INTRODUCTION

Sleep is as fundamental to life as water and food. Sleep is essential for the brain to recover, recharge, and remove toxins at the end of each day.\(^1\,^2\) It allows for the formation of new synapses, consolidation of memories, and regeneration of neurons.\(^3\) Unfortunately, high stress levels, artificial lights, and fast-paced lifestyles mean that people are getting low quality sleep, and less of it. Chronic sleep loss dramatically impairs cognitive function but it has also been implicated in obesity, cardiovascular disease, and psychiatric, gastrointestinal, and reproductive disorders.\(^4\,^5\) Sleep Benefits™ offers a three-prong approach to help fall asleep, improve sleep quality, and stay asleep.

SLEEP DEPRIVATION

Sleep disorders are one of the most common complaints encountered in medicine and psychiatry because of their negative effects on quality of life.\(^6\) One-third of all Americans experience a sleep disorder in their lives. Each year, between 20% and 40% of adults complain of difficulty sleeping at some point and about 17% consider it to be a serious problem.\(^6\) Americans report that they are getting 1.5-2 hours less sleep per night, on average\(^7\) and forty-four percent of shiftworkers report insufficient sleep.\(^8\)

Sleep deprivation first and foremost affects cognitive functions: memory, attention, executive function, mood, and response time which can lead to hazardous situations.\(^1\,^2\,^3\) Even two nights of recovery sleep does little to counteract the effects of sleep deprivation.\(^9\) Psychiatric disorders, affective disorders, addiction, and dementia are associated with sleep disturbances.\(^10\) Sleep deprivation has been associated with a higher incidence of car accidents, comparable to driving under the influence of alcohol.\(^3\)

Sleep is vital not only for neurological health, but for overall health and function as it “significantly impacts almost all aspects of human behavior.”\(^11\) Lack of sleep increases all-cause mortality\(^2\) and sleep deficits have been implicated in obesity and weight gain,\(^4\) cardiovascular disease, chronic fatigue, and gastrointestinal and reproductive disorders.\(^5\) Sleep deprivation can damage mitochondria in nerve cells\(^12\) and increase inflammation.\(^13\) Therefore, sleep hygiene and corrected sleep patterns (with a minimum of seven hours of sleep per night) are a fundamental component of a comprehensive health plan.

Ingredients in Sleep Benefits™ influence sleep systems that are under the control of GABA, melatonin, serotonin, dopamine, and cortisol. The formula promotes a calm, positive mood, relaxation, a healthy response to stress, and supports cognitive function for a healthier night’s sleep.
Sleep is critical for the brain to recover, recharge, and remove toxins.\textsuperscript{1,2} During sleep, new synapses are formed, memories are consolidated, and neurons are regenerated.\textsuperscript{3} Melatonin, the hypothalamic-pituitary-adrenal (HPA) axis, and aminergic and cholinergic neurons in the brainstem modulate sleep and wakefulness.\textsuperscript{7,14} Circadian rhythms in cortisol release are dictated by the HPA axis, which follows a distinct 24 hour pattern. The suprachiasmatic nuclei (SCN) of the hypothalamus is often referred to as the “master clock of the circadian rhythm” because of its central role in sleep and wake cycles.\textsuperscript{5,15}

A normal cortisol rhythm over the course of the day indicates healthy HPA function and normal sleep-wake cycles. The circadian rhythm of cortisol is established in early infancy.\textsuperscript{16} Cortisol is responsible for the normal awakening response, arousal, and alertness. Before waking, corticotropin releasing hormone (CRH) and vasopressin (AVP) are released in a pulsatile fashion leading to adrenocorticotrophin (ACTH) synthesis and release of cortisol by the adrenal medulla.\textsuperscript{17} Cortisol follows a characteristic diurnal pattern: a daily peak 30 minutes after rising and tapering over the course of the day until it reaches its lowest level at nighttime as a person prepares for sleep. Changes in lighting, feeding schedules, activity, and stress disrupt this diurnal pattern.\textsuperscript{17}

Melatonin and GABA are also important players in the circadian rhythm. Melatonin is a neurohormone synthesized in the pineal gland and is specifically involved in the onset of sleep.\textsuperscript{18,19} Melatonin release is synchronized with the typical hours of sleep and the release of melatonin each day is correlated with the most dramatic increase in nocturnal sleepiness.\textsuperscript{19} Melatonin levels decrease with nighttime light exposure and with increasing age.\textsuperscript{18}

GABA is an inhibitory neurotransmitter strongly implicated in the initiation and maintenance of sleep.\textsuperscript{20} GABA suppresses arousal systems and inhibits neurotransmitters that encourage wakefulness. In addition, GABA is essential for moderating the HPA stress response.\textsuperscript{20}

The HPA axis is responsible for the circadian rhythm and the stress response, the latter of which triggers a domino effect of hormones to ensure survival in the face of danger. Under acute stress, physiologic processes that promote “fight or flight” are favored while resources are shunted away from processes involved in rest, recovery, and health maintenance.\textsuperscript{17}
A stressor activates both the HPA axis and the sympathetic adrenomedullary system (SAM) in the brain. HPA axis activation with acute stress eventually leads to the release of the glucocorticoid, cortisol, from the adrenal glands into the blood to affect function and metabolism at various levels. Because of cortisol's system-wide harmful effects, there are many feedback inhibition loops in place to limit its bioactivity. The stress pathway also triggers norepinephrine and epinephrine production by the adrenal glands.

A healthy stress response is short-lived and returns to baseline the instant the stressor is removed. Chronic stress, however, can eventually override the feedback loops and cortisol's effects on the body can go unchecked. A glucocorticoid response that is elevated, extended, or inadequate can impair a person's adaptation to stress, increase or decrease HPA axis activity, interfere with sleep patterns, and is considered a health risk.²¹,²²

**SLEEP, STRESS & METABOLISM**

Sleep and stress have a bidirectional relationship, each one influencing the other.⁷ Chronic stress can alter HPA function and interfere with the circadian rhythm, leading to sleep disturbance and resulting disorders such as insomnia, depression, and anxiety.²² Stress decreases rapid eye movement (REM) sleep, slow-wave (deep) sleep, and delta power (a measure of intensity of non-rapid eye movement sleep).⁷

On the other hand, sleep deprivation increases cortisol levels,²³ disturbs HPA homeostasis and the sympathetic adrenomedullary system, and ultimately throws off the biological clock, eventually affecting arousal and metabolism. Without REM sleep, a person cannot easily adapt to, and recover from, stressors.²² It's easy to see how a vicious cycle can arise; with chronic stress and sleep deprivation, ultimately causing maladaptive changes to HPA function.⁷,¹⁴

<table>
<thead>
<tr>
<th>POOR SLEEP</th>
<th>HIGH STRESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases cortisol</td>
<td>Decreases REM sleep</td>
</tr>
<tr>
<td>Decreases recovery from stress</td>
<td>Decreases deep sleep</td>
</tr>
<tr>
<td>Increases weight gain, CVD, diabetes</td>
<td>Decreases intensity of NREM sleep</td>
</tr>
<tr>
<td></td>
<td>Increases sleep disturbance and sleep disorders</td>
</tr>
</tbody>
</table>

Poor sleep harms human metabolism and alters glucose homeostasis.⁸ Short sleep duration is a predictor for weight gain and a risk factor for developing insulin resistance, diabetes, and cardiovascular disease.⁷ Shiftworkers have higher rates of overweight, obesity, and type 2 diabetes, pointing to a clear link between the circadian clock and metabolism.⁸

*These materials have not been reviewed by the U.S. Food and Drug Administration (FDA). This product is not intended to diagnose, treat, cure or prevent any disease. These materials are for physician education purposes only. Not for consumer distribution. www.davincilabs.com.
Alterations to HPA function lead to downstream effects on neuroendocrine levels, especially cortisol, norepinephrine, epinephrine, and dopamine. Excess cortisol and cortisol metabolites can increase glucose and insulin levels and this may explain the association between obesity and sleep disturbance. Further support of this hypothesis is that HPA hyperactivity has been documented in humans and animals with diabetes.

**SLEEP BENEFITS™ FORMULATION**

A comprehensive formula to promote healthy sleep patterns should modulate or minimize the stress response and support the natural sleep-wake cycle. Sleep Benefits™ has been formulated to work from three different angles to improve total sleep time and quality: getting to sleep, supporting sleep quality, and staying asleep.

1: GETTING TO SLEEP

Bluenesse®, a clinically studied lemon balm extract, Suntheanine®, the gold standard form of L-theanine and GABA, work together to support the relaxation response in order to set the stage for a good night’s sleep.

Bluenesse® is a branded form and proprietary extract of lemon balm, standardized to 6% rosmarinic acid. Lemon balm has been used traditionally to support a healthy stress response and promote healthy sleep habits. It has been used to treat cognitive disorders and has cholinomimetic and antioxidant activity. German Commission E has approved Melissa officinalis extract for the treatment of nervous insomnia.

In clinical research, lemon balm has been shown to support a calm, positive mood, memory, focus and learning. It supports levels of GABA through supporting normal GABA transaminase inhibition, acts as a receptor agonist for muscarinic acetylcholine receptor M1, thereby exerting supportive effects on the central nervous system (CNS), and it supports normal cortisol levels.

Lemon balm reduces excitability, anxiety, stress, and sleep disturbance in human studies. It also improves mood, cognitive performance, and dementia.

In animals, lemon balm has reduced corticosterone levels and increased GABA levels in the hippocampus. In acute stress simulation, lemon balm increased mathematical processing, showing that it can reduce the adverse intellectual effects of stress.
In a pilot study, a standardized M. officinalis extract reduced anxiety, anxiety-associated symptoms, and lowered insomnia. Initial, middle, and delayed insomnia were improved. Those who had moderate difficulties falling asleep and restless nights at the beginning of the study, found they had no sleep difficulties after treatment and experienced restorative rest. Their rate of awakening after falling asleep also decreased.26

**Suntheanine® L-Theanine** is 100% pure pharmaceutical grade L-theanine, the primary amino acid found in green tea leaves.28 L-theanine supports concentration, focus, deep muscle relaxation and improved quality sleep, probably through its action on glutamate, serotonin, and dopamine neurotransmission.29 Theanine increases alpha brain wave activity in humans which may explain its calm and relaxing effect.30 Theanine may counteract the stress response, as it has been shown to reduce heart rate, blood pressure, and salivary immunoglobulin A, even under acute stress.30 Children with ADHD showed higher total sleep time, lower nocturnal motor activity, and a trend for less wakefulness after sleep onset when they were given Suntheanine.31

**GABA** is an inhibitory neurotransmitter that helps to initiate and maintain sleep by suppressing arousal signals in the brain. Pharmacologic agents that enhance GABA levels are well known to induce sleep and are used to treat insomnia.20 People with primary insomnia have been shown to have lower levels of GABA throughout the brain and those who wake up frequently after sleep onset or who have poorer sleep quality, also have decreasing brain levels of GABA.32 Normal GABA levels are therefore critical to a healthy sleep pattern.

**2: SUPPORTING QUALITY SLEEP**
Melatonin is among the most powerful sleep support nutrients and is historically used to support a deep, restful and refreshing sleep cycle.

**Melatonin** is involved in the circadian rhythm. Darkness leads to a spike in melatonin which promotes the onset of sleep. Melatonin has a number of physiological activities including regulation of circadian rhythms, antioxidant, immune-promoting, and it helps to clear free radicals.33 Secretion of melatonin decreases with age, which may begin as early as 30 years of age.34 It is believed that melatonin dysregulation is caused by the suprachiasmatic nucleus, the “master clock of the circadian rhythm,” thereby causing a loss of noradrenergic control of the pineal gland.33

Studies have shown that melatonin increases total sleep time, relieves daytime fatigue, resets the sleep-wake cycle, helps with insomnia, initiates sleep onset, and prevents a phase shift (which means wake and sleep times are shifted earlier or later than normal).35,33 Five randomized, placebo-controlled studies showed an improvement in nocturnal sleep in Alzheimer’s patients.33 Safe and well-tolerated,36 melatonin and its analogs help to initiate, promote, and maintain sleep.18,19 These changes bring about better quality sleep and greater mental, physical and emotional rejuvenation.

*These materials have not been reviewed by the U.S. Food and Drug Administration (FDA). This product is not intended to diagnose, treat, cure or prevent any disease. These materials are for physician education purposes only. Not for consumer distribution. www.davincilabs.com.*
On the other hand, low melatonin contributes to sleep disturbance. It has been reported in Alzheimer’s, post-menopausal women with sleep disturbance, cancer, metabolic syndrome, type 2 diabetes, mood disorders, rheumatoid arthritis, and abnormal levels of melatonin disturbance have been seen in obesity.

3: STAYING ASLEEP
Sensoril® Ashwagandha is intimately connected to the sleep cycle, circadian rhythm and can have profound effects on the quality of sleep. In addition, nourishing the adrenal glands can also provide metabolic support and balance blood glucose levels, which are very important for staying asleep.

Sensoril® Ashwagandha (Withania somnifera) has been used for centuries in Ayurvedic medicine to enhance memory and overall cognitive performance, due to its modulation of the neuroendocrine-immune system. Ashwagandha extracts have been reported to influence cholinergic and GABA-ergic neurotransmission.

Ashwagandha shows anxiolytic effects in humans and animals. Human studies with Ashwagandha show promising results, significantly decreasing reports of stress and anxiety on validated scales and even lowering blood cortisol levels in one study. However, further well-designed studies are needed to confirm these findings.

Ashwagandha has been studied for its effects on the CNS, particularly in preventing conditions of stress and neurodegenerative diseases. Pharmacological studies show that it has antioxidant, hypnotic, and neuroprotective properties. Ashwagandha improved reaction time and maintained psychomotor abilities in subjects under stress. It does not cause sedation; instead, it eases the mental stress bundle, permitting effective mental and psychomotor performance.

Animal studies show that treatment with Ashwagandha lessens the effects of chronic stress and improves stress tolerance. Components of the extract can facilitate the regeneration of axons and dendrites in neurodegenerative diseases and prevent neuronal death in animals. In rats, Ashwagandha promoted healthy sleep after sleep deprivation. Animals pretreated with Ashwagandha fell asleep more quickly, woke up less frequently and had more total sleep time and more non-rapid eye movement sleep than controls.

*These materials have not been reviewed by the U.S. Food and Drug Administration (FDA). This product is not intended to diagnose, treat, cure or prevent any disease. These materials are for physician education purposes only. Not for consumer distribution. www.davincilabs.com.
CONCLUSIONS

Sleep is fundamental for cognition, metabolism, quality of life, and longevity. Stress can disrupt the HPA axis, hormones, and neurotransmitters that orchestrate circadian rhythms. Likewise, sleep deprivation can cause stress, maladaptive changes to the HPA axis and cortisol elevations, perpetuating sleep disorders. A comprehensive sleep formula naturally supports sleep onset, sleep quality, and decreased waking after falling asleep. By supporting the body’s natural circadian rhythms and addressing stress and HPA axis dysfunction, Sleep Benefits helps to ensure a good night’s sleep.

SLEEP BENEFITS™

SUPPLEMENT FACTS

Serving Size 2 Capsules
Servings Per Container 30

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABA (Gamma-Aminobutyric Acid)</td>
<td>500 mg</td>
</tr>
<tr>
<td>Sensoril® Ashwagandha (Withania somnifera) Root and Leaf Extract</td>
<td>250 mg</td>
</tr>
<tr>
<td>Bluenesse® (Melissa officinalis) (Lemon Balm Extract)</td>
<td>150 mg</td>
</tr>
<tr>
<td>L-Theanine (Suntheanine® Brand)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Melatonin</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

*Daily Value not established.

Other ingredients: hypromellose (capsule), microcrystalline cellulose, vegetarian leucine.

Sensoril® is a trademark of Natreon, Inc. and is protected under U.S. Patents 6,153,198 and 7,318,938.
Bluenesse® is a trademark of Vital Solutions.
Suntheanine® L-Theanine is Patented and Licensed by Taiyo International, Inc.