

# Innovation in **STRESS & SLEEP**



Holy Basil



Everyday &  
Acute Stress



Non-habit  
forming

## HOLIVER<sup>TM</sup>

Stress Less | Find Calm | Sleep Sound



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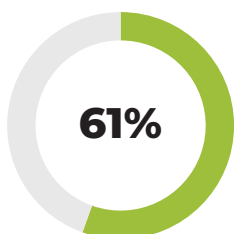
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## STRESS AND SLEEP IMPACT

Angst and stress are extremely common among adults today, more so than ever.

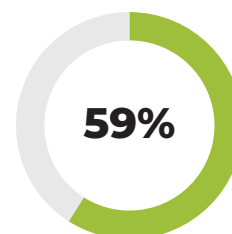
A February 2023 survey conducted, found that about 61% of Americans say their stress level is at an all-time high, 55% people say they are unable to enjoy life because of stress, while 59% assert that stress negatively impacts their relationships.



Americans say their stress level is at an all-time high



People say they are unable to enjoy life because of stress



Assert that stress negatively impacts their relationships

Generationally, according to this survey, Millennials and Generation Z at 55% are nearly twice as likely as Baby Boomers at 30% to struggle to function due to stress.



**55%**  
Millennials



**55%**  
Generation Z



**30%**  
Baby Boomers

High chronic stress is known to impact sleep duration and quality. According to 2022 data from The Sleep Foundation, 54.4% of respondents to a SleepFoundation.org survey said that stress and anxiety were the top reasons they have trouble falling asleep. Further, the National Heart, Lung, and Blood Institute estimates that up to 70 million people in the US alone have difficulty in sleeping.



**70 million people**  
In the US have ongoing difficulty in sleeping.



**Stress is common among all age groups and generations causing various negative impact on life**



**Insufficient sleep and poor sleep quality are causing sleep dysfunctions affecting day-to-day life**

Elevated stress levels can have detrimental effects on the immune system, potentially compromising its functionality. This can increase tension and feelings of irritability, loss of interest, or nervousness. Additionally, stress often disrupts sleep patterns, causing racing thoughts that hinder restful sleep, which further causes sleep issues. It can also strain relationships due to feelings of frustration and exhaustion, reduce productivity and focus, trigger anger issues, contribute to weight gain through unhealthy coping mechanisms like overeating and impede concentration as the brain remains vigilant for potential threats. Furthermore, everyday stress has significant implications on long-term health. Therefore, reduction in stress levels can support healthy living & healthy aging.



### Impact on health due to increase in stress levels and sleep dysfunction



Weak Immunity



Tension



Irritability



Nervousness



Disrupts sleep



Frustration



Exhaustion



Reduced focus



Anger



Weight gain



Overeating



**Increase in stress levels and sleep disorders have an impact on many body systems and may negatively impact mental, physical and overall health.**

**The prevailing scenario presents the need for a natural product that is clinically proven and safe in alleviating stress and enhancing sleep quality.**



## HISTORICAL USE OF HOLY BASIL/TULSI

Commonly used in Ayurveda, Holy Basil is an adaptogen, balancing different processes in the body and is also helpful for adapting to mental and physical stress. Marc Cohen, author of a published review, described, "Cultivation of Tulsi plants has both spiritual and practical significance that connects the grower to the creative powers of nature, and organic cultivation offers solutions for food security, rural poverty, hunger, environmental degradation and climate change. The use of Tulsi in daily rituals is a testament to Ayurvedic wisdom and provides an example of ancient knowledge offering solutions to modern problems."<sup>1</sup>



In Ayurveda, as its English name implies, Holy Basil/Tulsi is the second most holy plant in India, followed by lotus. It is considered to be sattvic, which means "essential purity." It is also known as "The Incomparable One," "Mother Medicine of Nature" "The Queen of Herbs" "Elixir of life".<sup>2</sup>

In Ayurveda, Holy Basil is considered one of the foremost adaptogenic herbs, and helps the body cope with stress, promotes mental clarity, supports rejuvenation & promote sleep.<sup>3,4,5</sup>

### SCIENTIFIC NAME

*Ocimum tenuiflorum*  
Syn. *Ocimum sanctum*

### ENGLISH NAME

Holy Basil

### COMMON NAMES

"Tulsi", "The Incomparable One,"  
"Mother Medicine of Nature"  
"The Queen of Herbs" "Elixir of Life".

### AYURVEDA

5000 Years

## MODERN RESEARCH

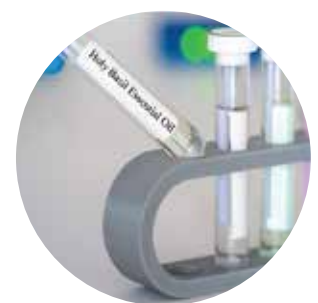
The total publications on *O. tenuiflorum* are 1014, with 24 human clinical studies.

**1014**

The total publications  
on *Ocimum*

**24**

The total clinical studies  
on *Ocimum*



A recently conducted and published comprehensive literature review of human studies with Holy Basil had a positive conclusion about its use as a supplement for promoting health. The authors pooled data from 24 studies reporting therapeutic effects on immunity, metabolic health, cardiovascular health and brain function. The authors write, "The reviewed studies reinforce traditional uses" and suggest that Holy Basil is an effective botanical supplement for promoting health and wellness.<sup>6</sup>

With such a strong platform of traditional use and recent human clinical trials, Natural Remedies' R&D began the journey of developing Holixer™, the Holy Basil with the X-factor in stress and sleep management.

## ABOUT HOLIXER™

Holixer™ - Holy Basil/Tulsi (*Ocimum tenuiflorum*) extract. Traditional Ayurvedic knowledge and use, plus modern research led Natural Remedies™ to develop an ingredient that comes with a potential to help millions of adults in alleviating stress and support healthy sleep.

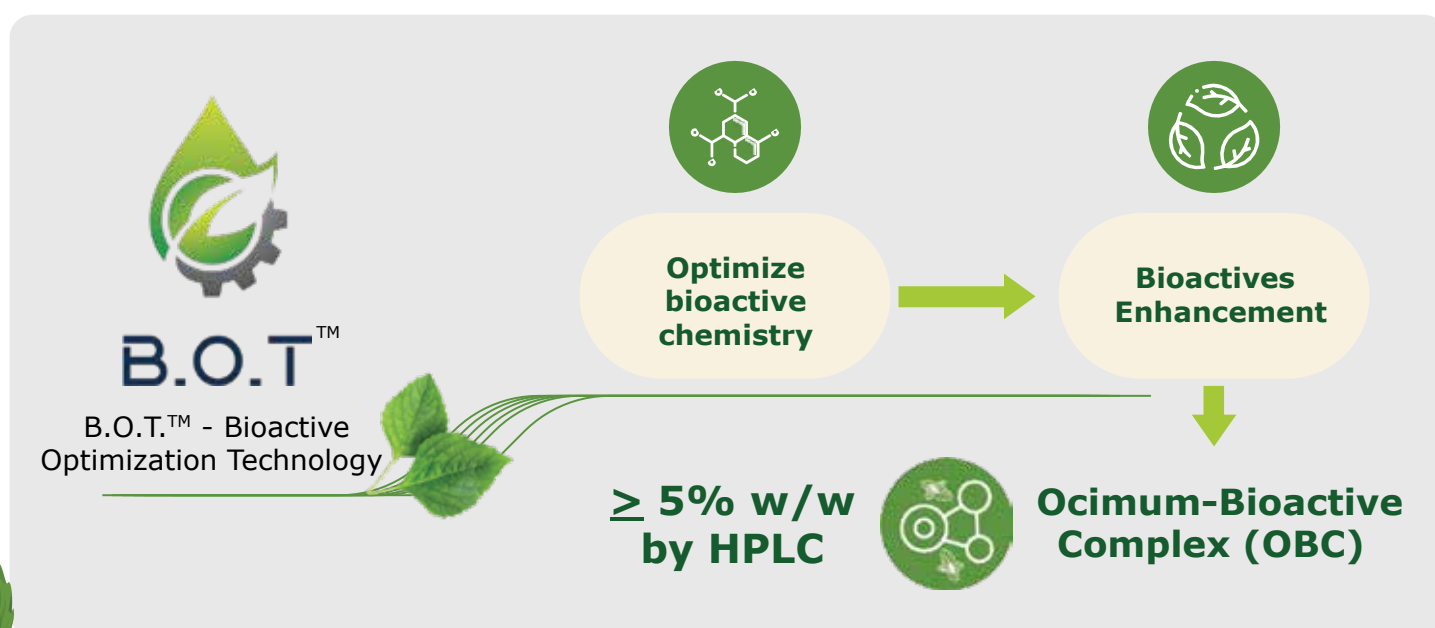


## THE INNOVATION: BIOACTIVE OPTIMIZATION TECHNOLOGY



Natural Remedies' R&D worked diligently for five years to create Bioactive Optimization Technology (B.O.T.™), a systematic technique that preserves the multiple bioactive compounds in Holy Basil and optimizes their innate capabilities, making the herb extract effective at a dose of 250 mg.

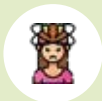
This bioactives-enhancement technology results in Ocimum-Bioactive Complex (OBC™), providing our brand partners and their consumers with a measurable, distinctive Holy Basil herbal extract that is unparalleled.



## HOLIXER™S HUMAN CLINICAL EVIDENCE

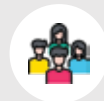
A two-arm, parallel-group, randomized double-blind placebo-controlled human trial showed that Holixer™ provides measurable and perceived benefits to alleviate stress and improve sleep quality along with quality of life.

The study included 100 participants who all fulfilled the criteria of having stress and problems with achieving sufficient and quality sleep. The participants consumed either 250 mg Holixer™ or placebo daily for 8 weeks and were evaluated for stress response and sleep quality using both subjective and objective parameters.



### Condition:

Healthy participants with stress & sleep problems



### Participants:

100 volunteers  
(n=50 in each group)



### Dose:

250 mg/day



### Duration:

8 weeks



### Evaluation - Stress:

**Subjective:** Perceived stress scale (PSS), Visual analogue scale (VAS)

**Objective:** Hair cortisol, Salivary cortisol, Salivary alpha amylase (sAA), Blood Pressure



### Evaluation - Sleep:

**Subjective:** Athens Insomnia Scale (AIS)

**Objective:** Fitbit®



### Evaluation QOL:

**Subjective:** PROMIS 29

**HOLIXER™**  
Stress Less | Find Calm | Sleep Sound



### OUTCOME:

**Holixer™ demonstrated significant improvements in stress and sleep score compared to placebo.**

# HOLIXER™ AND EVERYDAY STRESS

## Everyday Stress:

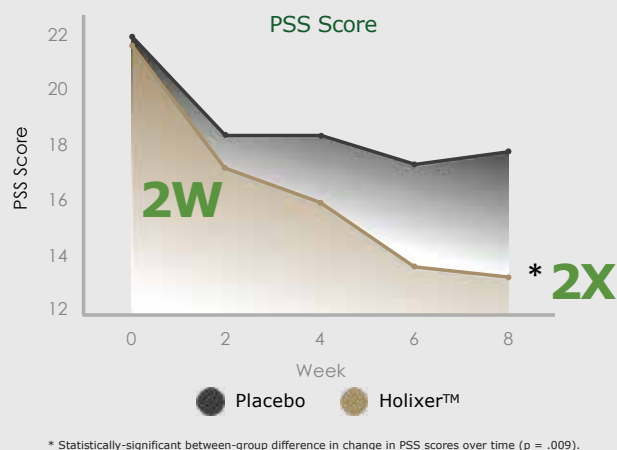
The study on Holixer™ analyzed both the globally recognized types of stress: Everyday/Chronic Stress and Acute Stress on both subjective as well as objective parameters.

Chronic stress was measured employing the Perceived Stress Scale (PSS) & Hair Cortisol measurement, which is a unique evaluation unlike the commonly used blood cortisol levels.

Results demonstrated that those in the Holixer™ group began to show improvements in PSS as early as two weeks, and also exhibited reduced stress scores twice that compared to placebo. Holixer™ showed a significant 38% reduction in PSS at 8<sup>th</sup> week.

## Results - Everyday stress: Perceived Stress Scale (PSS) - Subjective

Effect of Holixer™ & Placebo on change in the PSS


**2W**

Holixer™ starts showing effect within two weeks

**2X**

Holixer™ reduced the stress scores by two times compared to placebo

PSS scores ranges



0-13:  
Low Stress



14-26:  
Moderate Stress



27-40:  
High Perceived Stress

**OUTCOME: Holixer™ showed significant reduction in Perceived Stress Score with 38% vs placebo.**



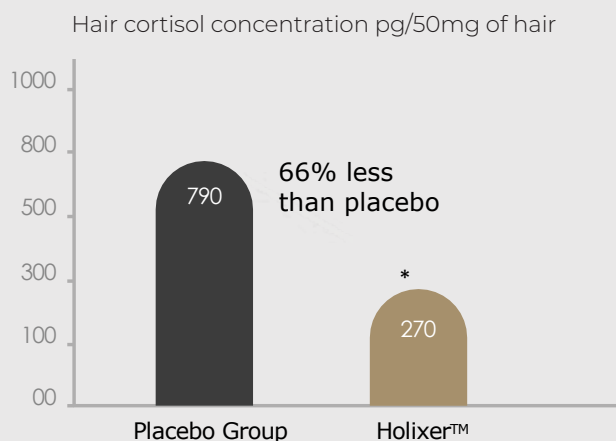
**Holixer™ significantly helped lower stress levels from moderate to low.**



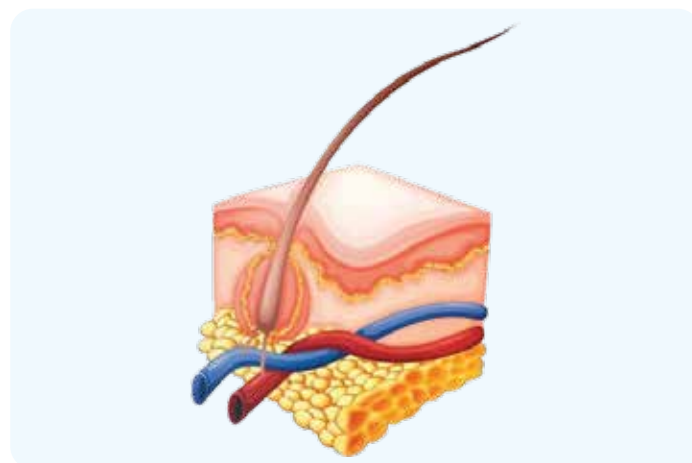
# HOLIXER™ AND EVERYDAY STRESS

## Results - Everyday stress: Hair cortisol - Objective

Effect of Holixer™ & Placebo on change in Hair cortisol concentration



Hair cortisol, unlike the blood cortisol levels, is a unique evaluation used in this trial to evaluate everyday/chronic stress. Here's why: Blood cortisol measurement provides just a snapshot of cortisol levels at a specific point in time and may be impacted by other factors.



However, the hair cortisol measurement method provides a long-term retrospective assessment of cortisol secretion over a period of weeks or months. This method is particularly valuable for examining chronic/everyday stress as well as evaluating the efficacy of stress management interventions over time. Hair cortisol concentration measurements showed that Holixer™ provided statistically significant lower hair cortisol concentration compared to placebo by 66%.<sup>7</sup>

66%

Reduction in hair cortisol compared to placebo



Unique Evaluation

**OUTCOME:** Holixer™ showed statistically significant lower hair cortisol concentration compared to placebo.



Holixer™ proven to help cope with everyday stress events with significant improvement in subjective PSS score and objective evaluation of Hair Cortisol.

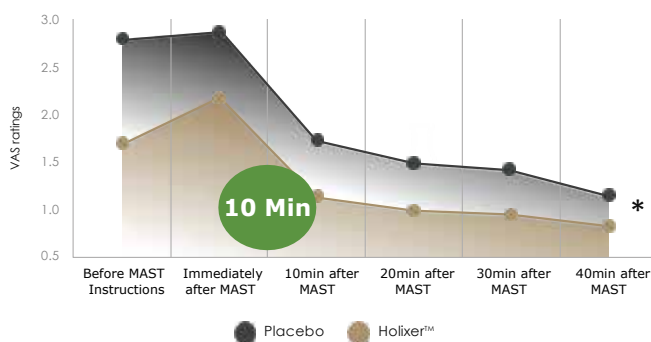
## HOLIXER™ AND ACUTE STRESS

Acute stress was measured by employing the Maastricht Acute Stress Test (MAST), which included visual analogue scale (VAS), salivary cortisol levels, Salivary Alpha Amylase (sAA) levels and blood pressure. MAST is a validated robust experimental stress test to induce acute stress phase, physical stress (e.g., cold induced pain) is combined with unpredictability, uncontrollability, and social evaluation in a mental arithmetic task.

Salivary alpha-amylase (sAA) is a valid and reliable marker of Autonomic Nervous system (ANS) activity in stress research and is therefore an important biomarker to consider in behavioral medicine. In VAS, Holixer™ showed its effect within 10 minutes. In all other three measurements of salivary cortisol, salivary alpha amylase and blood pressure the results were better within 10 mins. compared to placebo.<sup>7</sup>

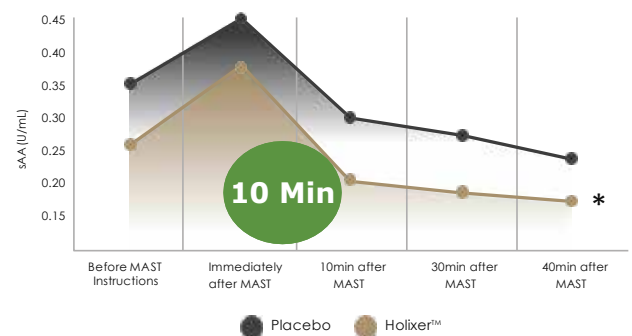
### Acute stress: VAS - Subjective

Effect of Holixer™ & Placebo on Visual analogue scale (VAS)



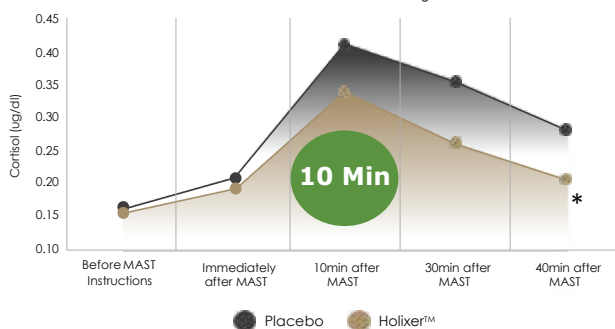
### Acute stress: Salivary alpha amylase (sAA) - Objective

Effect of Holixer™ & Placebo on Salivary alpha amylase



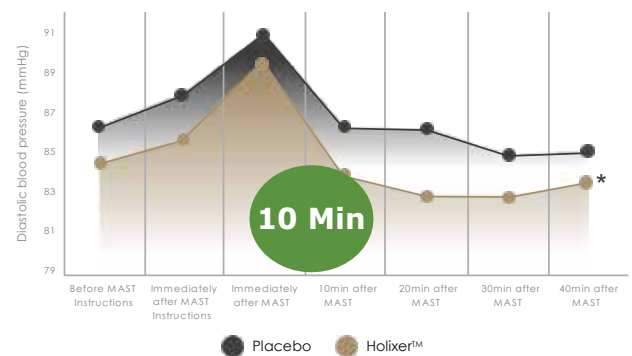
### Acute stress: Salivary cortisol - Objective

Effect of Holixer™ & Placebo on Salivary cortisol



### Acute stress: Blood Pressure - Objective

Effect of Holixer™ & Placebo on blood pressure



\* Statistically significant (p < .05), After 8 weeks of intake



**MAST: MAASTRICHT ACUTE STRESS TEST**



Physical Stressor



Mental Stressor

**10 MIN**

Holixer™ helped manage acute stress effectively within 10 Min.

**OUTCOME:** Holixer™ showed benefits in acute stress. It strongly correlated with reduction in VAS score, salivary cortisol, salivary alpha amylase & blood pressure within 10 minutes.





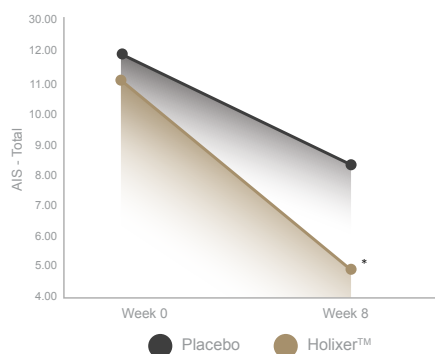
**Holixer™ proven to help manage acute stress with Maastricht Acute Stress Test (MAST), gold standard evaluation consist of physical & mental stressor.**

## HOLIXER™ AND SLEEP

Sleep was evaluated through the Athens Insomnia Scale (AIS) and Fitbit®. The AIS is a validated 8-item scale that assesses the sleep quality. The questions in AIS evaluate the areas of sleep onset, night and early-morning waking, sleepiness during the daytime, sleep time, sleep quality, duration and frequency of complaints, distress caused by the experience of insomnia, and interference with daily functioning. Those in the Holixer™ group showed a 50% improvement in the Athens Insomnia Scale over those in the placebo group. Fitbit® data from the Holixer™ group, which measured sleep efficiency percentage (total time asleep/total time in bed), showed that the Holixer™ group registered an average of approximately 91% at 8 weeks, compared to approximately 86.5% at baseline.<sup>7</sup>

### Sleep: Athens Insomnia Scale (AIS) - Subjective

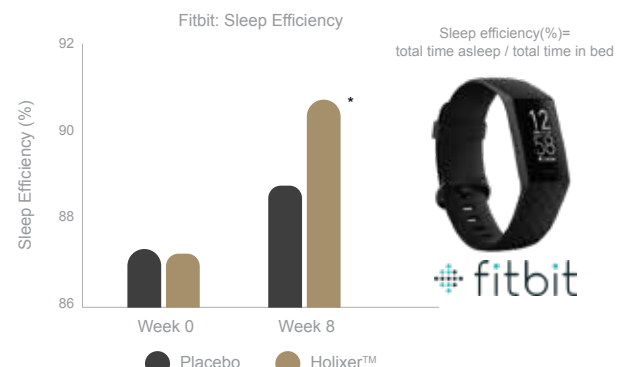
Effect of Holixer™ & Placebo on sleep



\*Statistically-significant ( $p \leq .025$ ).

### Sleep: Wearable Sleep tracker (Fitbit®) - Objective

Effect of Holixer™ & Placebo on sleep efficiency



\*Statistically significant from baseline

**48%** improvement in sleep quality as compared to placebo.

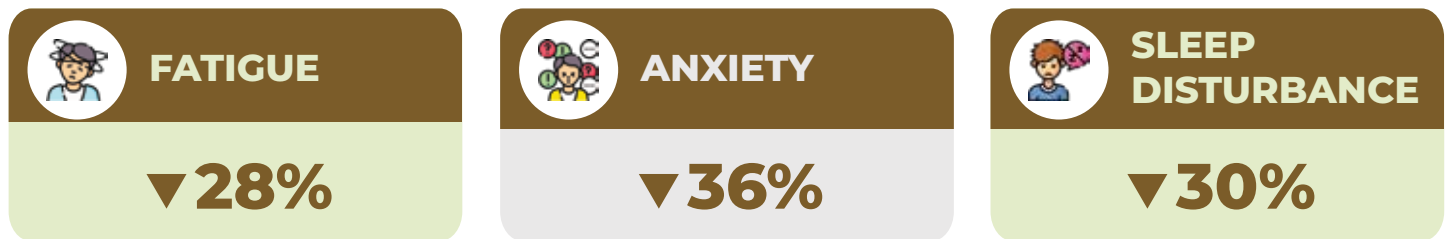
**3.5%** Significant improvement in sleep efficiency from the baseline.



**Holixer™ improved sleep quality and sleep efficiency.**

## HOLIXER™ AND QUALITY OF LIFE

Quality of life was measured through PROMIS 29 (Physical Function, Anxiety, Depression, Fatigue, Sleep Disturbance and Social).<sup>7</sup>



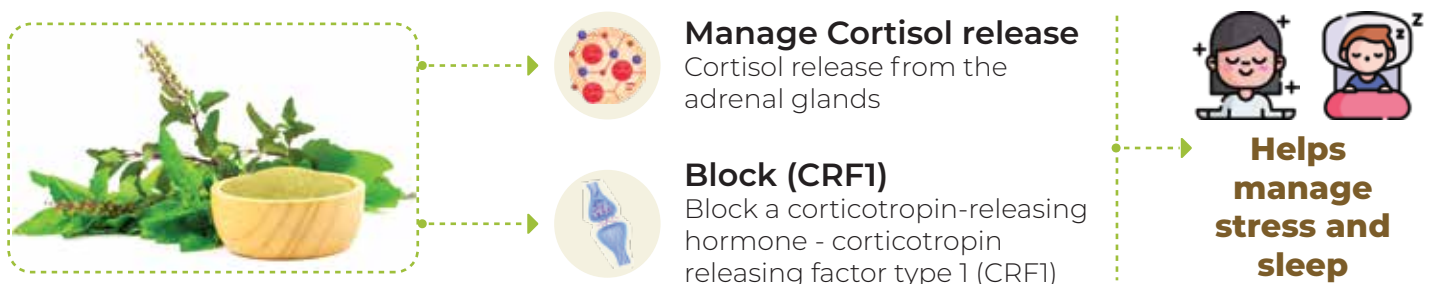
**Holixer™ helped improve quality of life.**

### Latest 2024 Sleep Study Ongoing | Sleep Lab | Polysomnography

Recent ongoing research shows that taking 250 mg prior to bedtime improves a key phase of the sleep cycle to help people have sleep continuity and stability (a key factor for sleep quality) and help fall asleep faster.

## HOLIXER™ MECHANISM OF ACTION

*In-vitro* and *in-vivo* research on Holixer™ has shown that it works through two closely related mechanisms. One is by inhibiting and/or reducing cortisol release from the adrenal glands. The other is through acting to block a corticotropin-releasing hormone -- corticotropin releasing factor type 1 (CRF1) -- which is secreted when a stressor is encountered. Both mechanisms provide a useful approach to alleviate the physiological effects of stress.<sup>7</sup>



***In-vitro* and *in-vivo* research on Holixer™ shown to manage stress & sleep.**

## POSSIBLE HEALTH CLAIMS#

The human clinical study on Holixer™ allows for the following health claims#:



### STRESS

- ▶ Helps maintain healthy cortisol levels during everyday stress
- ▶ Regular intake for 8 weeks helps the body quickly respond when facing acute stress
- ▶ Helps you work relaxed during everyday stress
- ▶ For resolving the irritability that ruins the day
- ▶ Helps to be calm during everyday stress
- ▶ Support resilience to combat everyday stressors



### SLEEP

- ▶ Day and night-time aid for everyday stress and occasional sleeplessness
- ▶ Helps improve sleep efficiency during occasional sleeplessness
- ▶ Non-drowsy calm aid
- ▶ Stay asleep longer during occasional sleeplessness naturally



### QUALITY OF LIFE (QOL)

- ▶ Helps in physical and mental well-being during everyday stress

#These statements have not been evaluated by the Food and Drug Administration.

## SUSTAINABILITY

Holixer™ has an attractive sustainability story that meets consumers' high standards. The raw material, Holy Basil plants, are grown and cultivated in accordance with Good Agricultural Practices (GAP), with natural nutrient-rich fertilizers and without the use of pesticides. The plants are harvested in accordance with Good Collection Practices (GCP), and the entire process allows for Natural Remedies to have end-to-end control over biomass.

Holixer™ sustainability involves:



**Regenerative Agricultural Practices**



**Pesticides Free**



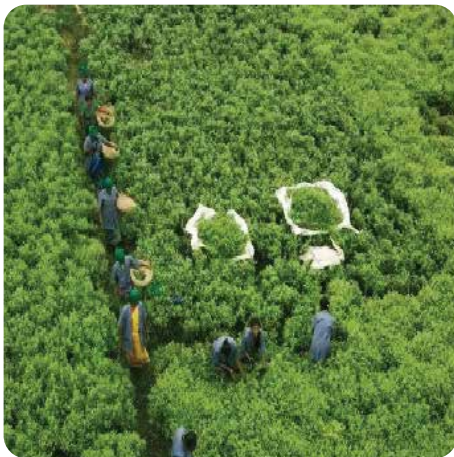
**Natural Fertilizers**



**Good Collection Practices**



**End-to-end Control Over Biomass**



## DOSE

Holixer™ is a unique solution for stress and sleep management that offers formulators the scope to be innovative and offers excellent formulations for excellent experiences amongst consumers.



**Dose: 250 mg/day  
(single or two divided doses)**



## FORMULATION ADVANTAGES

Holixer™ provides several key advantages in formulas addressing stress and sleep support products. Holixer™ -

- ▶ Has a mild palatable taste, reducing need for taste-masking agents
- ▶ Is 100% water-soluble
- ▶ Available in organic grades



**Taste:**  
Mild Palatable



**100% Water Soluble**  
(250 mg / 100 ml)



**Organic Grades**  
Available

## DOSAGE FORMATS

Holixer™ make it flexibly blend into any formulation & delivery system



**TABLETS**



**CAPSULES**



**GUMMIES**



**SHOTS**



**SACHETS**

## CONCLUSION

As people throughout the world deal with stress and stress related sleep issues, Holixer™ brings about a unique ingredient that is scientifically substantiated and clinically validated to improve the outcomes of your Stress & Sleep related formulations.



## REFERENCES

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Innovation in **STRESS & SLEEP**

# HOLIVER™

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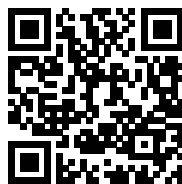


**B.O.T.™ &  
OBC™**

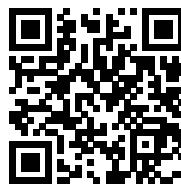
**Formulation  
flexibility**

**Validated by RDBPCT  
in stress & sleep**

Video



Website



Sustainability Story



**Want to know more?**

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