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^{1}H-NMR and UPLC-MS metabolomics: Functional tools for exploring chemotypic variation in *Sceletium tortuosum* from two provinces in South Africa

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ABSTRACT

Sceletium tortuosum (Aizoaceae) is widely recognised for the treatment of stress, anxiety and depression, as well as for obsessive compulsive disorders. A comprehensive intraspecies chemotypic variation study, using samples harvested from two distinct regions of South Africa, was done using both proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy of methanol extracts (N = 145) and ultra performance liquid chromatography-mass spectrometry (UPLC-MS) of acid/base extracts (N = 289). Chemometric analysis of the ^{1}H-NMR data indicated two main clusters that were region-specific (Northern Cape and Western Cape provinces). Two dimensional (2D) NMR was used to identify analytes that contributed to the clustering as revealed by the S-plot. The sceletium alkaloids, pinitol and two alkylamines, herein reported for the first time from *S. tortuosum*, were identified as markers that distinguished the two groups. Relative quantification of the marker analytes conducted by qNMR indicated that samples from the Northern Cape generally contained higher concentrations of all the markers than samples from the Western Cape. Quantitative analysis of the four mesembrine alkaloids using a validated UPLC-photo diode array (PDA) detection method confirmed the results of qNMR with regard to the total alkaloid concentrations. Samples from the Northern Cape Province were found to contain, on average, very high total alkaloids, ranging from 4938.0 to 9376.8 mg/kg dry w. Regarding the Western Cape samples, the total yields of the four mesembrine alkaloids were substantially lower (averages 16.4–4143.2 mg/kg). Hierarchical cluster analysis of the UPLC-MS data, based on the alkaloid chemistry, revealed three branches, with one branch comprising samples primarily from the Northern Cape that seemed somewhat chemically conserved, while the other two branches represented mainly samples from the Western Cape. The construction of an orthogonal projections to latent structures-discriminant analysis model and subsequent loadings plot, allowed alkaloid markers to be identified for each cluster. The diverse sceletium alkaloid chemistry of samples from the three clusters may facilitate the recognition of alkaloid profiles, rather than individual compounds, that exert targeted effects on various brain receptors involved in stress, anxiety or depression.

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1. Introduction

Sceletium tortuosum (L.) N.E. Br. (Aizoaceae) is the only one of eight species in the genus *Sceletium* that has been commercialised. The psychoactive properties of the plant have been attributed mainly to the presence of four mesembrine alkaloids (Fig. 1), particularly mesembrine and mesembrenone (Krstenansky, 2017).

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Abbreviations

COSY	^{1}H-^{1}H correlation spectroscopy
dry w.	dry weight
FIDs	free induction delays
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
HCA	hierarchical cluster analysis
HMBC	^{1}H-^{13}C heteronuclear multiple bond coherence
^{1}H-NMR	proton nuclear magnetic resonance
HSQC	^{1}H-^{13}C heteronuclear single quantum coherence
HSQC-TOCSY	heteronuclear single quantum coherence-total correlation spectroscopy
ICH	International Conference on Harmonisation
LC-UV/MS	liquid chromatography-ultraviolet detection/mass spectrometry
LOD	limit of detection
LOQ	limit of quantification
MS	mass spectrometer
m/z	mass-to-charge ratio
N	number of specimens/samples
NC	Northern Cape
nd.	not detected
NMR	nuclear magnetic resonance
OPLS-DA	orthogonal projections to latent structures-discriminant analysis
PC	principal component
PCA	principal component analysis
PDA	photodiode array
qNMR	quantitative nuclear magnetic resonance
RSD	relative standard deviation
Rt	retention time
TOCSY	total correlation spectroscopy
TSP	sodium 3-trimethylsilyl [2,2,3,3-^{2}H4] propanoate
UPLC-MS	ultra performance liquid chromatography-mass spectrometry
UPLC-PDA	ultra performance liquid chromatography coupled to photodiode array detection
UPLC-PDA/MS	ultra-performance liquid chromatography coupled to photodiode array detection and tandem mass spectrometry
UPLC-QToF-MS	ultra performance liquid chromatography-quadrupole time-of- flight-mass spectrometry
UV	ultraviolet
WC	Western Cape

A patent (USA patent 6,288,104) was filed in 1997 for the use of mesembrine and related compounds for treating a range of psychiatric and psychological conditions, including depression and drug dependence (Gericke and Van Wyk, 1999). The best researched commercial product is marketed under the trade name Zembrin® and consists of a standardised hydroalcoholic extract of the aerial parts of the plant (Murbach et al., 2014).

Sceletium tortuosum occurs naturally in the Western, Eastern and Northern Cape provinces of South Africa, where small-scale cultivation for commercial use is currently practised. The plant is particularly abundant in the Knersvlakte and Upper Karoo regions (Northern Cape), the Great Karoo and Ceres Karoo and more moist parts of the Western Cape Province, and is also found in the Namaqualand Rocky Hills (spanning the Western and Northern Cape provinces) (Gerbaulet, 1996). Populations native to the southern regions of Africa, including the Khoikhoi and San, have valued the beneficial properties of *Sceletium* species for centuries (Ilardi et al., 2009). Dried leaves of *S. tortuosum* are used in traditional practices to elevate mood and to alleviate anxiety and tension. Plant material is usually chewed, but is also smoked or taken as an infusion (Van Wyk and Gericke, 2003).

Shikanga et al. (2012) established the variability in the mesembrine-type alkaloid content of 151 specimens of wild *S. tortuosum* specimens, harvested from 31 localities in the Western Cape region of South Africa, using gas chromatography-mass spectrometry (GC-MS) analysis of the acid/base extracts. Five chemotypes were identified, based on the mesembrine-type alkaloid composition, using hierarchical cluster analysis (HCA) and principal component analysis (PCA) of the GC-MS data. They reported that individual chemotypes were not restricted to particular

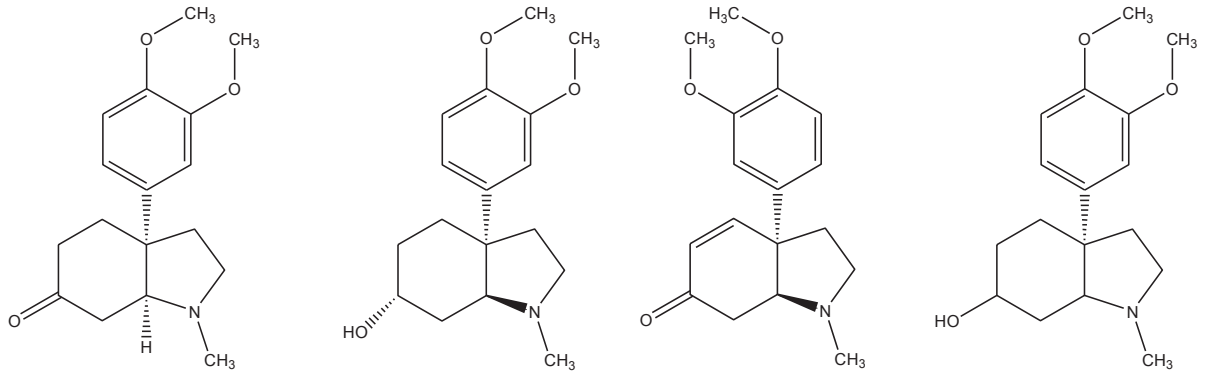

Fig. 1. Structures of the four mesembrine alkaloids associated with the central nervous system effects of *Sceletium tortuosum*.

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