23	H	Me	O	dehydrojoubertriamine

Table 7. Dehydrojoubertiamine-type (VII) *Sceletium* alkaloid.

3.6.3. Joubertiamine (VIII)

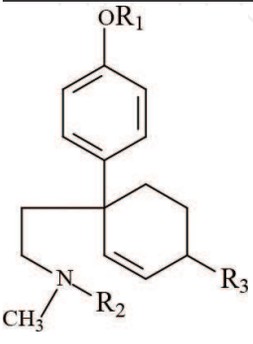
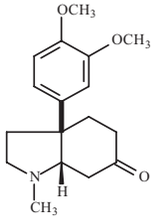
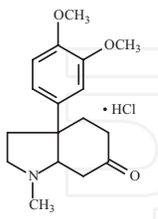
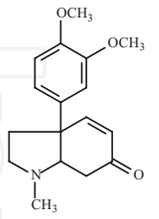
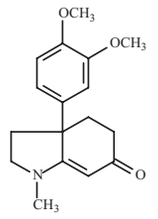
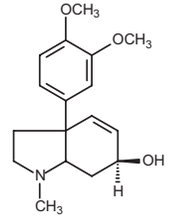
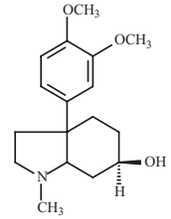
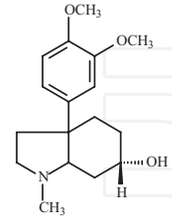
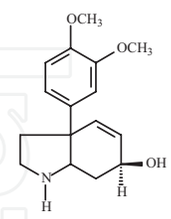
	No.	R1	R2	R3	Compound
	24	H	Me	O	Joubertiamine
	25	Me	Me	O	O-methyljoubertiamine

Table 8. Joubertiamine-type (VIII) *Sceletium* alkaloids.

Structure[21]								
Alkaloid	(–)-Mesembrine	(–)-Mesembrine HCl	Mesembrenone	Δ^7 Mesembrenone	Mesembrenol	(–)-Mesembranol	Epimesembranol	(–)-N-Demethylmesembranol
MW	289.36	325.80	287.36	287.36		291.39	291.39	275.15
MF	$C_{17}H_{23}NO_3$	$C_{17}H_{23}NO_3.HCl$	$C_{17}H_{21}NO_3$	$C_{17}H_{21}NO_3$	$C_{17}H_{23}NO_3$	$C_{17}H_{25}NO_3$	$C_{17}H_{25}NO_3$	$C_{16}H_{23}NO_3$
Description	Pale yellow viscous liquid	Needle-shaped crystals	Pale yellow viscous liquid	Low melting solid	Pale brown crystalline powder	Cubic crystals	Pale brown oil	–
OR$[\alpha]_D^{20}$	-55.4° (MeOH)	-8.4° (MeOH)	racemic	–	–	-32°($CHCl_3$), -30° (C_2H_5OH)[†]	-3.2° (C_2H_5OH)[†]	-13°
BP	*186–190°C	–		–				
MP		205–206°C	[†]88–89°C	–		144–145°C		178–185°C
Reference	[4], *[13]	[4]	[4], [†][7]	[4]		[4], [†][7]	[4], [†][7]	[4]

MW, Molecular weight; MF, molecular formula; OR, optical rotation; BP, boiling point; MP, melting point; MeOH, methanol.

Table 9. Physicochemical characteristics of mesembrine-type *Sceletium* alkaloids.

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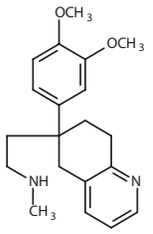
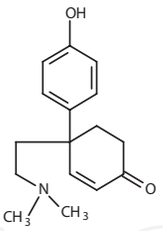
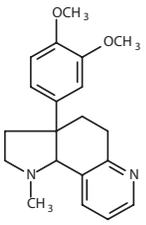
Structure			
Alkaloid	Tortuosamine	Joubertiamine	*Sceletium* A4
MW	326	325.80	324.18
MF	$C_{20}H_{26}N_2O_2$	$C_{17}H_{25}NO_3$	$C_{20}H_{24}N_2O_2$
Description	–		Pale white semi-solid
OR$[\alpha]_D^{20}$		-32°($CHCl_3$)*, -30° (C_2H_5OH)†	*+131°
BP			
MP			†153–154°C
References	[4]	*[4], †[7]	*[4], †[8]

MW, Molecular weight; MF, molecular formula; OR, optical rotation; BP, boiling point; MP, melting point; MeOH, methanol.

Table 10. Physicochemical characteristics of some typical non-mesembrine-type *Sceletium* alkaloids.

The physicochemical characteristics of various Sceletium alkaloids—mesembrine-type and non-mesembrine-type alkaloids are compiled in **Tables 9** and **10**.

4. Extraction, isolation, synthesis and characterization of *Sceletium* alkaloids

Natural products are known to contain complex chemical components. Hence, it is essential that active components in such products are identified and analyzed by validated methods to ensure product quality. The development and validation of the requisite analytical method and procedures for QC can only be achieved by testing the product using qualified reference substances.

Several methods have been reported for the extraction and isolation of these alkaloids from *Sceletium* species. In 1937, Rimington and Roets [14] described their extraction procedure of *Sceletium* alkaloids, and subsequently in 1957, Bodendorf and Krieger [6] published a different extraction procedures. Popelak and Lettenbauer, in 1967 [7], reported the isolation of some alkaloid bases along with mesembrine and mesembrinine and prepared their hydrochloride salts. Arndt and Kruger [9] reported an extraction procedure of the aerial parts of *Sceletium joubertii* to obtain those relevant alkaloids.

Herbert and Kattah [10] in their biosynthesis study of alkaloids in *Sceletium subvelutinum* reported the isolation and purification of joubertiamine and related alkaloids. Jeffs et al. [8]

reported the extraction of alkaloids from *Sceletium namaquense* which yielded mesembrine, mesembrenone, *Sceletium* A4, N-formyltortuosamine, Δ^7mesembrenone, tortuosamine and some unidentified alkaloids. Smith et al. [15] extracted mesembrenol (Table 2, No. 9) {incorrectly designated as 4′-*O*-demethylmesembrenol and labeled (1) in their paper}, mesembrine and mesembrenone from Sceletium plant material. Gericke et al. [16] in their US patent application described the extraction of mesembrine-type alkaloids with a yield of between 15 and 35 mg per gram of "dry leaves."

Subsequently, Patnala [17] developed a relatively simple and inexpensive extraction and isolation procedure for *Sceletium* alkaloids. In general, Sceletium plant powder was extracted using ethanol by soxhlet extraction followed by alcohol removal and acidification. Hexane was used to wash the acidic solution and the organic phase discarded. Subsequently, ammonia solution was used to neutralize and result in alkaline solution, and the latter was further extracted with dichloromethane (DCM). The DCM fractions were collected into a round-bottomed flask and evaporated under vacuum to yield a brown viscous liquid containing alkaloids. Following the separation of components by column chromatography, collected eluents were spotted on a TLC plate (**Figure 4**). The TLC plate was first observed under UV_{254} which showed extensive related substances (*acetone-Track 3 and acetonitrile-Track 4*) and further sprayed with Dragendorff's reagent (**Figure 4**). The acetone fraction and the acetonitrile (ACN) fractions were found to contain alkaloids.

The ACN fraction was tested for its UV spectrum which showed a maximum at 298.2 nm was found to be Δ^7mesembrenone (**Figure 5**), and this fraction was further purified by preparative TLC.

In view of the fact that Sceletium species contain complex mixtures of closely related alkaloidal components, appropriate analytical methods for their separation and identification are

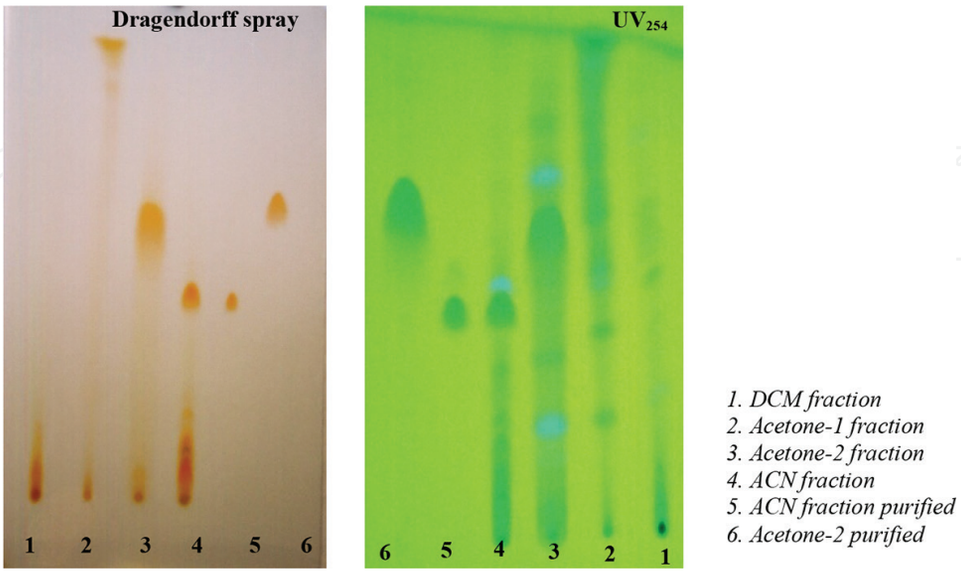


Figure 4. TLC plate of the column fractions by developed TLC method observed under UV_{254} and subsequently sprayed with Dragendorff's reagent for positive identification of alkaloids.

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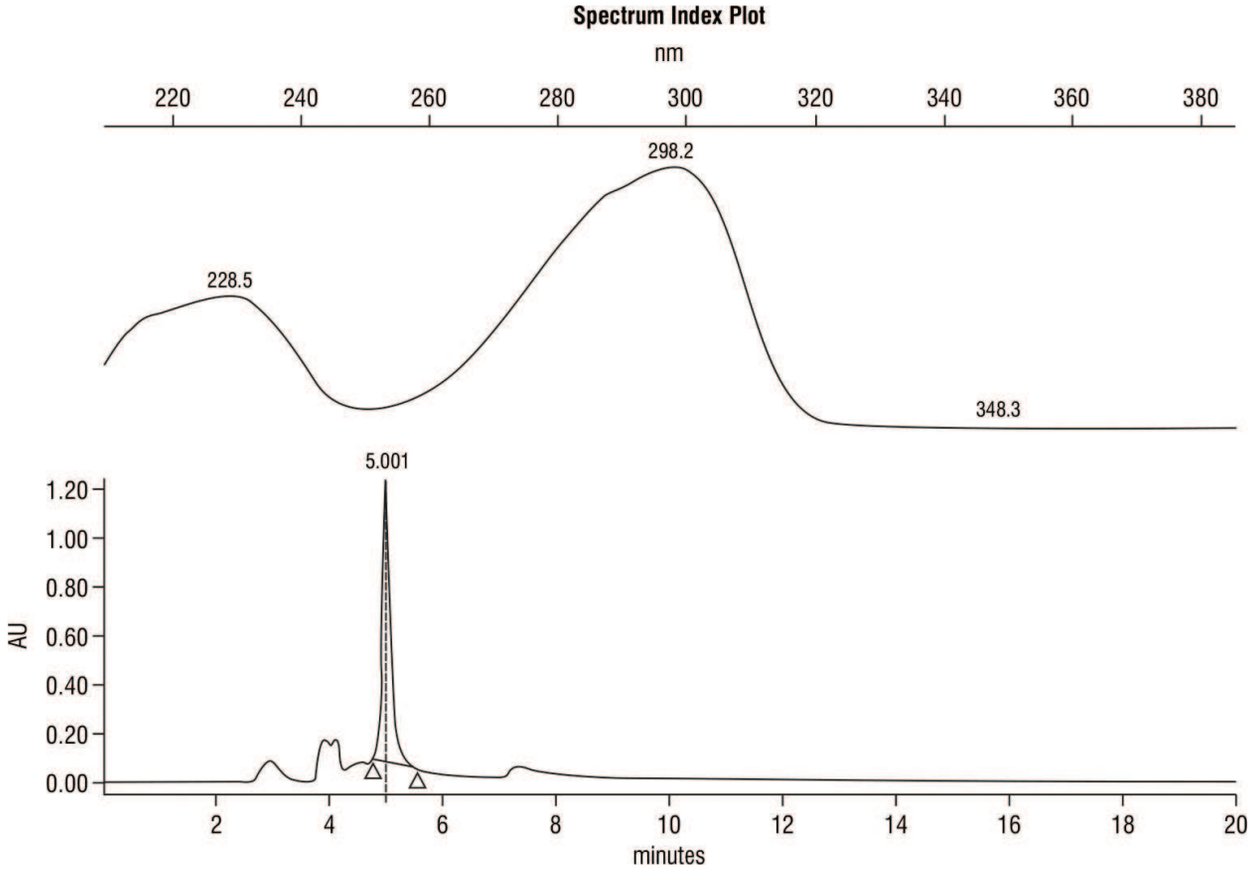

Figure 5. HPLC-PDA of ACN fraction-spectrum index plot (top) and chromatogram (bottom).

essential prerequisites for chemotaxonomic profiling of these species. Furthermore, the availability of relevant alkaloid reference standards is also necessary including the use of an analytical method with required specificity for fingerprinting. These foregoing considerations are essential to facilitate the proper identification of *Sceletium* species based on a chemotaxonomic approach [11].

5. Development of analytical methodologies for identification and quality control (QC) of *Sceletium* plant material and associated products

5.1. High-performance liquid chromatography (HPLC)

Chromatographic fingerprinting has been widely accepted and recommended by various regulatory authorities such as WHO [18], US-FDA [19] and EMEA [20] to assess the consistency of batch to batch dosage forms containing phytochemical components of the harvested plants. In the current international regulatory scenario, qualitative and quantitative analytical methods are considered mandatory.

Validated analytical methods to assay *Sceletium* plant material and dosage forms for relevant alkaloidal content were reported for the first time where a simple, accurate, precise, rapid and

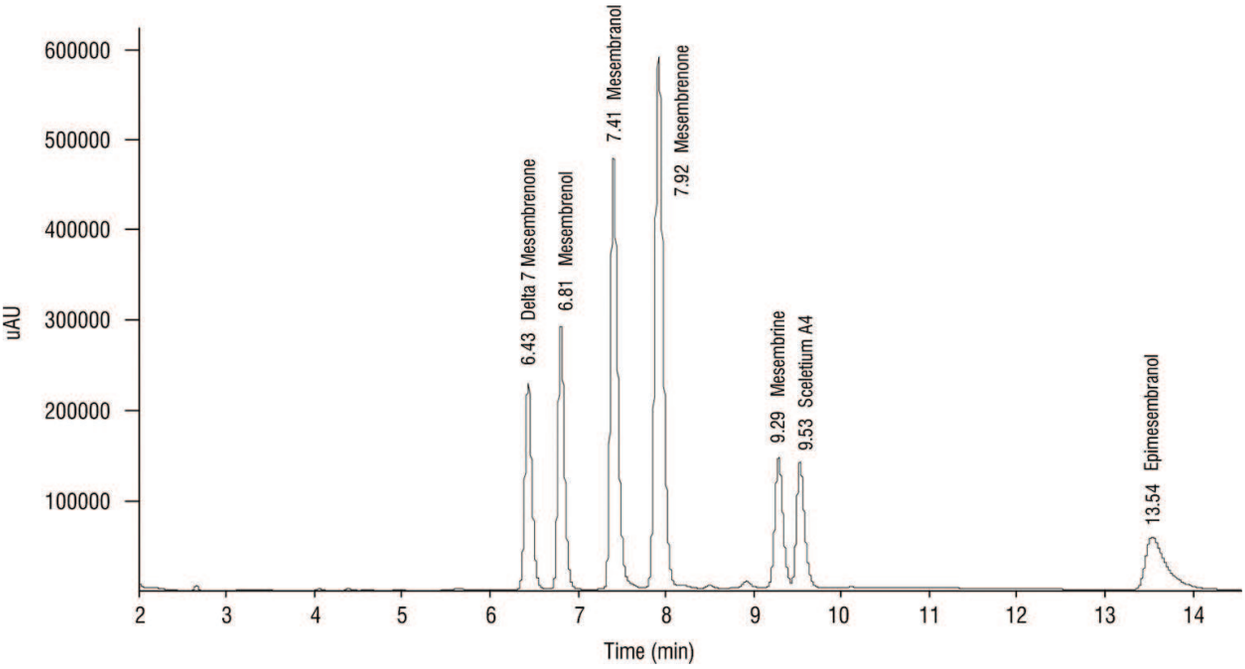

Figure 6. HPLC chromatogram of relevant standard Sceletium alkaloids.

reproducible HPLC method was developed for the identification and quantitative analysis of five relevant *Sceletium* alkaloids, Δ^7 mesembrenone, mesembranol, mesembrenone, mesembrine and epimesembranol. This method has also been successfully used to study chemotaxonomy of some *Sceletium* species and has provided impetus for the future development of quality monographs for plant and dosage forms containing *Sceletium* [21]. Subsequently, this method has been applied for the identification [22] and quantization of two additional alkaloids: Sceletium A4 and mesembrenol. **Figure 6** illustrates the chromatographic profile of the above-mentioned alkaloids.

5.2. LC-MS/MS

Since a number of variables including species differences, harvesting time, growing conditions, storage and processing contribute to the variation in phytochemical components in plants, it is therefore necessary to use appropriate and specific analytical methods to ensure quality which may affect the safety and efficacy of products prepared from plant material [23]. In particular, with respect to the *Sceletium* plant species which contain closely related mesembrine-type compounds of which some are epimers and have isobaric chemistries [17], specific methods are necessary. Since HPLC using UV detection cannot discriminate between such compounds, detection by MS enhances the accuracy and specificity of the analytical method, thereby reducing the risk of using an inappropriate *Sceletium* species for the indications on the product label [22]. In addition, this method proved valuable to monitor the fermentation process of *Sceletium* plant material [24]. Hence, the current qualitative LCMS method, and concurrent application of the previously reported quantitative assay method [22], provides valuable analytical procedures for the identification and QC of *Sceletium* plant material and its dosage forms. The application of the LC-ESI-MS tandem mass spectroscopy provides unique

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fragmentation patterns which facilitates the identity of specific alkaloid in complex matrices and thus provides valuable confirmatory data for chemotaxonomic studies [11].

5.3. Capillary zone electrophoresis (CZE)

Since alkaloids are relatively strong bases in general [25], they are good candidates for CE analysis. A CZE method was developed and validated and applied to fingerprint the presence of alkaloids in a marketed tablet product containing Sceletium plant material [26].

6. Ethnopharmacology

The use of specific herbal medicines varies depending on specific regions and ethnopharmacological experiences, which makes this form of treatment inconsistent. Safety and efficacy are major concerns due to poor documentation and a dearth of scientific research on this subject. The World Health Organization (WHO) notes that of 119 plant-derived pharmaceutical medicines, about 74% are used in modern medicine in ways that correlate directly with their traditional use as herbal medicines [27].

The traditional preparation of *Sceletium* known as "*Kougoed"* or "*Channa"* is a fermented preparation used by the native Bushmen of Namaqualand. Traditionally, its main use for its psychoactive properties involved a prior fermentation by the Khoisan tribe of southern Africa, who purported that the psychoactive effect of this plant is greatly enhanced [2, 3]. Based on this perception, *Sceletium* plants and their products are marketed with claimed improvements in mood and reduction of anxiety, when the fermented plant material is used either by chewing or smoking. In general, the fermentation process involves crushing the whole plant material or aerial parts which are then placed in sealed containers for several days and dried under natural sunlight. Patnala [17, 24] subsequently confirmed that the fermentation process transforms mesembrine to Δ^7mesembrenone and requires an aqueous environment together with the presence of light to facilitate such a transformation.

7. Biological activities and medicinal properties of *Sceletium alkaloids*

The study of the phytochemical composition of Sceletium was provoked as a result of anecdotal information describing the use of these plants by early inhabitants of Southern Africa [28]. Typical examples of medicinal use have been described in the Ethnopharmacology section above. It can be gleaned from current scientific literature that several scientific groups working on various aspects of Sceletium plants have focused on the biological activity of these alkaloids [29]. It should be noted that antidepressant activity of mesembrine-type alkaloids has been demonstrated in animal models, of which, where mesembrine has been the principal alkaloid. The antidepressant activity is reportedly based on selective inhibition of serotonin reuptake, and mesembrine has a weak narcotic effect [30]. A recent study indicates that high-mesembrine Sceletium extract is a monoamine releasing agent, rather than only a selective serotonin reuptake inhibitor [31]. Zembrin® a marketed product containing a standardized

extract of *Sceletium tortuosum* has been studied using human volunteers for its acute effects in the brain, and its pharmacological activity and potential therapeutic effect are reported to be based on the inhibiting reuptake of 5-HT and PDE4. It is suggested that a 25 mg dose of Zembrin® has the potential of reducing anxiety in humans [32].

8. Conclusions

Although eight *Sceletium* plant species have been formally classified in accordance with usual botanic taxonomy, we have observed the existence of various subspecies related to the tortuosum-type plants. Furthermore, the identified alkaloidal constituents vary between each of these plant species. In the tortuosum-type plants, mesembrenone (**Table 2**, No. 8), where the double bond occurs between C4-5; Δ7mesembrenone (**Table 3**, No. 15), where the double bond occurs between C7-7a; and the epimers, mesembranol and epimesembranol, clearly have closely related chemical structures. Hence, accurate identification and characterization is necessary to confirm the true identity of each species [22] in view of the close similarity between such chemical structures. such relevant information provides invaluable data to confirm the true identity of each species. These "tortuosum"-type Sceletium species contain mesembrine as the major alkaloid along with other minor alkaloids, Δ^7mesembrenone, mesembrenone and mesembranol and clearly differ from the other species. However, a subspecies of tortuosum type, *S. strictum* contains mesembrenone as the major alkaloidal component alongside mesembrine [11]. The above-mentioned information can be gleaned from published studies on *Sceletium* plants [17, 22, 24].

The advent and availability of modern instrumental techniques have provided valuable tools to identify differences between species based on phytochemical composition. Such approaches for taxonomical classification of plants and their species facilitate a superior and more accurate method which supersedes the classical techniques based on morphological aspects.

Although plants have been used for their medicinal properties for centuries relating back to biblical times, the interest and development of medicinal products containing plant material have grown exponentially where such products, often referred to a complementary medicines currently constitute and industry with sales of billions of dollars annually. However, there is growing concern relating to quality, safety and efficacy of such products where regulatory requirements relating to the provision of such necessary evidence currently leaves a lot to be desired and in instances have demonstrated undesirable risks to vulnerable users. Proper quality control requires the application of appropriate analytical techniques to assess the identity and quality of complementary medicines containing plant material. Quality control methods require access and availability to reference standards for each product which is marketed for medicinal use. As far as Sceletium-based products are concerned, the information relating to isolation, identification, quantification and purification of individual alkaloidal compounds found in Sceletium species provides valuable data for use in the quality control of medicines containing Sceletium plant material. While quality control is an essential component to ensure the quality of medicines, evidence of the safety and efficacy is further essential components, and it is important that such data are generated through clinical trials

in humans. Furthermore, the absorption, distribution, metabolism and elimination (ADME) of administered products and associated kinetics should be studied. Such studies require the development and validation of appropriate analytical techniques to monitor the active ingredient(s) and the resulting metabolite(s) where applicable.

Modern instrumental methods such HPLC, LC-MS, CZE and associated analytical technologies have been invaluable in developing profiles for fingerprinting, identification and characterization of the relevant alkaloids and their specific plant associations as well as serving as an important tool for QC purposes of plant material and herbal medicines containing *Sceletium*. In addition, such techniques are also necessary to study the safety, efficacy, ADME and kinetics of medicinal products containing plant material.

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