

Zembrin[®]

PATENTED
STANDARDISED
BOTANICAL
SCELETIUM
INGREDIENT

EXPERIENTIAL
STRESS
RELIEF

ENHANCED
MOOD

DECREASED
ANXIETY

IMPROVED
MENTAL
PERFORMANCE

INGREDIENT OVERVIEW

INDIGENOUS
KNOWLEDGE

CUTTING-EDGE
NEURO-SCIENTIFIC
RESEARCH AND
AGRICULTURAL
TECHNOLOGY

CLINICALLY
STUDIED

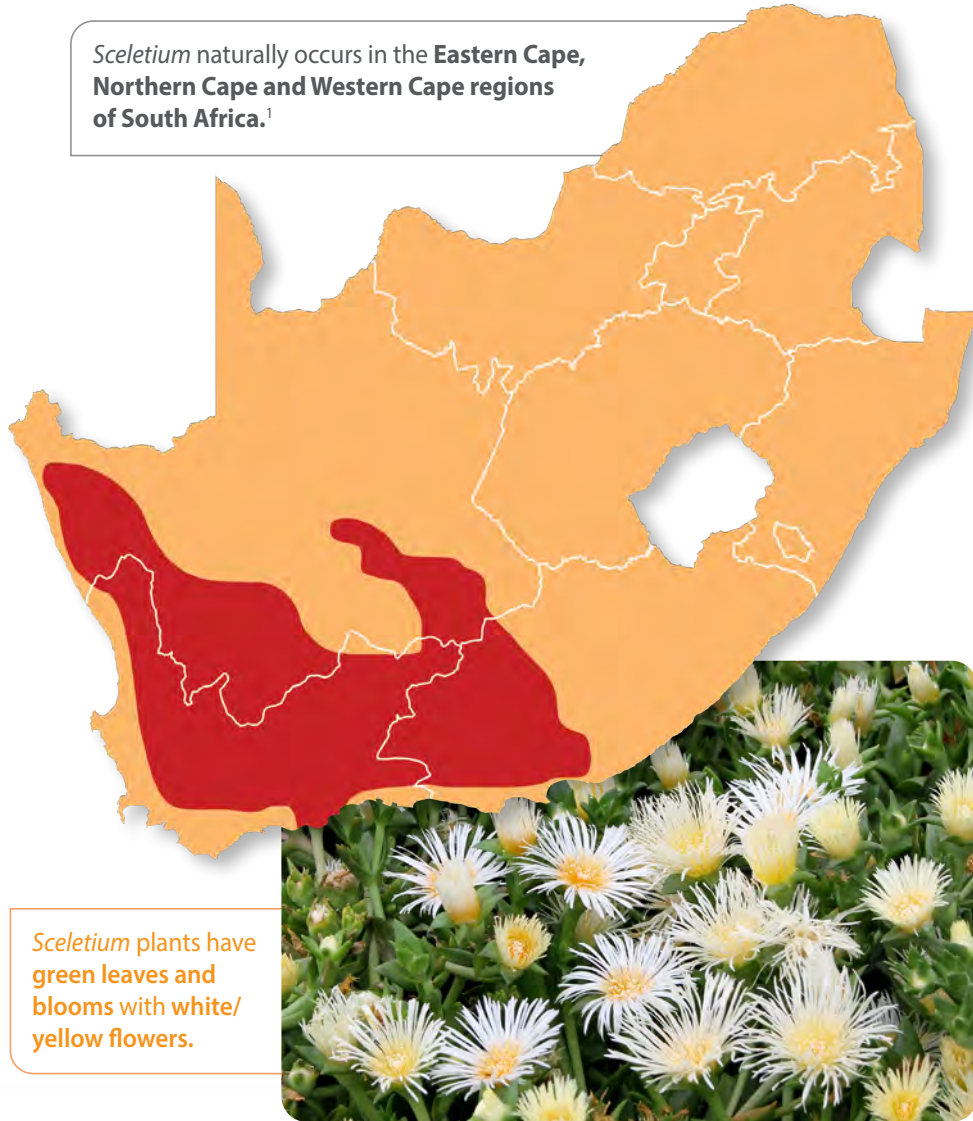


PHARMACEUTICALS
(PTY) LTD

Zembrin® – extract of the succulent plant *Sceletium*

SCELETIUM spp. | FAMILY: MESEMBRYATEMACEAE

Sceletium naturally occurs in the **Eastern Cape, Northern Cape and Western Cape** regions of South Africa.¹



Sceletium plants have green leaves and blooms with white/yellow flowers.

Natural Habitat

Drought resistant¹

Sceletium grows in a **harsh natural environment.**



©Nigel Gericke



The name *Sceletium* is derived from the Latin word "sceletus" (meaning **skeleton**) which refers to the prominent lignified veins visible in the dry and withered leaves.²

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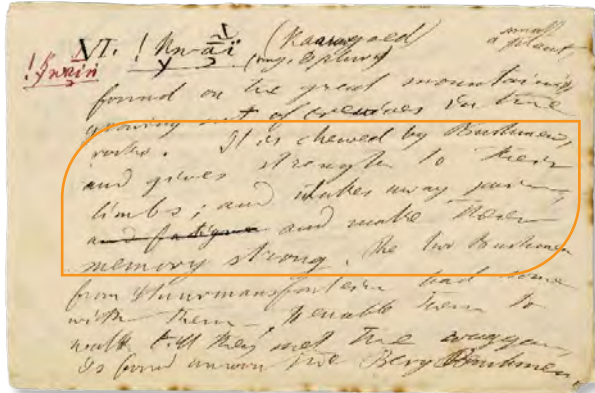
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Origins

Sceletium, known by the San people of South Africa as “kougoed”, has been used for millennia for its stress-relieving and mood-enhancing properties.

Sceletium use reported from 1685

German philologist, Wilhelm Bleek, documented his interaction in 1870 in the Cape with a bushman informant called //Kabbo.



“...it gives strength to their limbs, takes away pain and makes their memory strong.”

To this day, “kougoed” is held in high esteem by indigenous people as a versatile masticatory, tea, health tonic and herbal tincture.

Anecdotal evidence suggests that *Sceletium* has been used for the following:²

- Stress
- Stress of thirst
- Stress of hunger
- Colic and teething in infants

Photos are taken from Waterhouse G, De Wet GC, Pheiffer RH. 1979. Simon van der Stel's Journey to Namaqualand in 1685. Human & Rousseau, Cape Town and Manuscript reference: ms bc151-c4.3.1_006, University of Cape Town Libraries, Special Collection, Bleek and Lloyd archives.



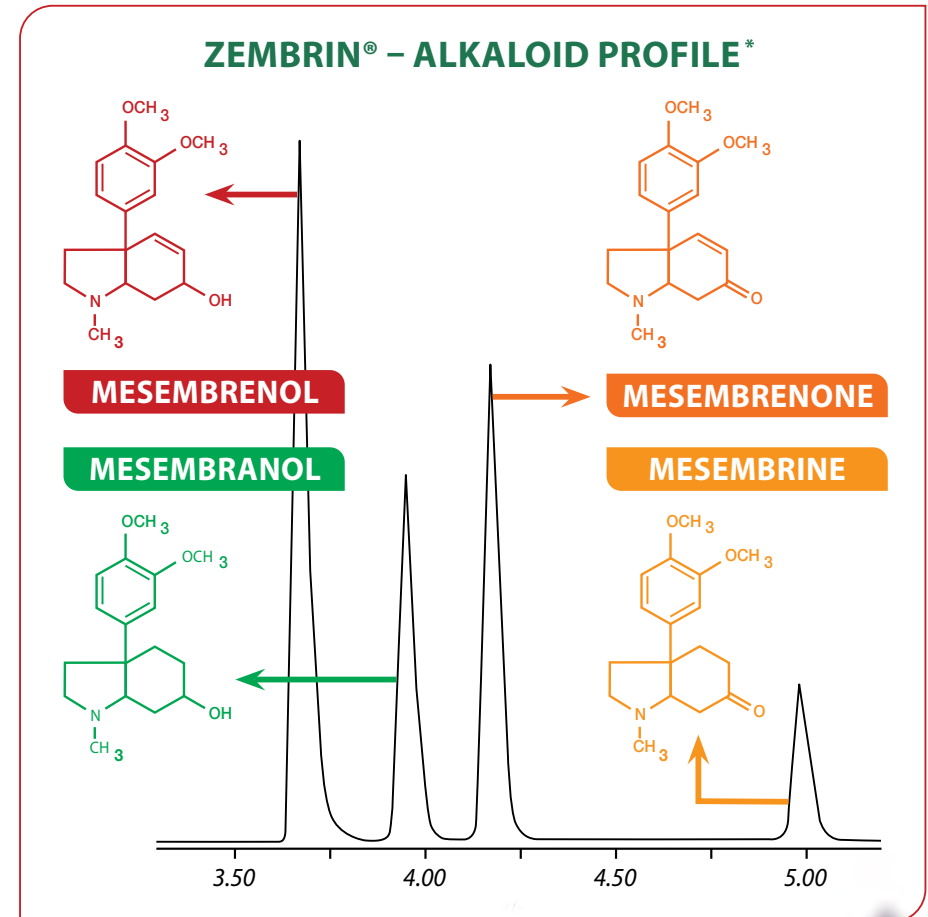
Wilhelm Bleek



//Kabbo

Zembrin® has a unique alkaloid profile

Zembrin® is a standardised extract of *Sceletium tortuosum* (L.) N.E. Br and/or *Sceletium crassicaule* (Haw.) L. Bolus. It is an extract with a unique alkaloid content and composition of the four main alkaloids, namely mesembrine, mesembrenone, mesembrenol and mesembranol.



* Waters Acquity™ Ultra Performance Liquid Chromatographic system with PDA detector (Waters, Milford, MA, USA) with Acquity™ UPLC BEH C18 column (150 mm × 2.1 mm, i.d., 1.7 µm particle size, Waters) maintained at 30 °C using a mobile phase composition at a flow rate of 0.3 ml/min with gradient elution and a 8.5 min running time.

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Mechanism of Action⁶

Zembrin® has a patented, unique dual mode of action as a potent inhibitor of 5-hydroxytryptamine (5-HT) reuptake and phosphodiesterase 4 (PDE4) activity. The advantage of dual inhibition of 5-HT uptake and PDE4 is rapid onset of action and the synergistic activity allowing low doses to be used with excellent tolerability.

Safety^{2,4,7-12}

The safety of Zembrin® has been confirmed by a full array of safety and toxicity evaluations. Zembrin® was found to be safe and well tolerated when used by healthy human subjects once daily for three months.

Clinical Data

Zembrin® is an evidence-based botanical ingredient that has been thoroughly studied for safety and efficacy in comprehensive preclinical as well as clinical studies. Due to its unique chemical composition, selected from highly variable naturally occurring plants, all preclinical and clinical safety and efficacy research applies only to our proprietary, standardised extract, Zembrin®, and not to other *Sceletium*-based products.

Preclinical Studies^{10,11,13}

- **Harvey et al.** conducted a broad pharmacological profiling of Zembrin® which confirmed a unique dual mode of action as a potent blocker of 5-HT and having powerful inhibitory effects on PDE4, which explains the clinical effects of preparations produced from *Sceletium tortuosum*.
- **Harvey et al.** compared the acute antidepressant-like properties of Zembrin® to escitalopram (ESC), in the Flinders Sensitive Line (FSL) rat, a genetic rodent model of depression. ESC 5 mg/kg and Zembrin® 25 mg/kg and 50 mg/kg were assessed. Zembrin® (25 and 50 mg/kg) and ESC (5 mg/kg) were found to be effective antidepressants after acute treatment in the FST, as assessed in FSL rats. Furthermore, Zembrin® 50 mg/kg proved to be equivalent to ESC.⁹
- Preclinical, in vivo, toxicological studies have been published by **Murbach et al.** The 14 day repeat dose study demonstrated a No Observed Adverse Effect Level (NOAEL) for Zembrin® of 5 000 mg/kg body weight per day, the highest dose studied. There were no behavioural, neurological, appetite or weight changes. A 90 day repeat dose study demonstrated a NOAEL for Zembrin® at the highest dose studied of 600 mg/kg body weight/day. These results confirm the absence of any acute or chronic toxicity of Zembrin®.

Clinical Studies^{3-5,7-9,14,15}

Eight pilot, double-blind, placebo-controlled clinical studies in healthy people have been completed and published, paving the way for future larger clinical trials in patient populations.

- Positive effects on wellbeing were noted by participants taking Zembrin®, including improved coping with stress, anxiety and mood disorders.
- Zembrin® has been proven to positively impact the electrical activity of the brain only two hours after ingestion and significantly improve key cognitive domains i.e. cognitive flexibility and executive function
- In a groundbreaking pharmaco-functional magnetic resonance imaging (fMRI) study, Zembrin® was found to have significant antianxiety activity after a single dose.
- Zembrin® has been proven to decrease perceived soreness following exercise, preserve range of motion following exercise, reduce perceived exertion and prevent exercise-related mood disturbances.

New Clinical Study

In April 2022, HG&H Pharmaceuticals initiated a large scale Zembrin® clinical trial at the Brain, Performance and Nutrition Research Centre, in the Faculty of Health and Life Sciences of Northumbria University, UK, under the supervision of Professor David Kennedy.

The clinical trial will evaluate the psychological effects of 8 weeks supplementation with *Sceletium tortuosum* and/or *Sceletium crassicaule* extract (Zembrin®): a randomised, double blind, placebo-controlled, parallel-group trial. This will be the largest scale trial on Zembrin® to date.



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Sceletium
INGREDIENT



**HG
&H**

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The only *Sceletium spp.* extract with published pharmacology

Zembrin® is the world's leading researched and clinically studied extract of *Sceletium tortuosum* and/or *Sceletium crassaule* developed over more than a decade by an international team of scientists and physicians. The effect of **Zembrin®** is experiential^{3-5,7} and fast acting, ensuring that the user experiences the benefits from the first dose.^{8,9}

The present indications for Zembrin®, as a dietary supplement,^{3-5,7,8,15} are...



TO HELP MANAGE STRESS & ANXIETY^{4,5,8}

Terms like anti-stress, calmness, focused, 'uplifted spirits' and 'improves sleep' are often used to describe the experiential effects of **Zembrin®**.^{3-5,7}

Zembrin® has great potential to be developed into a rapidly acting botanical drug for treating Major Depressive Disorder,⁸ and for treating cognitive decline in aging and in early Alzheimers Disease.³

Clinical studies have shown that **Zembrin®** delivers its benefits at the very low dose of 25 mg.^{3,5,7,8,14}

Applications

Zembrin® is a versatile and diverse ingredient that can be used alone or as a complementary ingredient in a wide range of products.¹²



DIETARY SUPPLEMENTS

Zembrin® makes a great addition to herbal remedies and dietary supplements. Popular forms include tablets, capsules, liquids and powders.



SPORTS NUTRITION

Zembrin® is the perfect partner for use in sports nutrition and performance supplements.



FOODS

Zembrin® is a self-affirmed GRAS ingredient making it suitable as an additional ingredient in prepared food products.



BEVERAGES

Zembrin® has successfully been used in various beverages.

It can be used in both alcoholic and non-alcoholic drinks. It also makes a great addition to herbal teas.



PET FOOD

Zembrin® can be used in nutritional products for pets.

It has been administered in clinical studies to both dogs and cats.



SNACKS

Zembrin® is an ideal addition to on-the-go snacks such as bars, spreads, chewing gums and salty grains.

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Claims

In a post-COVID world, there has never been a greater need for an experiential mental wellness ingredient that starts working after the first dose.¹⁶

	ANECDOTAL EVIDENCE	CLINICAL STUDIES
COGNITIVE FUNCTION	Zembrin® improves cognition (focus) ¹⁷	<p>Zembrin® improves mental performance^{3,9,15}</p> <p>Zembrin® enhances cognition³</p> <p>Zembrin® has been proven to positively impact the electrical activity of the brain only two hours after ingestion⁹</p> <p>Zembrin® significantly improves cognitive flexibility and executive function³</p> <p>Zembrin® improves processing speed, psychomotor speed and complex attention³</p> <p>Zembrin® improves working memory, attention control, response inhibition and concept formulation³</p> <p>Zembrin® improves ability to multitask, to adapt to rapidly changing directions and ability to intelligently utilise information³</p> <p>Zembrin® improves decision-making, impulse control and strategy formation³</p> <p>Zembrin® improves ability to exercise initiative, improves proper judgement, improves discipline, improves spontaneous ability to take action and improves goal-directed behaviour³</p> <p>Zembrin® significantly improves reactive performance to a visual stimulus when a cognitive stress is added to the task¹⁵</p>
STRESS & ANXIETY	<p>Zembrin® may help in the management of stress in everyday life⁸</p> <p>Zembrin® relieves stress of thirst²</p> <p>Zembrin® relieves stress of hunger²</p>	<p>Zembrin® offers experiential stress relief^{3,5,7}</p> <p>Zembrin® helps to moderate general feelings of stress and anxiety⁵</p> <p>Zembrin® decreases anxiety^{4,8}</p> <p>A single dose of Zembrin® may improve stress/anxiety levels⁵</p>

	ANECDOTAL EVIDENCE	CLINICAL STUDIES
MOOD	Zembrin® has great potential to be developed into a rapidly acting botanical drug for treating Major Depressive Disorder ⁸	<p>Zembrin® decreases depression⁷</p> <p>Zembrin® elevates mood⁷</p> <p>Zembrin® improves mood³</p>
SLEEP		<p>Zembrin® may improve sleep⁷</p> <p>Zembrin® may help with difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking¹⁸</p>
SPORTS NUTRITION		<p>Zembrin® decreases perceived soreness following exercise¹⁴</p> <p>Zembrin® preserves range of motion following exercise¹⁴</p> <p>Zembrin® reduces perceived exertion¹⁴</p> <p>Zembrin® prevents exercise-related mood disturbances¹⁴</p> <p>Zembrin® significantly improves exercise-related mood¹⁴</p>

	ANECDOTAL EVIDENCE	PRECLINICAL STUDIES	CLINICAL STUDIES
GENERAL	<p>Zembrin® offers exceptional efficacy²</p> <p>Zembrin® is fast-acting⁹</p> <p>Used for colic and teething in infants²</p>	<p>Zembrin® offers exceptional safety and tolerability¹²</p> <p>Despite long term daily use, <i>Sceletium</i> was shown to not have addictive properties, and screening for central nervous system targets associated with addiction support this¹⁶</p>	<p>Zembrin® offers experiential efficacy³⁻⁵</p> <p>Experience benefits from the first dose⁸</p> <p>Zembrin® offers exceptional safety and tolerability⁷</p> <p>Zembrin® delivers its benefits at the very low dose of 25mg^{3,5,7,8,14}</p>



PATENTED STANDARDISED BOTANICAL Sceletium INGREDIENT



PHARMACEUTICALS (PTY) LTD

Regulatory and IP Status

Safety Data Supports Food & Supplement Use

Dietary supplements

- Historical use
- NDI on-file at 25 mg/day

Regulatory

Zembrin® is sold in the USA market under self affirmed GRAS (Generally Recognised As Safe).

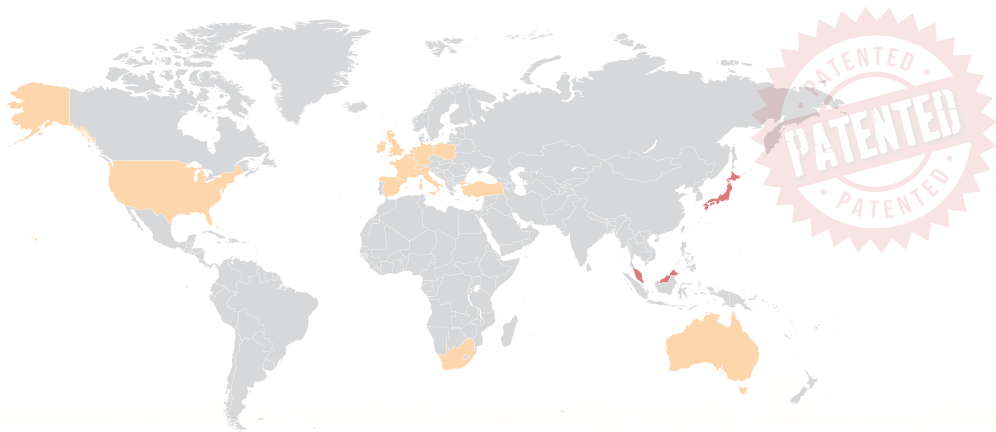
Zembrin® has been granted marketing authorisation by Health Canada as a nonprescription natural product with Product Licence NPN 80088325.

Zembrin® is now registered in India by the Food Safety and Standards Authority of India. Additional regulatory submissions are currently underway in other markets.

Patents and trademarks

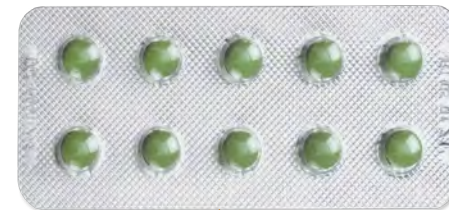
Zembrin® is patent protected by international patents and new patent applications in a number of countries including Australia, Europe (Belgium, France, Germany, Italy, Netherlands, Poland, Spain, Switzerland), Ireland, India, South Africa, Turkey, the United Kingdom and the USA.

Zembrin® is also trademark registered as Zembren® (Malaysia) | Zenbrin® (Japan) | Eletium®.



Purchasing Zembrin®

Zembrin® is a patented and standardised extract of *Sceletium tortuosum* and/or *Sceletium crassicaule* and is available for purchase in the following pack sizes:



EXTRACT AND TABLET
SAMPLES AVAILABLE
ON REQUEST



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Product Specification Sheet

PRODUCT NAME: ZEMBRIN® | PRODUCT CODE: SCE04

	SPECIFICATION	TEST METHOD
01 PRODUCT DESCRIPTION	Plant part used	Aerial parts
	ID testing of raw material used	Description
	Traceability code: SDM-Lot Number	<i>Scelletium tortuosum</i> (L.) N.E. Br <i>Scelletium crassicaule</i> (Haw.) L. Bolus
	Phytochemical fingerprint	Liquid chromatography
02 PHYSICAL DATA	Common name	Scelletium plants
	Carriers used	≤ 70% Maltodextrin ≤ 2% Silicon dioxide
	Plant : Extract ratio	2 : 1
	Appearance	Milled powder
	Colour	Light brown to brown
	Aroma	Characteristic smell
	Flavour	Characteristic
	Particle size	≥ 95% through 80 mesh
	Solubility in water	Freely soluble to slightly soluble
	Bulk density	0.4 - 0.6 g/cm ³
03 CHEMICAL DATA	Total alkaloids	≥ 0.35% - ≤ 0.45%
	Mesembrenone + Mesembrenol	≥ 60% contribution to total alkaloids
	Mesembrine	≤ 20% contribution to total alkaloids
	Mesembranol	≥ 5% contribution to total alkaloids
	Moisture	≤ 7.0%
	Total heavy metals	≤ 10.0 ppm
	Total arsenic	≤ 0.5 ppm
	Lead	≤ 2.0 ppm
	Cadmium	≤ 0.5 ppm
	Mercury	≤ 0.5 ppm
	Residual solvents (ethanol)	≤ 5000 ppm (USP <467> / Directive (EU) 2009/32/EC)
	Pesticides	USP <565> and EU Reg (EC) No. 396/2005
	Contaminants	EU Reg (EC) No. 1881/2006 and amendments
	Total plate count	≤ 10 000 cfu/g
	Yeast & mould	≤ 1 000 cfu/g
	BTGNB*	≤ 100 cfu/g
	Salmonella	Absent cfu/25 g
Escherichia coli	Absent cfu/10 g	
Total coliforms	< 10 cfu/g	
Staphylococcus aureus	Absent cfu/10 g	
Pseudomonas aeruginosa	Absent cfu/10 g	
04 MICRO-BIOLOGICAL DATA	Extraction method	Water : ethanol extraction and spray dried
	Packaging configuration	1 kg & 5 kg in aluminium foil bags each placed individually in LDPE bags, packed in HDPE drums
	Storage	Store in original packaging in a cool, dry place at room temperature
	Shelf-life	3 years
	Special instructions	This extract is very hygroscopic and should be kept sealed until used
	Country of plant origin	South Africa
	Country of extract manufacture	Spain
	Non-allergens/gluten	This product does not contain any of the food allergens cited in EU Reg (EC) No. 1169/2011
	Non-BSE/TSE	None of the ingredients in the product are of animal origin
	Non-irradiation	This material has not been subjected to irradiation
	Nanomaterial	This material is not produced using nanotechnology and is free from nanoparticles
05 ADDITIONAL INFORMATION	Non-GMO status	This product is neither considered genetically modified nor derived from any genetically modified organisms, as defined by the EU Reg (EC) Nos. 1829/2003, 1830/2003 and amending legislation

Johannesburg, 10 March 2021
Quality Assurance Manager
Shingirai Katsinde

Kosher certified by Star-K Kosher Certification
Halal certified by Instituto Halal

*BTGNB = Bile-tolerant gram-negative bacteria

Global Presence

7 DISTRIBUTORS



8 COUNTRIES



72 PRODUCTS ...and counting

OVER 200 MILLION DOSES SOLD TO DATE



PATENTED STANDARDISED BOTANICAL SCELLETIUM INGREDIENT



PHARMACEUTICALS (PTY) LTD

Sustainability

Zembrin® is a socially responsible, ecologically sustainable, vertically integrated and fully traceable botanical ingredient



All raw plant material used in the production of **Zembrin®** is cultivated exclusively for HG&H Pharmaceuticals (Pty) Ltd from a proprietary selection of non-GMO seeds. *Sceletium spp.* are a protected species and wild harvesting is not sustainable for commercial products.



Sustainably cultivated using a carefully controlled seed bank

HG&H Pharmaceuticals committed to use only cultivated plant material in the production of **Zembrin®** to avoid depleting threatened wild plant stocks, and to ensure consistent product quality. This was achieved through investment in a highly successful, socially compliant crop development programme and annual cultivation of a proprietary selection of *Sceletium tortuosum* and/or *Sceletium crassicaule* on a large commercial scale.



Social Responsibility

Zembrin® was awarded the first Integrated Export and Bioprospecting Permit by the Ministry of Water and Environmental Affairs in Pretoria, South Africa, in December 2009. This was in recognition of its environmentally sustainable production and socially responsible indigenous benefit-sharing agreement.



Representatives from The South African San Council visiting the farm



"This benefit-sharing agreement is seen, not only by the San Council, but by the SA Department of Environment, Forestry and Fisheries as being the most solid agreement that there is. I would not be surprised if it is not the best benefit-sharing agreement that exists today."

Dr Roger Chennells,
Human Rights Attorney

A royalty is paid to the South African San Council on all **Zembrin®** sold, in recognition of the contribution of their indigenous knowledge to the development of **Zembrin®**.

This was formalised through a groundbreaking benefit-sharing agreement signed in February 2008 between HG&H Pharmaceuticals (Pty) Ltd and the South African San Council to support both the Paulshoek and Nourivier communities in the Northern Cape Province of South Africa.

The royalties are used for educational purposes, assisting parents who cannot afford school uniforms and school fees, and to fund farming and agricultural projects.

"The proceeds from every kg sold helps the community", says Director of the South African San Council, Collin Louw.

Zembrin®

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Sceletium
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Endorsements

International best practice **benefit-sharing agreement** with South African San Council.

To date, **Zembrin®** is the only *Sceletium spp.* extract **endorsed by the South African San Council.**

1st ever export permit from South African government, full compliance under the Biodiversity Act.

Biodiversity leadership hailed at UN Nagoya conference by the South African Minister of Environment.

Ecologically sustainable plant production and cultivation, to EU and Global GAP.

Reliable supply chain and validated QC through own propagation and production.

The endorsement of **Zembrin®** is supported by the exclusive use of the South African San Council endorsement stamp and their trademarked logo on products containing **Zembrin®**.



AWARDS

- The Functional Ingredients Magazine Editor's Choice Award was given to **Zembrin®** for the 2013 most sustainable ingredient.
- The Indigenous Plant Use Forum gave **Zembrin®** the Best Product award in 2013

Zembrin® in Summary



CLINICALLY STUDIED

The most studied *Sceletium* extract in the world.^{3-5,7-9,14,15}



FULLY TRACEABLE

Strict adoption of quality control measures with EU-GMP.



SELF-AFFIRMED GRAS

(Generally Recognised As Safe) in the USA market.



LOW DOSE

Proven safety and efficacy at 25 mg.^{3,5,7,8,14}



DUAL ACTING

Research has shown its dual mechanism of action.¹⁰



EXPERIENTIAL

Users can feel the difference it makes.^{3-5,7}



SAFE

Researchers have thoroughly studied the safety.^{2,4,7-12}



WELL TOLERATED

Safety studies have shown that **Zembrin®** is easily tolerated.⁷



FAST ACTING

Has a positive effect on the brain in just 2 hours.⁹



ECOLOGICALLY SUSTAINABLE

No wild farming and depletion of indigenous stock.



SOCIALLY RESPONSIBLE

A royalty is paid to the indigenous community.

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From seed to extract – the **Zembrin**[®] manufacturing process



1 SOWING THE SEEDS

Sceletium spp. are protected plants. This is why HG&H Pharmaceuticals does not harvest from the wild but rather grows its own *Sceletium spp.* plants from a carefully controlled seed bank – a challenging task, because, despite its hardy character, *Sceletium* needs optimum conditions to flourish.



2 UNDER THE NETS

Once grown, the seedlings are transplanted from their trays into bags protected by shade netting.



3 GROWING SEASON

Sceletium spp. only grows for 3 to 5 months of the year and is dormant during summer. In fact, that's where its name comes from: In Latin the word *sceletus* means skeleton and it refers to the leaves dying back and leaving only a skeleton of branches behind.



4 HARVESTED BY HAND

Once mature, the plants are skilfully harvested whole, without the root. Our experienced team of harvesters cut the plants by hand in a laborious process that takes time and dedication. Trained supervisors oversee the harvesting of every crop to ensure that the most stringent quality measures are adhered to.



5 CAREFUL PREPARATION

Once the plant material has been harvested it is checked for foreign matter, washed and placed on drying racks.



6 FROM WET TO DRY

From the drying racks, the plant material goes into our industrial ovens and is dried until it meets our specified moisture range.



7 IT'S IN THE BAG

Once dried, the raw plant material is sorted, tested to ensure that it meets our strict moisture and phytochemical profiles, and placed into bags.



8 GIVING IT STEAM

Each bag of dry plant material undergoes a strict steam sterilisation process before being moved into cold storage.



9 WORLD-CLASS EXTRACTION

The dried plant material is converted into standardised powdered extract in a world-class EU Certified Good Manufacturing Practice facility.



10 CONSISTENT QUALITY YOU CAN TRUST

Each of our manufactured lots is tested for contaminants, moisture content, particle size, bulk density, solubility, DNA and phytochemical composition to ensure compliance with our standard specification. Now our extract is ready for sale.

ROOTED IN NATURE

PERFECTED BY SCIENCE

Zembrin[®]

THE WORLD'S LEADING RESEARCHED AND STANDARDISED Sceletium EXTRACT



PHARMACEUTICALS
(PTY) LTD

Contact us

Our experienced and passionate team is ready to assist you with your queries or orders - contact us today.

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SELECTED SAFETY INFORMATION: CONTRAINDICATIONS: Hypersensitivity to ZEMBRIN[®] or any of the inactive ingredients of ZEMBRIN[®]. **WARNINGS AND SPECIAL PRECAUTIONS:** Do not use with any psychiatric medication, including mood stabilisers, antidepressants and anti-anxiety medication. Any changes in medication should be discussed with your doctor or psychiatrist. There are no reports that ZEMBRIN[®] affects the ability to drive a vehicle or operate machinery. Users must take reasonable care until they know how they react to ZEMBRIN[®]. **PREGNANCY AND LACTATION:** Safety during pregnancy and lactation has not been established. Do not use during pregnancy. **SIDE EFFECTS:** No severe adverse reactions have been reported. Side effects that may occur are mild or moderate and transient, and include mild headache, abdominal discomfort or nausea. Should any adverse reactions occur, discontinue use immediately.



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