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While modern medicine often focuses on mental illness, it is time for us to focus on improving mental wellness.

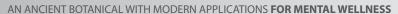
Poor mood, declining cognition, stress and anxiety are the areas of high concern.

The relation between these areas is tightly connected in the following ways:

- Stress/anxiety decreases cognitive function, learning and memory.¹
- A person may have trouble with cognitive function, not realising that it is worry (stress and anxiety) that is impacting their mental performance.
- When we have trouble focusing or concentrating, we often feel stressed or anxious.

As if this was not bad enough, poor mental wellness can impact most aspects of our lives, including cardiovascular health,¹ the immune system,² gastrointestinal problems,¹ hormone issues,¹ weight control,³ elevated blood sugar⁴ and pain,⁵ not to mention our relationships, difficulties at work, home, school and many other areas.







Who is impacted? Inside the numbers

In short, we are all impacted by stress and other mental wellness struggles. This is highlighted by the stress and anxiety statistics which may be exacerbated by events such as the COVID-19 pandemic.

Stress and Anxiety Pre-pandemic

- In 2017, 44 % of Americans surveyed frequently experienced stress in their daily lives.⁶
- 54 % of people aged 18 to 29 frequently experienced stress.⁶
- In 2019, about one-third of people globally reported feeling stressed, worried and/or angry.⁷
- 49 % of women frequently experienced stress.⁶
- 10 % of people were affected by anxiety in North America, Western Europe and Australia/New Zealand.⁸

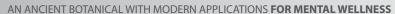


Effect of the COVID-19 pandemic

- Nearly 80 % of Americans said that the COVID-19 pandemic was a significant source of stress in their lives.⁹
- There was a significant increase in mental health problems in the general population in the first year of the pandemic.¹⁰
- Each of the following was reported to have been experienced by about half of working adults globally because of the COVID-19 pandemic:¹¹
 - Stress due to changes in work routines and organisation, increased by 55 % globally
 - Stress due to family pressures such as childcare, increased by 45 % in South Africa, 64 % in Saudi Arabia and 18 % in the Netherlands.
- Nearly one in five adults said their mental health was worse in 2020 than in 2019.
- The World Health Organization claimed that the COVID-19 pandemic triggered a 25 % increase in the prevalence of anxiety and depression worldwide.¹³

While stress and anxiety have become the elephant in the room, mood and cognition issues also impact millions of people and are significant mental wellness concerns.







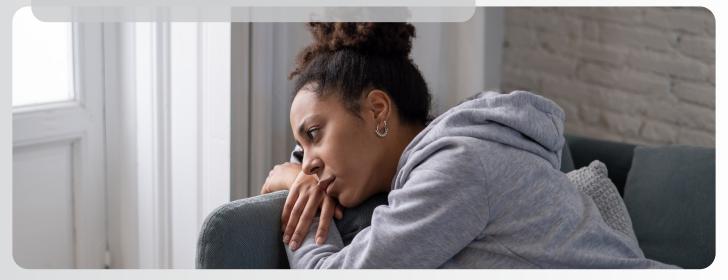


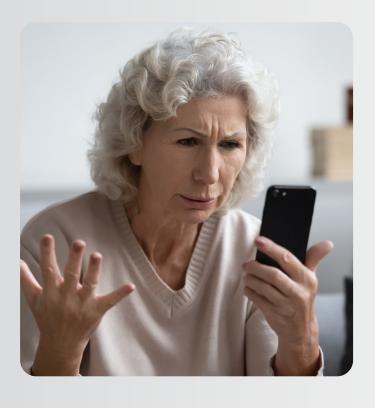
Mood

- The COVID-19 pandemic triggered a 25 % increase in mood issues worldwide.¹³
- Nearly one in five Americans have a problem with mood disorders.¹⁴



Nine hundred and seventy million represents the number of people globally with any mood type disorder. 15





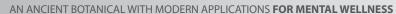
Cognition

- Globally the estimated number of people with dementia will increase from 47 million in 2015 to more than 140 million in 2050.
- Sixteen million Americans are living with Cognitive Impairment.¹⁷
- One in nine Americans aged 45 and older say they are experiencing declines in thinking ability.
- Among those aged 45 and older who were living alone, 14 % said they were suffering from declines in mental function.¹⁸

ZEMBRIN® to the rescue











Zembrin® to the Rescue

This ancient South African botanical ingredient sourced from *Sceletium tortuosum* and/or *Sceletium crassicaule* is trademarked and marketed as **Zembrin**®.

The numbers mentioned previously are a driving force as to why **Zembrin**® should be a top consideration for inclusion in mental wellness products. It answers many of the world's most pressing mental wellness needs. For a millennium, *Sceletium* plants have been consumed by the San and Khoi people of South Africa for its stress-relieving and mood-enhancing properties. Even today, these indigenous people hold this remarkable botanical in great esteem. In the last several decades,

modern medicine has sought to uncover what makes this plant so unique.

This paper will examine why **Zembrin**® is considered a gold standard for those seeking a cutting-edge mental wellness ingredient.

Sceletium use was reported from 1685



What is **Zembrin®?**

Simply put, **Zembrin**[®] is derived from the succulent Sceletium plants (Sceletium Tortuosum (L) N.E. Br & Sceletium Crassicaule (Haw.) L. Bolus), native to South Africa. These plants have green leaves and blooms with white and vellow flowers. The name is derived from the Latin word "sceletus" (meaning skeleton) because the prominent veins on the dried leaves give the plant a skeletal appearance.19



History of Sceletium spp.

The use of this plant dates back at least one thousand years. Historically, the plant was used by native San hunter-gatherers and Khoi people to quench their thirst, fight fatigue and for healing, social and spiritual purposes.

The first recorded knowledge of the *Sceletium tortuosum* plant came from Dutch explorers in 1610. Still, the San people and the Khoikhoi people used "Kanna" in the ancient pre-history of the African continent.

The Dutch explorers and traders found the plant so valuable that they named it in their Dutch language as "kougoed" and traded it in the Far East.²⁰

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.

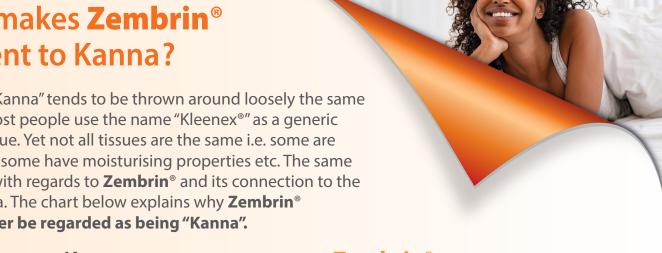






What makes **Zembrin®** different to Kanna?

The name "Kanna" tends to be thrown around loosely the same way that most people use the name "Kleenex®" as a generic term for tissue. Yet not all tissues are the same i.e. some are rough, thin, some have moisturising properties etc. The same holds true with regards to **Zembrin®** and its connection to the name Kanna. The chart below explains why **Zembrin**® should never be regarded as being "Kanna".



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Generic term for Sceletium products

Phytochemical make-up

Levels of psycho-

active alkaloid

Mesembrine

Zero guarantee that the product contains the beneficial alkaloids

High risk of high levels of mesembrine

Studied Not clinically studied

Dosing Can range from 200 mg to 500 mg

Use Used recreationally for its euphoric effect

Growing and Harvesting Technique

Usually wild-harvested and uncontrolled growing

Social No social responsibility Responsibility programmes in place

Zembrin®

Patented and trademarked Sceletium extract

Standardised alkaloid profile for each batch

No risk of having high levels of mesembrine

Most clinically studied Sceletium spp. extract (8 double-blind, placebocontrolled studies...and counting)

Clinically proven dose of 25 mg

Used to help with mood, stress, anxiety and cognition

Sustainable and scalable cultivation. HG&H Pharmaceuticals has a bioprospecting permit and fulfills the conditions set out in the Nagoya protocol

Royalties paid to the communities whose indigenous knowledge contributed to the development of Zembrin®







Zembrin® is unique

Zembrin® is the **only patented**, **standardised and clinically studied** *Sceletium spp*. extract on the market. **Zembrin®** contains a unique alkaloid content and composition of the four alkaloids: mesembrine, mesembrenone, mesembrenol and mesembranol. It took five years to select the correct species of *Sceletium* and ensure that the required horticultural practices were honed to grow the crop. Special care was taken to make the proprietary selection of the non-GMO *Sceletium spp*. used in the production of **Zembrin®**



Zembrin® is cultivated exclusively for HG&H Pharmaceuticals (Pty) Ltd (the proprietary owners of Zembrin®) and no others.

The unique chemical fingerprint of **Zembrin**® is quantified with a wide range of analytical methods, including botanical matching (DNA identification), HPTLC and HPLC.

Other products referred to as Kanna do not come close to this meticulous process.

HPTLC = high performance thin layer chromatography. HPLC = high performance liquid chromatography.





The proof is in the Science

Nothing speaks louder than science! Considerable time, effort and money have been spent on substantiating the safety and efficacy of **Zembrin**[®]. Due to uniqueness of **Zembrin**[®], as mentioned on the previous page, comprehensive preclinical and clinical studies have been carried out. Below you will find summaries of the clinical studies conducted to date.



A study²¹ published in Food and Chemical Toxicology evaluated the potential toxicity of **Zembrin**[®]. A 14-day trial was performed with rats given up to 5000 mg/kg bw/day, while a 90-day study administered up to 600 mg/kg bw/day of **Zembrin**[®]. In the 14-day study, there were no mortalities, and the rats exhibited normal behavioural and physical conditions with no significant abnormalities in clinical signs. The 90-day study concluded that there were no observed adverse effect levels, no mortalities and the rats exhibited normal behavioural and physical conditions with no significant abnormalities in clinical signs. These results confirm the absence of any acute or chronic toxicity of Zembrin®.





Safety and Tolerability in Humans

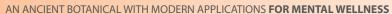
A published human clinical trial²² was completed to evaluate the safety and tolerability of two doses (8 mg and 25 mg once daily) of **Zembrin®** in healthy adults. The research showed that both doses of **Zembrin**[®] were well tolerated. In addition, there were **no apparent differences in vital** signs, physical examination, ECG, body weight, haematology or biochemistry parameters from beginning to end.

Applying a 100-fold uncertainty factor to compensate for inter- and intra-species differences, results can be extrapolated to an acceptable daily intake of 420 mg by a **70 kg human** (well above the suggested daily intake of 25 mg per day). Zembrin® is well tolerated.











Efficacy

Mood, stress and anxiety

With regards to effectiveness, the study²² mentioned above in "Safety and Tolerability" also showed unsolicited positive effects on well-being in patient diaries among some participants taking **Zembrin®**, including **improved coping with stress and sleep difficulties**. While this is not a definitive clinically proven impact, it is worth noting as the following studies will add to these observations.

Ideally, either stopping stress where it starts in the brain, or being able to slow down the process of feeling its effects would be the best approach to managing stress. Stressful events trigger a response from the amygdala and hypothalamus (considered to be the stress centre of the brain). One study²³ looked at the effectiveness of a single dose of **Zembrin®** in using fMRI to reduce anxietyrelated amygdala reactivity and amygdalahypothalamus coupling. The results showed that **Zembrin**® reduced amygdala reactivity and "decoupled" amygdalahypothalamus connectivity. This impact slows and/or decreases the impact of stressful events in the brain and proves the antianxiety effects of Zembrin®.

Two other studies using a double-blind, placebo-controlled design evaluated the effects of a single dose of **Zembrin**® (25 mg) on laboratory stress and anxiety in 20 healthy volunteers.²⁴ In the first study, participants completed 20 minutes of multitasking, and in study 2, participants completed a 5 minute simulated public speaking task. The results showed that when both studies were "Taken together, results indicate that a single dose of Zembrin® can ameliorate laboratory stress/anxiety response in healthy volunteers".²⁴

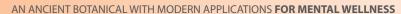


Cognition effects

A study²⁵ with 21 cognitively healthy adults examined the neurocognitive effects of **Zembrin**® and assessed the safety and tolerability of **Zembrin**®. Each participant took 25 mg of **Zembrin**® daily for three weeks in a randomised placebo-controlled three week cross-over design. **Zembrin®** had significantly improved cognitive set flexibility and executive function compared with the placebo group. In addition, positive changes in mood and sleep were found. **Zembrin®** was also well tolerated.

Another study²⁶ with 60 healthy volunteers consuming either a 25 mg or 50 mg dose of **Zembrin**® evaluated its impact on the brain's electrical activity during cognitive processing and emotional challenges. The results showed that, in comparison to the placebo, Zembrin[®] induced frequency changes in the brain, which have been related to enhanced attention and memory. These results may represent a positive action of Zembrin® on cognitive and emotional processes in the brain. Additionally, a greater degree of calmness and memory can be extrapolated from the increases in alpha2 waves.





Active/Sports Nutrition

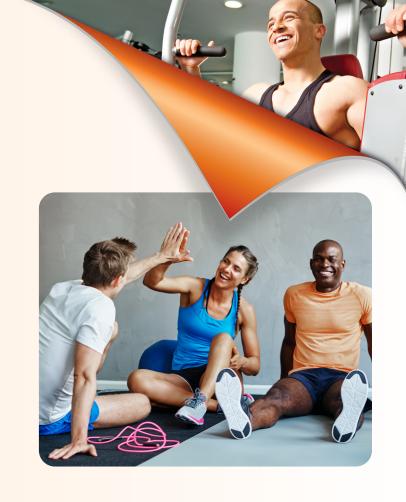
A study²⁷ designed to investigate the use of **Zembrin**® on muscle soreness, markers of muscle damage, mood and exercise performance following unaccustomed resistance exercise in 16 untrained women showed that short-term **Zembrin**® supplementation resulted in lower perceived soreness and greater preservation of a range of motion versus results seen in the placebo group.

While mood worsened from baseline in all groups, the group taking Zembrin® did not decline as much as the placebo group. The researchers concluded that Zembrin® supplementation might effectively reduce the markers of soreness and preserve mood, following unaccustomed eccentric exercise.



In all, eight pilot double-blind, placebocontrolled clinical studies in healthy people have been completed and published,^{22-27,57,58} 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 anti-anxiety activity after a single dose.

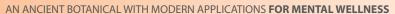


 Zembrin® has been proven to decrease perceived soreness following exercise, to preserve range of motion following exercise, to reduce perceived exertion and to prevent exercise-related mood disturbances.

More Science is Coming

A new clinical trial has commenced at the Brain, Performance and Nutrition Research Centre, 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 eight weeks supplementation with Zembrin®: a randomised, double-blind, placebo-controlled, parallel group trial. This study will be the first large-scale trial involving Zembrin®.





What makes **ZEMBRIN**® tick? Mechanisms of Action

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. The study mentioned previously regarding the fMRI results validated these two mechanisms of action.²³

A paper published in the *Journal of Ethnopharmacology*²⁸ conducted broad pharmacological profiling of **Zembrin**®, which confirmed a unique dual mode of action as being a potent blocker of 5-HT and having powerful inhibitory effects on PDE4.

The study showed that:

- the alkaloid mesembrine was the most active against 5-HT, while
- the alkaloid mesembrenone was active against both the 5-HT transporter and PDE4.



Stress/Mood Products are not all equal



Looking at any health food store's "stress/mood" section can make your head spin.
Which ingredient should be taken for what?
What makes **Zembrin**® different to the abundance of other stress ingredients in the

Simply put, we need to look at:

- the mechanisms of action
- the dose required

market?

- the time it takes to work (onset), and
- the side effect profile.



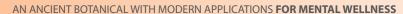


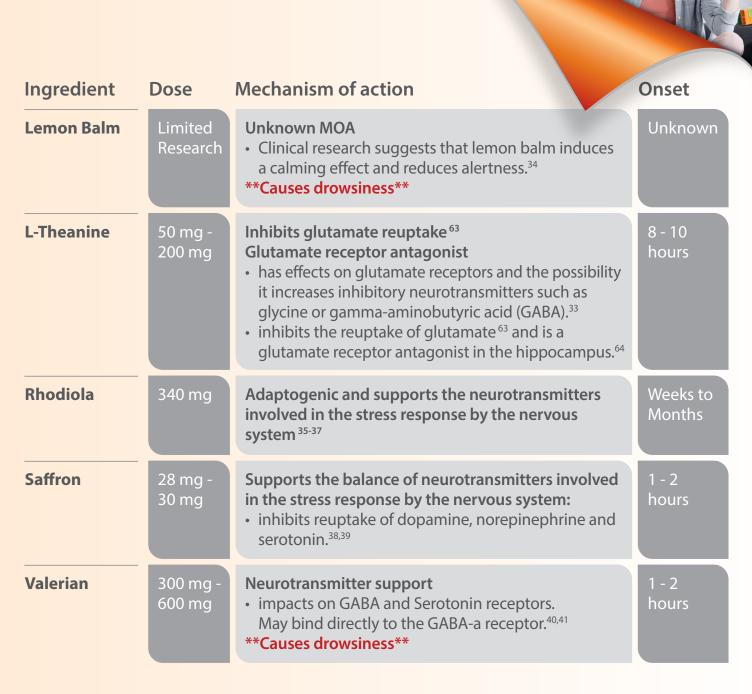
What makes **ZEMBRIN**® different from other Mental Wellness Ingredients?

The table below lists some of the commonly used ingredients for stress and their dose, mechanisms of action, onset and any precautions in **red**.

Ingredient	Dose	Mechanism of action	Onset
Zembrin®	25 mg	Neurotransmitter support • phosphodiesterase-4 (PDE4) and serotonin (5-HT) reuptake inhibition. ²³ Impact on the amygdala (stress centre of the brain).	2 hours
5-HTP	150 mg - 800 mg	Neurotransmitter support • increases the production of serotonin by the central nervous system. ²⁹	Unknown
Ashwagandha	125 mg - 600 mg	 Adaptogenic Neurotransmitter support suppresses stress-induced increases of dopamine receptors in the corpus striatum of the brain.³⁰ enhances serotonergic transmission through modulation of the postsynaptic serotonin (5-HT) receptors.³¹ 	Weeks to Months
Bacopa	300 mg	Adaptogenic Neurotransmitter support • inhibits acetylcholinesterase activity. ³²	Weeks to Months
CBD/Hemp	???	More research is needed.	Unknown
GABA	100 mg - 200 mg up to 3x per day	Exerts both sedative and anxiolytic effects 59,60 • effects at the cellular level. 59,60	1 - 2 hours
Holy Basil	500 mg	Adaptogenic	Weeks to Months
Lactium®	150 mg - 300 mg	Neurotransmitter support • stimulates activity of the GABA neurotransmitters. ⁶²	7 - 15 days







It is significant to note that when addressing stress, most consumers are looking for something that "takes the edge off", while not negatively impacting their quality of life. For decades, the ingredients which work quickly have often come with unwanted side effects such as drowsiness and fatigue. The most popular "fast-acting" ingredients for stress are passion flower, valerian and kava, and all

three come with drowsiness as a side effect. **Zembrin**®, on the other hand, is fast-acting (starts working within two hours)⁵⁷ and no reports have been made about **Zembrin**® causing drowsiness. Looking at the table above, **Zembrin**® provides benefits across the board, at a low dose, is fast acting and has no known adverse effects.²²⁻²⁷





Feel Good while you are **Feeling Good**

As we can see, **Zembrin**® offers a "feel good" effect by improving the three critical areas of mental wellness – stress and anxiety, mood and cognition.

If you need more reasons to "feel good" about Zembrin®, it is vertically integrated and traceable and has a tremendous "feel good" social responsibility and sustainability story.

In 2009, **Zembrin**[®] was awarded the first **Integrated Export and Bioprospecting** Permit by South Africa's Minister of Water and Environmental Affairs in Pretoria, South Africa, in recognition of its environmentally sustainable production and socially responsible indigenous benefit-sharing agreement.



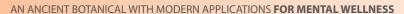
Social Responsibility



- 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.







Sustainability with a Twist

Sceletium spp. are a protected species, and wild harvesting is not sustainable for commercial products. Realising this, HG&H Pharmaceuticals (Pty) Ltd are committed to using only cultivated plant material in the production of Zembrin® to avoid depleting threatened wild plant stocks and ensure consistent product quality.



The process to achieve Sustainability

Zembrin® is the result of many years of research into the botany, chemistry, selection and cultivation of *Sceletium*. Initial fieldwork found that indigenous people could point out locations where traditionally used *Sceletium* plants were regarded as 'strong' and potentially euphoria-inducing. In contrast, adjacent sites with identical-looking *Sceletium* plants were considered to be 'mild' and used for stress.

Analytical work determined that the euphoria-inducing plants were exceptionally high in the alkaloid mesembrine. These plants are typically fermented traditionally to enhance even further the euphoriant potential. Analytical work was also carried out

using the "mild" plants which showed they had a lower total alkaloid content, and the alkaloid composition was low in the alkaloid mesembrine.

To have a safe, reproducible, "mild" product suitable for functional foods and supplements, seed stock for the cultivation of **Zembrin®** was taken from the plants with **low alkaloid** content and **low mesembrine** composition. All subsequent work aimed to maintain a large gene pool of plants with the responsible alkaloid content and composition.

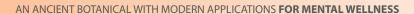
The process ensured a reproducible raw material suitable for producing a consistent and safe extract. This provides more validation of how Zembrin® is different from Kanna.



By investing in a highly successful crop development programme and controlling the seed stock, **Zembrin®** can be produced on a large commercial scale.

DOESN'T SUSTAINABILITY FEEL GOOD?





It's okay to Brag

Here are a few "bragging points" for **Zembrin**®:

- An international best practice benefitsharing agreement exists with the South African San Council.
- Zembrin® is the only Sceletium spp. extract endorsed by the South African San Council.
- Recipient of the first ever export permit from the South African government, full compliance under the Biodiversity Act.
- Biodiversity leadership was hailed at the United Nations Nagoya conference by the South African Minister of the Environment.
- Plant production and cultivation are ecologically sustainable and conform to the European Union and Global Good Agricultural Practices.
- Reliable supply chain and validated quality control are ensured through own propagation and production.



Vertical Integration

Clearly and simply put, **Zembrin**® is vertically integrated from the SEED to the EXTRACT. Controlling all steps from the proprietary seeds, growing location, growing practices and extraction is essential to ensuring a quality finished ingredient. **Zembrin® offers peace of mind with its fully traceable vertical integration.**



ZEMBRIN® is Award Winning

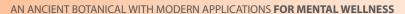
- The Functional Ingredients Magazine Editor's Choice Award was given to Zembrin® for the 2013 most sustainable ingredient.
- The Indigenous Plant Use Forum gave
 Zembrin® the Best Product award in 2013.

ZEMBRIN® is Patented and Trademarked

Zembrin[®] is patent protected by international patents and new patent applications in several countries, including Australia, Europe (Belgium, France, Germany, Italy, Netherlands, Poland, Spain, Switzerland), Ireland, India, South Africa, Turkey, United Kingdom and the USA. **Zembrin**[®] is also trademark registered as Zembren[®] (Malaysia), Zenbrin[®] (Japan) and Eletium[®].







Outside the box formulating with **ZEMBRIN®**

Stress is recognised as being a risk factor for other health challenges we all may face. When formulating for success, strong consideration for adding a successful stress and anxiety ingredient can add value and differentiation from other formulations.



The following areas of health have stress, anxiety and mood as contributing risk factors: 1

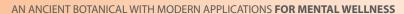
- Cardiovascular health
- Memory
- Concentration
- **Blood sugar control**
- Sleep
- Gastrointestinal Health 2,42-46
 - digestion and absorption of nutrients into the body
 - changes in gut bacteria
 - GFRD
 - Dyspepsia (abdominal pain-upper) middle part of the stomach)
 - erosion of the digestive lining.
- Immune weakness²
- Skin Health 47
 - Acne
 - Hair loss
 - Hair thinning
 - Eczema (Atopic dermatitis)
 - Psoriasis
 - Rosacea
 - Scalp rash
 - Hives
 - Slow Healing
- Fatigue 48
- Erectile Dysfunction 49,50
- Sex Hormone reduction 51,52
- Decreased sexual desire 53
- Pain 54,55
- Headaches 56



Due to the connection between stress and anxiety to cognition issues, the addition of **Zembrin**[®] to a cognitive formulation would provide a double benefit. Not only does **Zembrin®** show effects directly on cognition, but it is also a powerful agent for dealing with stress and anxiety too. The benefit is a onetwo punch for your finished product.

While there is no current research directly connected to using **Zembrin**® for these health concerns above, adding Zembrin® to help address the underlying risk factor of stress and anxiety can only help the end-user take a step in the right direction towards better health.





Regulatory

Zembrin® is sold in the USA market under selfaffirmed GRAS (Generally Recognised As Safe) and has been granted marketing authorisation by Health Canada as a non-prescription natural product with Product License NPN 80088325. **Zembrin**[®] has been registered in India by India's Food Safety and Standards Authority. Additional regulatory submissions are currently underway in other markets.



Samples available on request.

Summary: Putting a Bow on ZEMBRIN®

The best way to sum up **Zembrin**[®] is this: **Zembrin®** offers many opportunities to make health claims in cognitive function, stress/ anxiety, mood and sports nutrition. In addition, a complete claims dossier can be made available for those seeking more indepth information.

You can also mention the feel-good stories of social responsibility, sustainability, vertical integration and traceability. Finally, let's not forget that **Zembrin®** is also experiential.

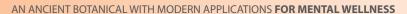
Consumers these days want to be able to "feel" their supplements working, and Zembrin® will give you this offering. Throw in the patents, trademarks, awards and possibilities to market products "outside the box," and you have a clear winner in Zembrin®.

ZEMBRIN® is:

- Great for Mental Wellness Stress, anxiety, mood and cognition.
- The most clinically studied Sceletium extract in the world - Eight pilot, doubleblind, placebo-controlled clinical studies.
- Fast Acting Clinically proven to positively impact the electrical activity of the brain only two hours after ingestion.
- Experiential Zembrin[®] users feel the difference it makes to their mental wellbeing, which guarantees repurchase.

- Low Dose Proven safety and efficacy at 25 mg. Great for formulation development as a single ingredient or combination product.
- Safe Researchers have thoroughly studied the safety of **Zembrin®**.
- **Easily Tolerated** Yes, safety studies have shown that **Zembrin®** is well tolerated.
- **Socially Responsible** A royalty from every kilogram of **Zembrin**® sold is paid to the African tribes that contributed their indigenous knowledge to the development of this patented extract.
- Ecologically Sustainable No wild farming and depletion of indigenous stock.
- Feel Good Story If we were going to pick a slogan for **Zembrin**[®], it might be "Feel good while you're feeling good." **Zembrin**® is the mental wellness ingredient with a truly feel-good story.
- Fully Traceable Strict adoption of quality control measures with EU-GMP.
- Dual Acting Research with Zembrin® has shown that it has a dual mechanism of action.
- Not a conventional pharmaceutical anti**depressant** - but it helps with uplifting spirits and improving mood.
- Not a stimulant but it helps with alertness and improves mental performance.





References

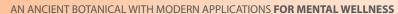
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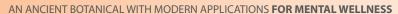
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