

Award-Winning

HOLIVER[®]

Stress Less | Find Calm | Wake Fresh

Gold Standard

CORTISOL SUPPORT



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Benefits of Holixer®

Cortisol Dysregulation:

The Stress-Sleep Link



For millions around the world, a good night's sleep has become increasingly out of reach driven largely by rising stress. Globally, 1 in 3 adults struggle with sleep¹, and for more than half, the root cause is stress and anxiety². Moreover, over 50% of individuals with sleep disturbances have elevated cortisol levels.³

A Market Growing as Fast as the Problem

Stress Support Supplements Market⁴

**\$5.67
billion**

2024 - 5.67 USD billion
2033 - 10.25 USD billion
CAGR - 7.25%.

Sleep Supplement Market⁵

**\$7.5
billion**

2025 - 7.5 USD billion in 2025
2035 - 12.8 USD billion
CAGR - 5.4%
The natural segment leads with 58.4% share, driven by consumer preference for herbal and plant-based formulations.

These trends reflect not just market growth but a global unmet need for holistic solutions that break the stress-sleep cycle and restore balance.

Breaking the Stress-Sleep Cycle at Its Root

Stress activates the Hypothalamic-Pituitary-Adrenal (HPA) axis, raising cortisol to help manage immediate challenges. When this response becomes chronic, elevated cortisol disrupts circadian rhythms, making it harder to fall or stay asleep.

Elevated chronic cortisol can lead to unrestorative, fragmented sleep, increased anxiety and emotional reactivity, next-day fatigue and reduced cognitive clarity. Over time, disrupted sleep further impairs cortisol regulation where stress disturbs sleep and poor sleep amplifies stress. Disrupted sleep then alters regulation of neuropeptides that regulates the sleep wake cycle, thereby leading increased emotional reactivity and reducing resilience.⁶ This carries long-term consequences, including weakened immunity, cognitive and mood disturbances, metabolic issues, and accelerated aging. Consumers increasingly seek solutions that not only promote

sleep but break this cycle to restore long term balance. True restoration requires more than sedating the mind. It requires rebalancing the biology behind it.

Cortisol imbalance & chronic stress lie at the root of most sleep disturbances.

While certain conventional sleep interventions may provide short-term relief, they are often associated with concerns such as dependence, tolerance, cognitive impairment, and disruption of natural sleep architecture.^{7,8} This has opened the door to non-habit-forming alternatives. Botanicals like standardized saffron extracts show benefits for mild, stress-linked sleep issues, yet their effects on micro-structural, unfragmented and restorative sleep are limited. Valerian faces challenges with extract consistency due to unstable constituents like valepotriates.⁹

Melatonin remains the most recognized natural option for circadian alignment, but absorption variability, drug interactions, and inconsistent dosing raise concerns, and long-term use may diminish effectiveness.^{10,11} Formulators are therefore moving toward low-dose melatonin + botanical blends supported by robust safety data. Also, magnesium aid relaxation through N-Methyl-D-Aspartate (NMDA) regulation and Gamma-Aminobutyric Acid (GABA) enhancement, though evidence is constrained by deficiency variability and digestive effects from certain salts.^{12,13}

These gaps reflect a rising demand for natural solutions targeting stress and sleep health at its core.

A Broader Industry Shift

Addressing the underlying cause of sleep disturbances particularly chronic cortisol dysregulation helps restore natural sleep architecture, and support quality sleep. As science advances, standardized botanicals such as holy basil are demonstrating the potential of natural, evidence-based solutions for unfragmented sleep that culminates in restoring physiological and mental health benefits and next day optimal functioning.

Exploring The Holy Basil Space

As next-generation natural solutions reshape the stress and sleep category, Holy Basil (*Ocimum tenuiflorum*) is emerging as a standout botanical. Traditionally revered in Ayurveda for calming the mind and enhancing resilience, it is now being recognized by modern science for its influence on the HPA axis, cortisol regulation, sympathetic activity, and sleep pathways. This positions Holy Basil uniquely at the intersection of tradition and biology addressing both stress and sleep together. With global demand rising for effective natural solutions, Holy Basil offers a compelling answer. Holixer® leads this space by bringing scientific rigor, standardized actives, and clinically validated outcomes to this centuries-old adaptogen.

Award Winning Holixer®: Precision Science

Holixer® stands apart because the discovery is rooted in our unique, proprietary Bioactive Optimization Technology (B.O.T)™. This technology ensures that Holixer® is standardized to Ocimum Bioactive Complex (≥5% w/w by HPLC) to ensure consistent levels of five key phytoactive compounds. As a clinically validated extract, Holixer® opens a new frontier in cortisol regulation, stress and sleep management bringing modern science to a revered traditional botanical.

Our Unique Strengths



Innovative

Developed with B.O.T technology to maximize efficacy



Clinically Proven

Backed by clinical trials



Safe

Designed for daily use & non-habit forming

Innovative: Bioactive Optimization Technology (B.O.T)™

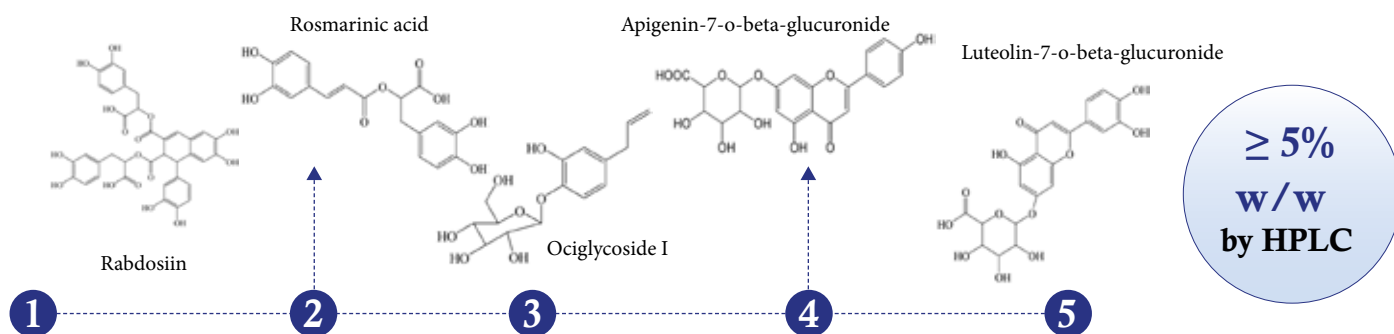
Natural Remedies leverages its proprietary, Bioactive Optimization Technology (B.O.T)™. This state-of-the-art technology combines the principles of chemistry and biological sciences to deliver a bioactive optimized extract, characterized by high bioactivity at low dose. The approach encompasses full spectrum activity, ensuring the delivery of an ingredient with enhanced efficacy, robust safety profile and with significant impact.

Natural Remedies follows two phase process in this endeavour. The initial discovery phase involves designing multiple fractions, guided by a new product need. These fractions may encompass diverse characteristics, such as polar or nonpolar properties or hydro actives components, etc. Approximately 50 to 60 leads are generated, subsequently subject to rigorous screening, utilizing mathematical models, predictive screening methodologies and biological studies, to generate a comprehensive dataset. This dataset comprises information pertaining to the effects of individual fractions and their combinations, predictive effects of these combinations, and the interactive effects of specific phytoactive fractions. The subsequent optimization phase focuses on refining the identified lead. This is achieved through an iterative process involving the integration of

phytochemical and biological investigations, culminating in a bioactive-optimized extract that exhibits high and targeted bioactivity at a reduced dose. It uses intelligent combinations of fractions to achieve synergistic actions to form Ocimum Bioactive Complex (OBC). The key phytochemicals in Holy Basil are optimized for maximum effectiveness. This process has yielded Holixer® a standardized Holy Basil extract demonstrating clinical efficacy at a dose of 250mg per day.



Ocimum Bioactive Complex (OBC)



Holixer®: Receptor Functional Assay and In-Silico Evidence

Advanced in silico molecular docking studies confirm that Holixer®'s five optimized phytoactives exhibit strong and selective binding affinity to key neurological receptors involved in stress and sleep regulation including Galanin, MCH, Melatonin, and Orexin 1 & 2. These findings indicate a meaningful potential for Holixer® to modulate central pathways governing stress response and sleep architecture.

Complementary receptor functional assays further substantiate these observations, demonstrating that Holixer® functions as an agonist on sleep-promoting pathways and an antagonist on arousal-associated pathways. Collectively, this integrated evidence base provides strong scientific support for Holixer®'s capacity to facilitate sleep initiation, promote restorative sleep quality, and attenuate hyperarousal and stress signalling.

Holixer®: Preclinical Validation of Safety and Stress-Relieving Potential

Preclinical research published in PLOS One demonstrated Holixer®'s antistress activity using two in vivo models: the swim endurance test in mice and the forced swim test in rats. Holixer® increased swim endurance, reduced corticosterone elevation, supported by in vitro studies showing inhibition of cortisol release and significant CRF1 receptor antagonism.¹⁴

Its safety profile, published in Drug and Chemical Toxicology, confirmed no mutagenic or clastogenic effects across bacterial, in vitro, and in vivo assays. Holixer was also shown to be safe in acute toxicity studies up to 5 g/kg in rats.¹⁴

Together, these findings establish Holixer® as a non-genotoxic, well-tolerated extract with robust preclinical evidence supporting its role in safe, effective stress management.



Human Trial: Clinically Proven “Alert Calm”

In a randomized, double-blind, placebo-controlled clinical study, Holixer® was evaluated for its impact on stress and sleep in one hundred healthy adults experiencing moderate stress. Participants received 250 mg of Holixer® daily for eight weeks. Over the course of the study, Holixer® demonstrated meaningful benefits across everyday stress, acute stress response, sleep quality, and overall well-being.

Everyday stress was assessed using both the perceived stress scale and hair cortisol, a robust biomarker of long-term stress. Participants supplemented with Holixer® showed a clear reduction in psychological and biochemical markers of stress, including a 37% reduction in perceived stress scores from baseline and a 66% decrease in hair cortisol compared with placebo, underscoring Holixer®’s ability to manage chronic stress.

To evaluate resilience under acute stress, the Maastricht Acute Stress Test (MAST) was employed. This standardized protocol alternates five cycles of hand immersion in freezing water with mental arithmetic tasks to induce both physical and psychological stress. Stress markers including salivary cortisol, salivary alpha-amylase, and blood pressure were recorded to quantify stress reactivity. Individuals receiving Holixer® exhibited a noticeably calmer and more controlled response, with rapid relief within just 10 minutes, accompanied by significant reductions in salivary cortisol, and lower sympathetic activation. These results highlight Holixer®’s capacity not only to reduce chronic stress but also to enhance the body’s ability to manage acute stress challenges.

Equally compelling improvements were observed in sleep outcomes. Participants taking Holixer® experienced marked benefits on the Athens Insomnia Scale, achieving a 48% greater improvement than placebo, while objective Fitbit® measurements confirmed significant gains in sleep efficiency. These enhancements in restorative sleep translated into broader improvements in daily functioning. PROMIS-29 scores reflected meaningful increases in quality of life, including 28% reduction in fatigue, 36% reduction in anxiety, and 30% reduction in sleep disturbance.¹⁶



↓ **10 mins**

Rapid relief from
acute stress
(reduced salivary cortisol)*



↓ **2 weeks**

Marked reduction in
perceived stress

• 1st Botanical Ingredient Validated to Reduce Hair Cortisol •

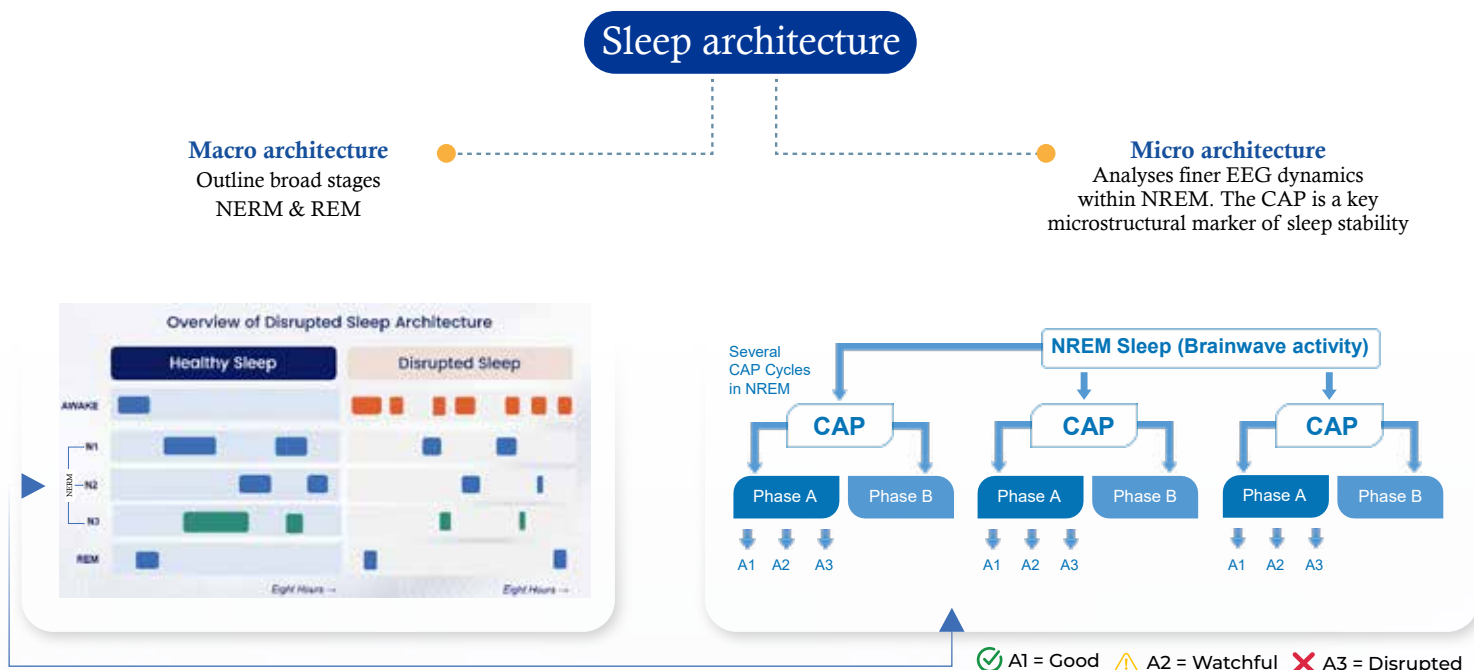


Taken together, the findings demonstrate that Holixer® delivers clinically validated dual action effectively reducing stress while restoring healthy sleep, with benefits evident across subjective assessments, & objective biomarkers.

*After 8 weeks of intake

Sleep Structure and Stability: A Closer Look

For years, most sleep aids and supplements have focused on broad metrics such as total sleep duration or time spent in rapid eye movement (REM) and non-rapid eye movement (NREM) sleep rather than addressing the finer details of sleep microarchitecture. Increasingly, research is focusing on a more nuanced layer of sleep science: microarchitecture. One key marker in this area, the Cyclic Alternating Pattern (CAP) during NREM sleep, is emerging as a valuable indicator of stability and depth in restorative rest.



Total sleep time looks identical, but the disturbed sleeper spends lesser time in N3 deep sleep and experiences frequent microarousals.

Restorative sleep quality goes beyond duration, it depends on the stability of sleep micro-architecture, especially the Cyclic Alternating Pattern (CAP) during NREM sleep. A higher proportion of A1 activity reflects deep, stable, and restorative sleep, while A2/A3 indicate fragmentation. Enhancing A1 is a key neurophysiological target for truly unfragmented sleep. This clinical study of Holixer has also examined sleep microarchitecture, suggesting that Holixer help stabilize CAP- A1 rates, within non-REM sleep patterns and reduce fragmentation.^{17,20}

A Global First: Sleep Microarchitecture

Holixer marks a significant milestone in sleep science by becoming the first botanical ingredient globally to demonstrate measurable improvement in sleep microarchitecture unfragmented dimension of sleep validated through gold-standard polysomnography (PSG).

In an independent clinical study involving seventy adults, participants received 250 mg of Holixer® daily for eight weeks. The findings were remarkable: Holixer® produced a 95% improvement in CAP A1 rate, the marker most closely associated with stable, deep, unfragmented NREM sleep. An increase in A1 activity is widely recognized as the clearest indicator of improved sleep continuity, enhanced stability, and stronger restorative capacity at a neurophysiological level.

This shift toward higher A1 dominance translates into fewer night-time awakenings, smoother transitions between sleep stages, and deeper recovery processes that help support cognitive, emotional, and physical restoration.

Actigraphy provided complementary evidence. Participants experienced faster sleep onset, fewer disturbances through the night, and a more consistent sleep-wake rhythm. These improvements align closely with what consumers seek today sleep that is not only longer, but genuinely restorative.

Holixer® also demonstrated meaningful benefits on the Insomnia Severity Index (ISI). Participants exhibited a 50% improvement in sleep quality from baseline. Taken together, these findings establish Holixer® as a new benchmark in natural restorative sleep solutions.²¹



**Based on deep sleep analysis by polysomnography

Holixer® Mechanism of Action:

Dual-R Action

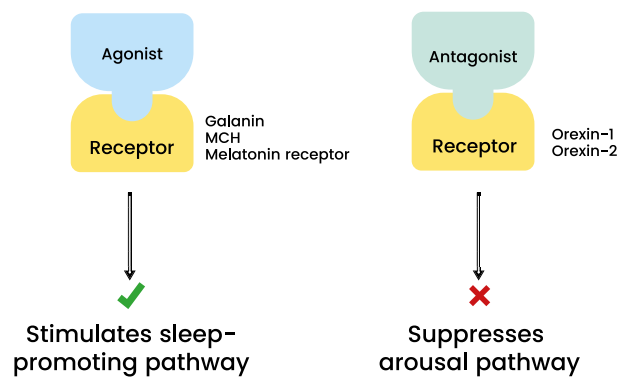
RESET: The Stress Axis

Modulates the HPA axis

- Balances cortisol
- CRF1 receptor antagonist

RESTORE: The Natural Sleep–Wake Rythm

Modulates multiple neuropeptide receptors



Chronic stress disrupts both the HPA axis and the Sympathetic Nervous System. Holixer® helps reset these systems by inhibiting CRF1 receptor activity, reducing cortisol and lowering sympathetic drive evident through decreased salivary α -amylase and more stable cardiovascular responses during stress. Together, these effects help shift the body from a state of hyperarousal to a more regulated and adaptive stress response.

Holixer® then restores sleep physiology through targeted modulation of key neuropeptide receptors. By agonising Galanin, MCH, and Melatonin receptors and simultaneously antagonising Orexin-1 and Orexin-2, it strengthens sleep-promoting pathways while suppressing arousal. Clinically observed improvements in CAP A1 activity, sleep continuity, and overall sleep quality reflect this deep, restorative influence on sleep microarchitecture.

Through this integrated RESET and RESTORE mechanism, Holixer® addresses both the cause and the consequence of stress-related sleep disturbances providing a scientifically coherent and clinically validated pathway to calmer days and more restorative nights.



A Sustainably Crafted Ingredient Backed by HerbSecure™



Global Regulatory Advantage

- ✓ GRAS – Affirmed Advantage
- ✓ FSSAI Approved
- ✓ Korea – MFDS IAFF Approval
- ✓ Korea – MFDS General Food Approval
- ✓ Complementary Medicine in ANZ



Why Choose Holixer® ?



Clinically validated

Validated by cortisol biomarkers & CAP A1



Award-winning

Mind and Mood

HOLIXER®



Trusted Worldwide

23 countries
>50+ global brands



Water soluble

Formulation flexibility



Sustainably Sourced

Transparent & reliable

Awards Accoladed Globally

WINNER
NUTRA
INGREDIENTS USA
AWARDS 2025

Ingredient of the Year:
Mind & Mood award.



WholeFoods
MARKETPLACE
Wholesome and Sourcing the Natural Products Industry

Natural Choice Award in the Stress/
Sleep Support category (2024).



Vitafoods
India **V**

First Runner-Up in the
Innovation Zone.



HOLIVER[®]

Stress Less | Find Calm | Wake Fresh



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