Sleep Aid

Practitioner Dietary Supplement Reference Guide

This information is educational material for dotFIT-certified fitness professionals.

This literature is not to be used to imply that dotFIT products may diagnose, cure, or prevent disease.

SUGGESTED USE: As a dietary supplement, adults should take 1-2 capsules, 30 minutes before bedtime. Consume with 8 oz. of your favorite beverage.

Supplement Facts

Servings Size: 2 Capsules
Servings Per Container: 60

	Amount Per Serving	% DV
Magnesium (from Magnesium Glycinate, Magnesium Malate and Magnesium Citrate)	100mg	24%
Lemon Balm (Stem and Leaf) Extract	300mg	*
Hops (Flower) Extract	150mg	*
5-HTP	50mg	*
Melatonin (Immediate-Release)	2.5mg	*
Melatonin (Extended-Release)	2.5mg	*

*% Daily Value not established.

120 caps = 2-4month supply

Timely increases melatonin (sleep hormone) and serotonin (calming neurotransmitter) levels. The ingredients, have been shown to improve the overall quality of sleep for persons with common sleep disorders (better sleep efficiency and reduced sleep disturbances) including:

- Enhancing relaxation before bedtime, making it easier to fall and stay asleep
- Increasing total sleep time and shortening the time to fall asleep
- Enhancing sleep efficiency including REM, particularly with higher doses of melatonin (3-5gm).
- Reducing wakefulness and frequent awakenings.
- Support for insomnia and mitigation of jet-lag (adjusting an individual's circadian rhythms)
- Positive support for shift work sleep disorder (e.g., working night shifts, alternating schedules, etc.,)

Goal: Get relaxed, then fast asleep, quality sleep duration and wakeup refreshed

Melatonin (5mg)

Immediate (2.5mg) and extended release (2.5mg) for sleep efficiency

fast asleep, quality duration and wakeup refreshed

The melatonin hormone follows a distinct 24-hour pattern increasing after dark (signaling the body that it is nighttime promoting sleep onset), peaking during the night, and declining at dawn, thus, synchronizing your circadian clock

As the primary active ingredient in the Sleep formula, melatonin is often recommended as a natural alternative for individuals struggling with sleep disturbances due to aging, stresses, irregular schedules or jet lag

Melatonin

Summary of the Benefits of Melatonin Supplementation for Sleep and Its Mechanisms of Action

Mechanisms of Action:

1. **Regulation of Circadian Rhythms*:**

- Melatonin is a hormone secreted by the pineal gland follows a distinct 24-hour pattern. It increases after dark, peaks during the night, and declines at dawn. This cycle plays a crucial role in synchronizing the circadian clock. It binds to MT1 receptors in the suprachiasmatic nucleus (SCN**) of the brain, subsequently suppressing neuronal firing, signaling the body that it is nighttime and promoting sleep onset.
- The circadian pacemaker, located in the SCN, coordinates physiological and behavioral rhythms. It regulates melatonin secretion, which, in turn, modulates the SCN's activity through a feedback mechanism.

2. Clock Gene Regulation

- Melatonin interacts with core clock genes (BMAL1, CLOCK, PER, CRY) to regulate circadian oscillations. It can modulate their transcription via receptor-dependent and independent mechanisms.

3. Promotion of Sleep Efficiency and Duration:

- In aging, melatonin receptor sensitivity decreases, and endogenous melatonin levels may decline, leading to disrupted sleep patterns. Supplementing with exogenous melatonin can compensate for these deficiencies, helping to consolidate sleep.

***Circadian rhythms (CRs) are 24-hour periodic oscillations governed by an endogenous circadian pacemaker located in the suprachiasmatic nucleus (SCN), which organizes the physiology and behavior of organisms**
****SCN is a small part of the brain that controls circadian rhythms and daily activities. It's located in the hypothalamus, and is sometimes called the brain's "master circadian pacemaker"**

•**Primary endogenous source** influencing the circadian clock (circulating) is the pineal gland
•**Other potential production sites:** Retina, gastrointestinal tract, skin, bone marrow, liver but most of circulating melatonin (affecting circadian rhythm) comes from the pineal gland.

Melatonin

Summary of the Benefits of Melatonin Supplementation for Sleep and Its Mechanisms of Action

Mechanisms of Action Continued:

4. Impact on Sleep Stages:

- **High-dose melatonin** increases **stage 2 non-REM sleep**, which is crucial for memory consolidation and physical restoration.
- It slightly decreases **slow-wave sleep (deep sleep)** while not significantly affecting REM sleep.
- High doses also lead to **shorter awakenings**, enhancing overall sleep continuity.

5. Effectiveness Across Different Circadian Phases:

- Melatonin supplementation improved sleep not only during the biological night (when endogenous melatonin is already present) but also during the biological day (when endogenous melatonin levels are low).
- Useful for shift workers or individuals with irregular sleep schedules.

Melatonin Sleep Related Studies

Specific Benefits of Melatonin Supplementation for Sleep:

- **Increases total sleep time** (by approximately 25 minutes on average in older adults).
- **Enhances sleep efficiency**, particularly with higher doses.
- **Improves sleep consolidation**, reducing wakefulness and frequent awakenings.
- **Beneficial for sleep during both nighttime and daytime**, making it useful for those with irregular sleep patterns.
- **Safe alternative to prescription sleep aids**, which may have adverse effects like increased fall risk, cognitive impairment, and dependency.

High dose melatonin increases sleep duration during nighttime and daytime sleep episodes in older adults

While 0.3mg melatonin had a trend towards increasing sleep efficiency overall, this was due to it's effects on sleep during the biological day. In contrast, 5 mg melatonin significantly increased sleep efficiency during both biological day and night, mainly by increasing the duration of stage 2 non-REM sleep and slightly shortening awakenings.
Conclusion: 5mg of melatonin supplementation is an effective intervention for improving the quality of sleep.

Conclusion: 3mg/d Melatonin supplementation over a four-week period is effective and safe in improving some aspects of objective sleep quality such as total sleep time, percentage of rapid eye movement and early morning wake time in middle-aged patients with insomnia

Effect of melatonin supplementation on sleep quality: a systematic review and meta-analysis of randomized controlled trials

Conclusion: Treatment with exogenous melatonin has positive effects on sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) in adults with primary sleep disorders, respiratory and metabolic disorders , but not with mental or neurodegenerative disorders

Takeaway: ***melatonin supplementation, particularly in higher doses (5 mg), is an effective intervention for improving sleep in adults by increasing sleep efficiency and duration. Its mechanism of action through circadian rhythm regulation and neuronal suppression in the SCN makes it a promising, natural alternative for individuals struggling with sleep disturbances due to aging, stresses or irregular schedules.***

- ***Unique contribution/activity: direct management of the human circadian clock through melatonin's*** **distinct 24-hour release patterns**

Melatonin dosages in specific conditions with positive outcomes

Melatonin has been studied across various clinical trials to address sleep disorders and other health conditions. Dosage recommendations vary depending on the specific condition being treated. Below is a summary of effective dosages identified in successful clinical trials:

1. Insomnia

- **General Population**: Clinical studies have utilized doses ranging from 0.1 mg to 10 mg, typically administered up to 2 hours before bedtime. ncbi.nlm.nih.gov
- **Elderly Patients**: Immediate-release melatonin at doses of 1 to 2 mg, taken 1 hour prior to bedtime, has been found beneficial. drugs.com

2. Delayed Sleep-Wake Phase Disorder (DSWPD)

- **Adults**: The American Academy of Sleep Medicine supports the use of melatonin for DSWPD. Strategically timed administration, typically 1 hour before the desired bedtime, is recommended. ncbi.nlm.nih.gov

3. Jet Lag

- **General Recommendations**: Lower doses (0.5 to 2 mg) taken preflight and higher doses (5 mg) postflight over a period of up to 4 days have been suggested to alleviate symptoms. drugs.com

4. Shift Work Sleep Disorder

- **Healthcare Workers**: trial successful doses range from 1 to 10 mg, taken in the morning after night shifts and before daytime sleep periods. No additional benefit was observed at doses above 5 mg. Starting with a low dose (e.g., ≤2 mg) is advisable to assess clinical effect. bpac.org.nz

Safety

While melatonin is generally considered safe, higher doses (≥10 mg) have been associated with side effects such as drowsiness, headache, and dizziness. A systematic review indicated that melatonin did not cause a detectable increase in serious adverse events or withdrawals due to adverse effects, but did appear to increase the risk of minor adverse events. onlinelibrary.wiley.com

Clinical/drug uses

5. Adjuvant Therapy

- **Solid Tumors**: Clinical trials have reported the use of oral melatonin at dosages of 20 mg/day as an adjunct in patients with solid tumors. drugs.com

6. Analgesia

- **Pain Management**: Dosages ranging from 3 to 10 mg/day have been used for various pain conditions. drugs.com

Consulting with a healthcare professional before starting melatonin supplementation is advisable, especially for individuals with underlying health conditions or those taking other medications. ncbi.nlm.nih.gov

Dosage Summary: melatonin dosages in successful clinical trials vary based on the condition being treated, with most studies employing doses between 0.5 to 10 mg. Starting with the lowest effective dose and adjusting as necessary is recommended to minimize potential side effects

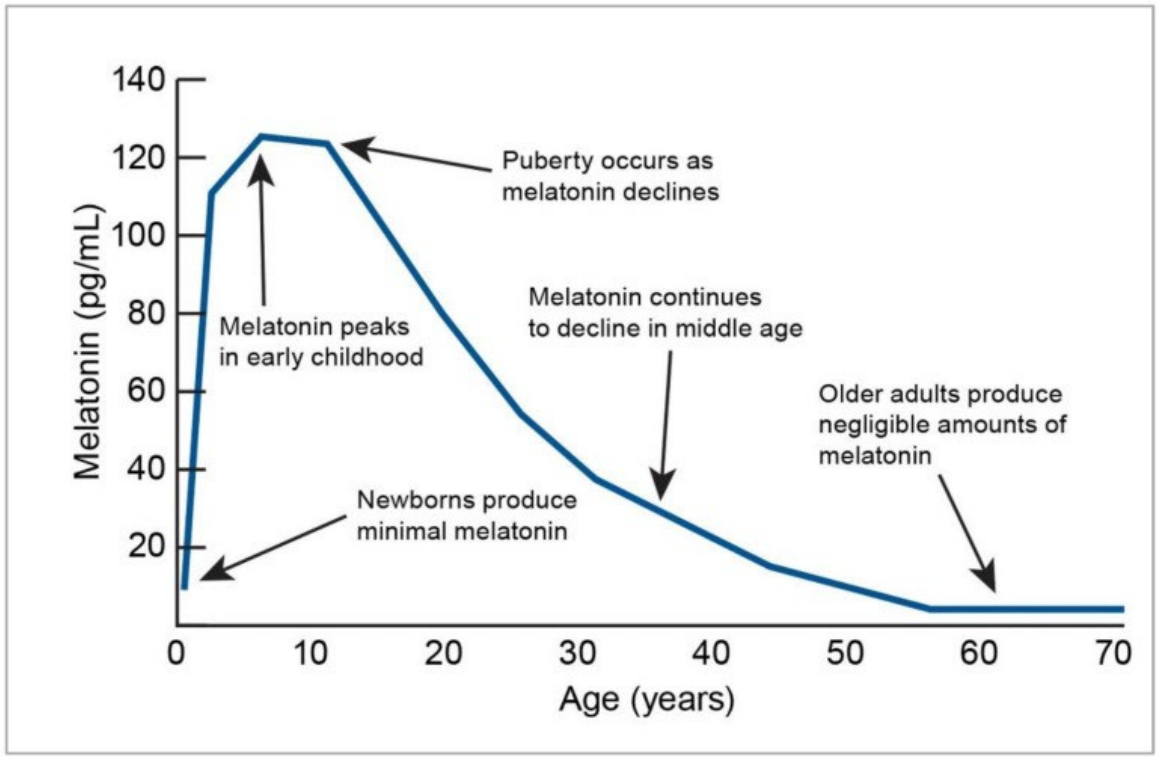
Melatonin somatic functions

Beyond Sleep – Just FYI

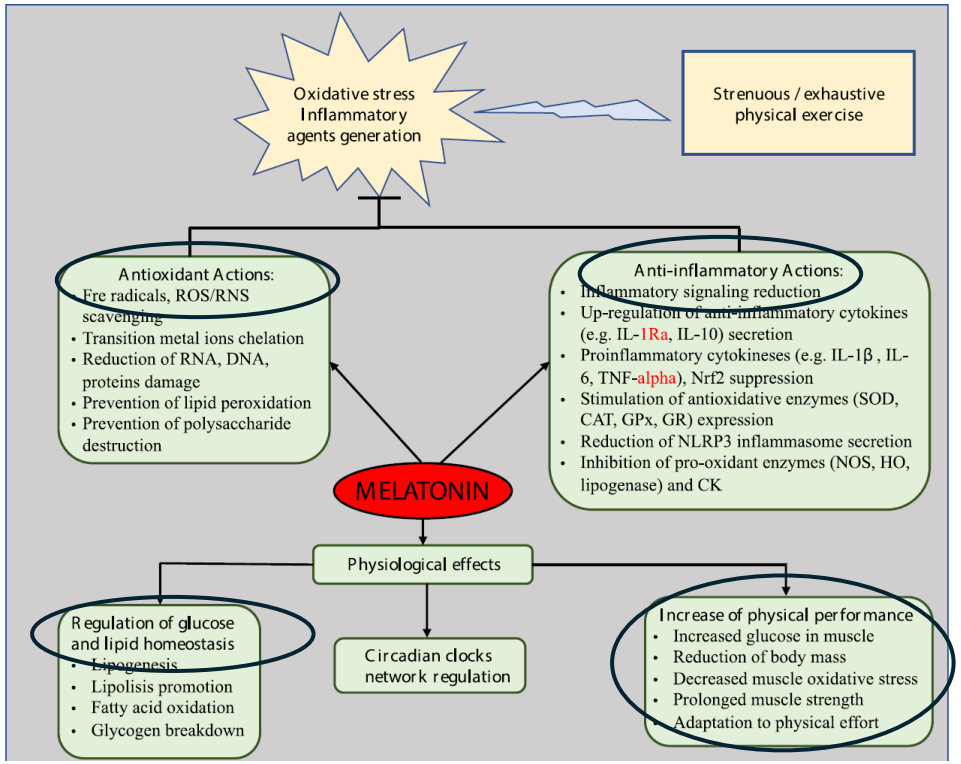
Dual sources of melatonin and evidence for different primary functions

Humans, have two sources of melatonin (pineal and extra-pineal) with different functions. 1) Pineal (gland), melatonin production is circadian with maximal synthesis and release into the blood and cerebrospinal fluid occurring during the night. Pineal melatonin has the primary function of influencing the circadian clock at the level of the suprachiasmatic nucleus and the clockwork in all peripheral organs (the blood melatonin) via receptor-mediated actions. Of the total amount of melatonin produced in humans, less than 5% is synthesized by the pineal gland.

Minich et al. Age-related decrease in melatonin in humans.



Simplified scheme for the biological functions performed by melatonin beyond sleep



2nd source of melatonin is from multiple body tissues, probably being synthesized in the mitochondria of these cells and makes up the bulk of the melatonin produced but is concerned with metabolic regulation including re-dox homeostasis and other critical metabolic effects. This melatonin synthesis does not exhibit a circadian rhythm and not released into the blood but acts locally in its cell of origin and possibly in a paracrine matter on adjacent cells and may be inducible under stressful conditions as in plant cells.

***The suprachiasmatic nucleus (SCN) is a small part of the brain that controls circadian rhythms and daily activities. It's located in the hypothalamus, and is sometimes called the brain's "master circadian pacemaker"**

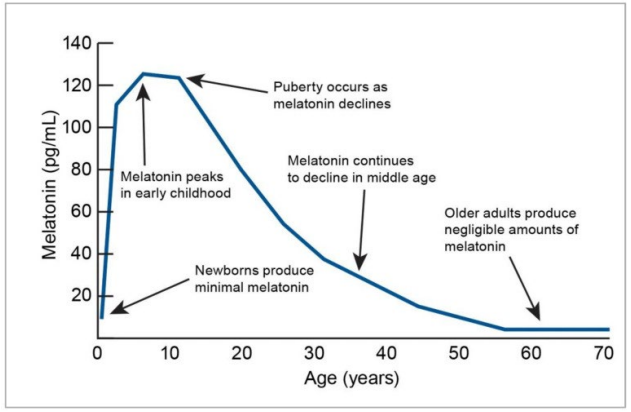
*Cellular redox homeostasis is an essential and dynamic process that ensures the balance between reducing and oxidizing reactions within cells and regulates a plethora of biological responses and events

Verma et al. 2024- - Crosstalk Between Aging, Circadian Rhythm, and Melatonin

Main points related to the interplay between aging, circadian rhythms (CRs), and melatonin, highlighting its mechanisms of action related to the circadian clock and age-related changes.

Melatonin and Circadian Rhythm Regulation (slide 2)

1. **Circadian Rhythms and the Suprachiasmatic Nucleus (SCN)***: The circadian pacemaker, located in the SCN, coordinates physiological and behavioral rhythms. It regulates melatonin secretion, which, in turn, modulates the SCN's activity through a feedback mechanism.
2. **Melatonin Secretion Cycle**: Melatonin, produced by the pineal gland, follows a distinct 24-hour pattern. It increases after dark, peaks during the night, and declines at dawn. This cycle plays a crucial role in synchronizing the circadian clock.
3. **Clock Gene Regulation**: Melatonin interacts with core clock genes (BMAL1, CLOCK, PER, CRY) to regulate circadian oscillations. It can modulate their transcription via receptor-dependent and independent mechanisms.



Aging and Circadian Disruptions

1. **Age-Related Decline in Melatonin**: Melatonin synthesis decreases significantly with age, contributing to circadian rhythm disruption (CRD), sleep disturbances, and metabolic dysregulation.
2. **Functional Decline in the SCN**: Aging affects SCN neurons by reducing light sensitivity, signal transmission efficiency, and intercellular connectivity, leading to weakened circadian signals.
3. **Impact on Health**: CRD in aging is linked to neurodegenerative diseases (e.g., Alzheimer's), cardiovascular disorders, and metabolic diseases. Chronic circadian misalignment accelerates aging and increases disease risk.

Crosstalk Between Aging, Circadian Rhythm, and Melatonin

Main points related to the melatonin's actions beyond sleep; as a protective agent in the aging process.

Melatonin as a Protective Agent Against Aging

1. **Antioxidant Role**: Melatonin functions as a potent antioxidant by neutralizing reactive oxygen species (ROS) and stimulating antioxidant enzymes, helping to mitigate oxidative stress, which is a major contributor to aging.
2. **Mitochondrial Protection**: Melatonin enhances mitochondrial function, reduces electron leakage, and prevents mitochondrial dysfunction—a key factor in cellular aging.
3. **Neuroprotective Effects**: Melatonin helps maintain neural health by preventing oxidative damage, supporting circadian homeostasis, and reducing neurodegeneration in aging brains.

Therapeutic Potential of Melatonin

1. **Chronotherapy**: Melatonin supplementation (MS) has been shown to improve circadian alignment, reduce sleep disturbances, and restore metabolic rhythms in older individuals.
2. **Possible Benefits for Longevity**: Melatonin treatment may extend lifespan and delay age-associated disorders by regulating oxidative stress, inflammation, and mitochondrial dysfunction.
3. **Clinical Applications**: While melatonin is considered a promising therapeutic agent for aging-related circadian disruption, further long-term clinical studies are needed to establish optimal dosing and treatment strategies

Conclusion (protective agent)

Melatonin's decline with age contributes to circadian misalignment, oxidative stress, and neurodegenerative disorders. Melatonin supplementation holds potential in mitigating aging-related circadian rhythm disorders and promoting healthy aging through its antioxidant and neuroprotective properties.

Supportive 5-HTP (50mg)

Supports sleep (and stress) by acting as a precursor to serotonin (“feel good hormone”) supporting nighttime melatonin (sleep/wake hormone)

In the Sleep Formula, 5-HTP is in a dosage (50mg) supportive of the product’s melatonin content, i.e., synergistic to the primary sleep agent – relaxation

5-Hydroxytryptophan (5-HTP): Natural Occurrence, Analysis, Biosynthesis, Biotechnology, Physiology and Toxicology

Summary of the Benefits of 5-HTP Supplementation for Sleep and Its Mechanisms of Action

5-HTP is a natural precursor to serotonin (5-HT) and to a certain extent also melatonin, two neurotransmitters critical for sleep regulation. It plays a physiological role in sleep, (stress and anxiety) and supplementation has been shown to improve sleep quality. In the dotFIT Sleep Aid, lower dose 5-HTP (50mg) plays a supportive/synergistic role to the primary sleep agent, melatonin.

Mechanisms of Action:

1. **Conversion to Serotonin:** 5-HTP is synthesized from tryptophan via the enzyme tryptophan hydroxylase (TPH). It is then decarboxylated to serotonin (5-HT), which plays a key role in mood regulation, cognition, and sleep.
2. **Melatonin Production:** Serotonin is further metabolized into melatonin (N-acetyl-5-methoxytryptamine), the hormone primarily responsible for regulating the sleep-wake cycle.
3. **Regulation of REM Sleep:** Studies have shown that 5-HTP supplementation increases rapid eye movement (REM) sleep. Normal subjects treated with 5-HTP exhibited an increase in REM sleep from 5% to 53% of the baseline.
4. **Modulation of Arousal States:** By increasing serotonin levels, 5-HTP may help regulate arousal to promote deeper sleep, reducing sleep disturbances such as night terrors.
5. **Improvement in Sleep Disorders:** Clinical studies indicate that 5-HTP supplementation is beneficial for sleep disorders like insomnia, parasomnias, and sleep-related anxiety.
6. **Interaction with Stress and Anxiety:** Since serotonin is linked to anxiety reduction, 5-HTP indirectly contributes to improved sleep by alleviating stress.

Maffei, M.E. 5-Hydroxytryptophan (5-HTP): Natural Occurrence, Analysis, Biosynthesis, Biotechnology, Physiology and Toxicology. Int. J. Mol. Sci. **2021**, 22, 181. https://dx.doi.org/10.3390/ijms22010181

5-Hydroxytryptophan (5-HTP): Natural Occurrence, Analysis, Biosynthesis, Biotechnology, Physiology and Toxicology

Benefits of 5-HTP for Sleep:

- **Enhances Sleep Duration and Quality:** Increased melatonin production leads to better sleep regulation.
- **Reduces Sleep Onset Latency:** Helps individuals fall asleep faster.
- **Supports Sleep in Individuals with Depression and Anxiety:** Addresses serotonin deficiency that often contributes to sleep disturbances.

Takeaway: Overall, 5-HTP supplementation* supports sleep by primarily acting as a precursor to serotonin (to some extent melatonin) which is essential for maintaining a healthy sleep cycle. Especially beneficial for individuals suffering from sleep disorders related to serotonin deficiencies, such as insomnia, depression-related sleep disturbances and sleep terrors.

- Unique contribution: enhancing serotonergic activities (calming, feel good neurotransmitter/hormone management)

Formula note: the Sleep Aid provides melatonin directly so low dose 5-HTP (50mg) can be synergistic through its calming mechanism, without causing too much sleepiness or interfering with SSRI medications

5-HTP Notes (FYI)

Typical dosing of *5-HTP alone* as a sleep aid

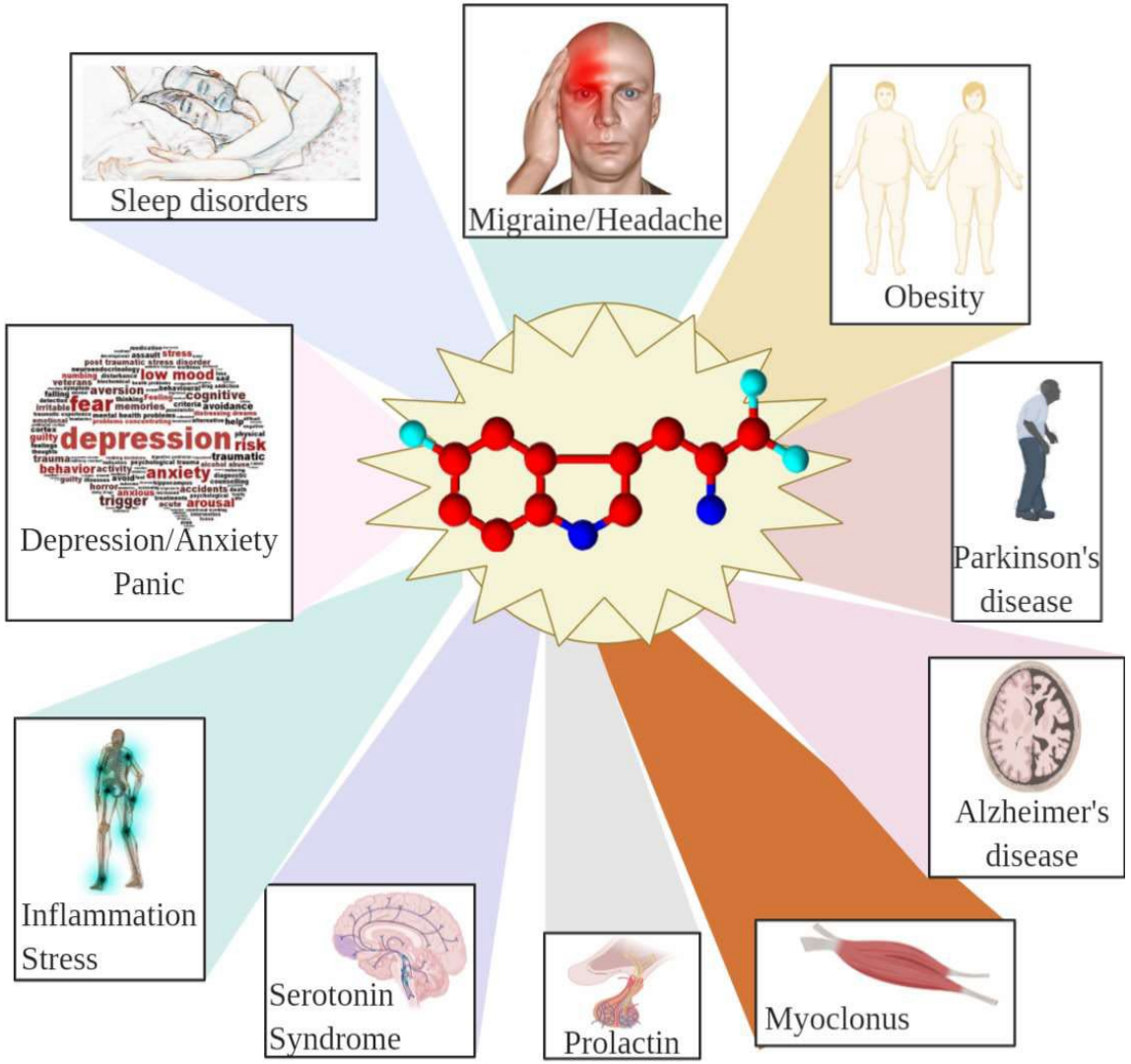
Starting with a dose of **50 mg and gradually increasing to 100–300 mg per day** before bedtime may help minimize side effects (minor nausea has been reported when 5-HTP was used at doses above 100 mg).

5-HTP is both a drug (synthetic) and a natural component of some dietary supplements as in the Sleep Aid as a natural ingredient.
5-HTP is produced commercially from the seeds of an African plant known as Griffonia simplicifolia (GS)*.

*Extraction from seeds of the GS is the typical approach for 5-HTP commercial production, because chemical synthesis is not economically feasible on a large scale.

Unless approved by your qualified doctor, don't take high dose 5-HTP with other medications that increase serotonin production including antidepressant drugs. Taking it with prescription sedative medications, such as Klonopin, Ativan, or Ambien, may cause too much sleepiness. **Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressant medications that work by increasing the levels of serotonin in the brain.**

FYI
Other uses of 5-HTP Supplementation/Drug Alone



- **Weight management:** 250–300mg, 30min prior to each meal, (750/d)
- **Mood enhancement:** 100 mg, twice daily
- **Fibromyalgia symptom relief:** 100mg, 3–4 times/d with meals for at least 2wk
- **Migraines:** 600mg per day for at least 6 months
- **Sleep aid:** 50–300 mg before bedtime

Summary of some effects of 5-HTP on humans. 5-HTP is a treatment of choice in the prophylaxis of migraine and headache and promotes decreased food intake and weight loss in obese patients. 5-HTP is used for treating depressive symptoms in Parkinson's and used as a diagnostic test for Alzheimer's. 5-HTP is useful to control some forms of myoclonus and significantly increases plasma human prolactin. Excessive 5-HTP generates serotonin syndrome. 5-HTP has the potential for use in the treatment of inflammation and oxidative stress. As a precursor of 5-HT, 5-HTP treatment is used to reduce depression, anxiety, and panic attacks. 5-HTP is associated with an increase in rapid eye movement (REM) sleep and reduces sleep disorder.

Supportive Lemon Balm (300mg)

Lemon balm (Melissa officinalis) is a bushy perennial herb in the mint family that has been used in food and traditional medicine for over two thousand years to treat anxiety, insomnia, menstrual irregularities, and other conditions.

In the Sleep Formula, Lemon Balm is in a dosage (300mg) supportive and additive (unique mechanism of action) to the product’s other ingredients collective effects on sleep quality.

Summary of Lemon Balm's (melissa officinalis [MO]) Mechanisms of Action on Calming, Sleep, and Anxiety, and Effective Dosages from Clinical Trials

Mechanisms of Action

Lemon balm (Melissa officinalis L.) exerts its calming, sleep-enhancing, and anxiolytic effects through multiple neurochemical pathways:

1. **GABAergic Activity is primary mechanism (g**amma-aminobutyric acid [GABA] is the brain's primary **inhibitory neurotransmitter - calming)**
   - Rosmarinic acid (RA) in lemon balm inhibits GABA transaminase (enzyme that breaks down **GABA)**, increasing GABA levels, which promotes relaxation, reduces anxiety and enhances sleep quality.
   - RA also binds to GABA_A receptors, enhancing their inhibitory effects, similar to benzodiazepines (medications that act as CNS depressants, commonly used to treat anxiety, insomnia, and seizures
2. **Interaction with the Serotonergic System**
   - Influences **serotonin (5-HT) modulation**, which plays a critical role in regulating mood and emotional stability.
   - Increased serotonin levels contribute to **anti-anxiety and antidepressant effects**, indirectly supporting better sleep
3. **Cholinergic Modulation - Acetylcholinesterase (AChE) and Monoamine Oxidase (MAO) Inhibition**
   - RA and terpenoids inhibit acetylcholinesterase, leading **to increased acetylcholine levels**, which may contribute to cognitive benefits and mood stabilization. (Inhibition of **MAO enzymes** helps **preserve serotonin and dopamine**, neurotransmitters linked to **mood stabilization and improved sleep patterns**.)
4. **Antioxidant, Anti-Inflammatory and Neuroprotective Effects**
   - The presence of flavonoids and phenolic acids reduces oxidative stress and inflammation, indirectly supporting brain function and emotional stability.
5. **Gut-Brain Axis Influence**
   - Lemon balm's antimicrobial properties and prebiotic effects on gut microbiota contribute to mood regulation through gut-brain signaling.
6. **Hormonal & Stress Response Regulation**
   - Lemon balm may modulate the hypothalamic-pituitary-adrenal (HPA) axis, reducing cortisol levels and mitigating stress-related symptoms

Summary of Lemon Balm's (melissa officinalis [MO]) Mechanisms of Action on Calming, Sleep, and Anxiety, and Effective Dosages from Clinical Trials

To improve sleep quality it is generally combined

Effective Dosages in Clinical Trials (mindful at high doses [>500mg] it functions as a drug)

Positive effects of lemon balm on anxiety, sleep, and psychological well-being have been observed across multiple populations and study designs. Effective doses include:

- **Children & Adolescents**
  - **Sleep & Anxiety**: 320 mg/day lemon balm combined with 640 mg valerian over 28 days improved restlessness and sleep quality.
  - **PMS-related Anxiety & Depression**: 1200 mg/day for three menstrual cycles reduced anxiety and sleep disturbances.
- **Young Adults (18-30 years)**
  - **Acute Stress & Mood Improvement**: 300-600 mg single doses improved cognitive performance and reduced stress.
  - **PMS-related Symptoms**: 1000 mg/day for two menstrual cycles reduced anxiety and sleep problems.
  - **Postpartum Blues**: 1500 mg/day for 10 days improved mood significantly.
- **Middle-Aged Adults (30-55 years)**
  - **Sleep Quality**:
    - 240 mg/day for 30 days in combination with valerian improved sleep quality in self-reports.
    - 1000 mg/day for four weeks significantly improved sleep in menopausal women.
  - **Anxiety & Mood**:
    - 400 mg/day for three weeks improved anxiety, depression, and well-being.
    - 2000 mg/day for eight weeks had an antidepressant effect comparable to fluoxetine.
- **Older Adults (55+ years)**
  - **Sleep & Anxiety in Cardiac Patients**: 1500 mg/day for seven days improved sleep and reduced anxiety.
  - **Dementia & Agitation**:
    - 500 mg/day for 24 weeks reduced agitation in Alzheimer's patients.
    - Lemon balm aromatherapy (two drops daily) reduced irritability and agitation in nursing home residents without dementia.

Summary of Lemon Balm's (melissa officinalis [MO]) Mechanisms of Action on Calming, Sleep, and Anxiety, and Effective Dosages from Clinical Trials

Conclusion & Population-Specific Benefits

Lemon balm is a safe and effective natural remedy for anxiety, stress, and sleep disorders, with broad applicability across different age groups, making it a promising alternative to pharmaceutical sleep aids . The strongest evidence supports its use in the **general including aging population** for:

- Reducing mild-to-moderate anxiety and stress.
- Improving sleep onset, quality and duration, especially in individuals with sleep disturbances.
- **Enhancing Mood and Emotional Well-being**
  - Supplementation **increased positive affect** (happiness, calmness) and **decreased negative affect** (anger, sadness) boosting emotional resilience
- **Promoting Cognitive Relaxation** (reducing c**ognitive hyperactivity)** without causing sedation or grogginess

Conclusion/Takeaway

While lemon balm (LB) shows promising effects across the lifespan, its safety profile and multi-pathway effects make it a compelling natural supplement for improving psychological well-being and sleep.

- Unique contributing pathways: increasing GABA levels (calming) via inhibiting its breakdown; mood stabilization (Cholinergic Modulation –increasing acetylcholine); cortisol reduction; prebiotic effects on gut microbiota contributes to mood regulation through gut-brain signaling.

Formula note: in the Sleep Aid formula, the LB dosage is designed to be supportive (emotional well-being/mood) and synergistic in increasing the efficacy and safety (allowing lower dosing) of the companion sleep ingredients such as melatonin and 5-HTP.

Supportive Hops Extract (150mg)

Hops have been used for centuries to flavor, preserve beer and as medicine

Hops Extract (Humulus lupulus L.): a dried, flowering part of the plant that is used to make medicine **commonly combined with other natural sleep agents taken for anxiety, insomnia and other sleep disorders**, restlessness, tension, excitability, attention deficit-hyperactivity disorder (ADHD), nervousness, and irritability. Use of hops for the treatment of mood disturbances, such as restlessness, anxiety, and sleep disturbances, is approved in the ***German Commission E-Monographs***. ***Hops are a co-factor supplied in a supportive synergistic dose (150mg) to enhance the outcomes of the primary actives, melatonin and 5-HTP.***

Yeom et al. 2024, Herbal and Natural Supplements for Improving Sleep: A Literature Review

Hops (Humulus lupulus) and Its Effects on Sleep and Calming including dosages and in combination

Mechanisms of Action

Hops exert their sedative and sleep-promoting effects through several neurochemical pathways:

1. **GABAergic Modulation**
   - The bioactive compounds in hops, particularly humulones and lupulones (alpha- and beta-acids), interact with **GABA-A receptors**, enhancing their inhibitory effects on the central nervous system leading to **increased relaxation and sedation**.
2. **Serotonergic and Melatonin Pathways**
   - Hops **increase serotonin and melatonin release**, both of which play a critical role in **regulating sleep-wake cycles**. Increased serotonin contributes to relaxation, while melatonin promotes **sleep onset and maintenance**.
3. **Chrononutrition Effects**
   - Hops compounds, in combination with tryptophan, have been shown to **support circadian rhythms**, reducing sleep disturbances related to **shift work, stress, and irregular sleep patterns**.

Benefits of Hops for Sleep and Relaxation

Hops have been evaluated in both standalone and combination formulations, demonstrating several key benefits:

- **Improved Sleep Quality**
  - Clinical studies suggest that **hops improve sleep efficiency** and promote **deeper, restorative sleep** when used alone or in combination with other sedatives.
- **Reduced Sleep Latency (Time to Fall Asleep)**
  - Individuals using hops supplements experienced **shorter sleep onset times**, particularly when hops were combined with **valerian root**.
- **Anxiolytic (Calming) Effects**
  - Due to its **GABA-enhancing** effects, hops **reduces anxiety**, making it beneficial for individuals experiencing **stress-related sleep disturbances**.
- **Support for Insomnia**
  - While **standalone hops (300-500 mg/day)** have shown moderate benefits, **hops (100-200mg/d) combined with valerian or melatonin** has demonstrated **stronger effects on improving sleep onset and duration**

Hops and Its Effects on Sleep and Calming including dosages and in combination

Hops as a Supportive Ingredient in Natural Sleep Formulations

Hops are commonly included in **multi-herb sleep supplements** to **synergistically enhance their sedative effects**. Some of the most popular **natural sleep formulations** that include hops are:

1. **Hops + Valerian Root (**300 mg valerian + 200 mg hops per dose)
    - This combination is one of the most **well-studied** and has been **shown to improve sleep onset, duration, and quality** more effectively than either herb alone.
2. **Hops + Melatonin**
    - Used to **regulate circadian rhythms**, particularly in individuals with **jet lag or shift-work sleep disorder**.
3. **Hops + L-Theanine + Magnesium**
    - This blend supports **relaxation, muscle relaxation, and stress reduction**, helping individuals fall asleep naturally.
4. **Hops in Non-Alcoholic Beer**
    - As a **food-based chrononutrient**, **hops in non-alcoholic beer** has been shown to **increase natural melatonin production** and promote relaxation before bed

Conclusion/Takeaway:

Hops alone is a promising natural sleep aid due to its ability to enhance GABAergic activity. Hops can enhance serotonin and melatonin production and shown to play a supportive role in improving the onset of sleep and quality. While standalone hops extracts (>300mg/d) show calming/relaxing benefits, combining hops (100-200mg/d) with melatonin (as in the Sleep Aid), or other calming ingredients (e.g., magnesium, lemon balm, etc.,) appears to provide greater sleep-enhancing effects.

- Unique contributions: exclusive interaction with **GABA-A receptors** enhancing their inhibitory effects on the CNS leading to **increased relaxation and sedation.**

Formula note: hops dosage in Sleep Aid (150mg) makes it a supportive co-factor in enhancing the overall product goal of improving sleep quality.

Supportive Magnesium (100mg*)

Magnesium (MG) is an essential mineral that plays a central role in ~800 biochemical reactions within the human body. In the bodies sleep systems MG supports melatonin synthesis, influences **circadian rhythm stability and** enhances **GABA-A receptor activity (**suppresses neuronal activity). Proper MG daily amounts can lead to improved sleep onset, duration and quality.

In the Sleep Aid formula, Magnesium glycinate/malate/citrate (highly bioavailable*) is in a dosage (100mg) supportive to its other ingredient content, and the MG in a daily MVM (100-200mg) & typical US diet (268 mg for men and 234 for women), which when totaled is ~450-550mg/d; this daily amount of MG, may also offer a unique mechanism of action to the product's other ingredients collective effects on sleep quality.

Background

MG is crucial in ~800 enzymatic reactions throughout the body. Thus, low levels negatively impact the entire organism including sleep.

Daily recommendation: 420mg/d for adults & children 4yrs & older (RDA 320-420mgs/d)

Food intake: 268mg men/234mg women (less for many sub-pops) resulting in subclinical magnesium deficiency in at least two-thirds (~50% below EAR*) of Americans (Europe and Brazil), thus MG is listed as a "nutrient of concern" by the Dietary Guidelines for Americans.

*Estimated Average Requirement (EAR): Average daily level of intake estimated to meet the requirements of 50% of healthy individuals

- Usually used to assess the nutrient intakes of groups of people and to plan nutritionally adequate (not optimal) diets for them.

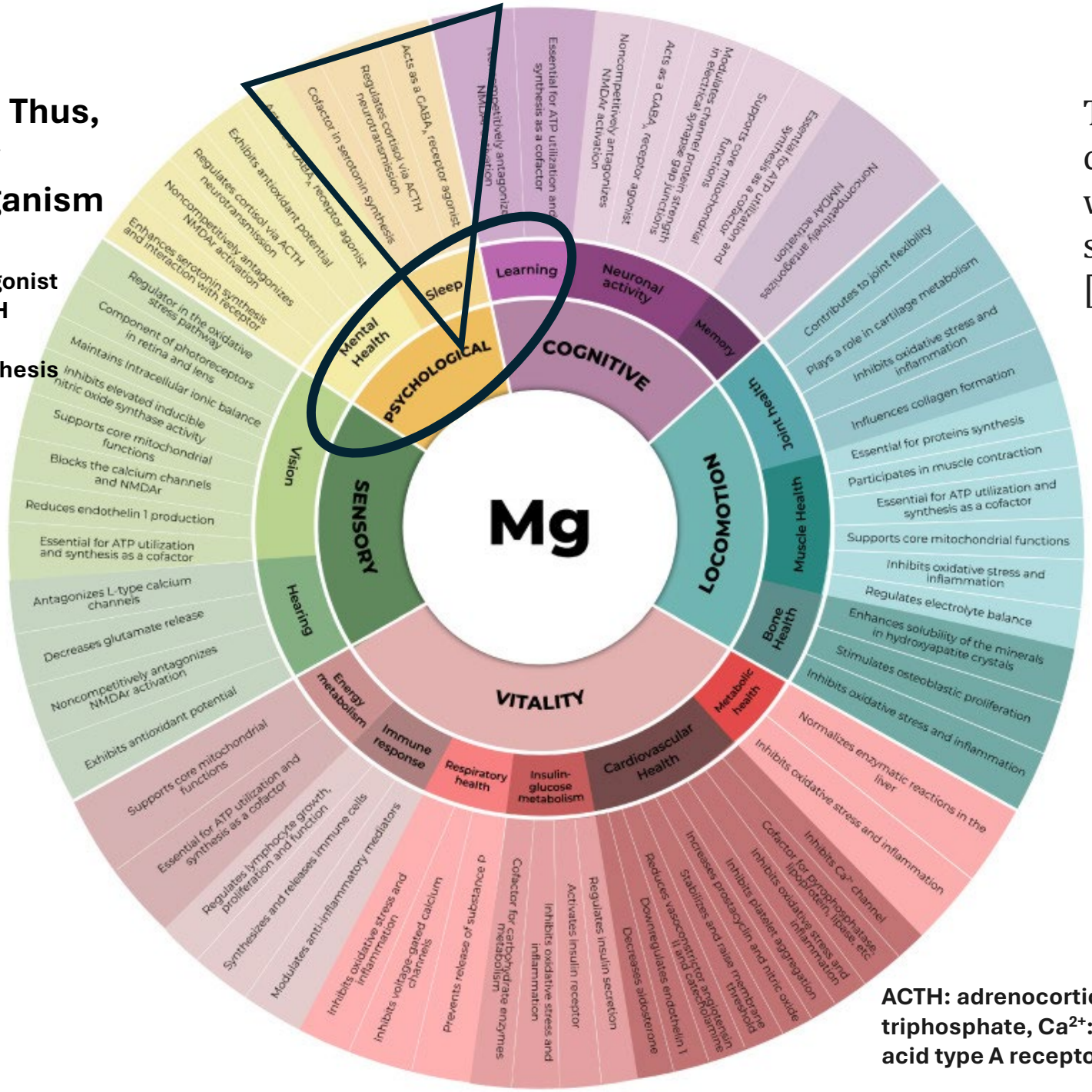
RDA: dietary intake level that is sufficient to meet the nutrient requirement* of **nearly all healthy** individuals in a particular life stage.

- RDAs: designed to eliminate deficiencies, not meant to be optimal & why current expert recommendation to support long-term health may be greater than existing RDAs

The recommended calcium to magnesium intake ratio is 2:1 to 3:1 (which is roughly what's in the blood) to improve bone health and reduce the risk of osteoporosis; regulate blood pressure, and support muscle function (individual needs may vary based on age, health, V-D intake etc.). **MG can compete with calcium for absorption** in the intestines, meaning a high MG intake relative to calcium could hinder the body's ability to absorb adequate calcium, potentially contributing to bone loss and muscle dysfunction over time. (UL from Supps only=350mg.d)

MG is crucial in ~800 enzymatic reactions throughout the body. Thus, low levels negatively impact the entire organism including sleep.

- **Acts as a GABA receptor agonist**
- **Regulates cortisol via ACTH neurotransmission**
- **Co-factor in serotonin synthesis**



The five domains of intrinsic capacity and the subdomains in which magnesium plays a significant role [20,22,23,24,25,26,27,28].

ACTH: adrenocorticotrophic hormone, ATP: adenosine triphosphate, Ca^{2+}: calcium cation, GABAA: γ-aminobutyric acid type A receptor, NMDAr: N-methyl-D-aspartate receptor.

Background

MG is crucial in ~800 enzymatic reactions throughout the body. Thus, low levels negatively impact the entire organism including sleep.
Daily recommendation: 420mg/d for adults & children 4yrs and older (RDA 320-420mgs/d)
Food intake: 268mg for men & 234mg for women (much less for many sub-pops) resulting in subclinical magnesium deficiency in at least two-thirds of Americans (Europe and Brazil).

MG Supplementation (MGS) rationale for sleep is generally rooted in its under-consumption from diet (**silent hunger**), limiting MGS benefits to specific populations

- Triage effect: limited availability of MG from food alone will be routed to its most important enzymatic reactions that are necessary for daily survival (e.g., indispensable for maintaining genomic stability, DNA repair and protection, ATP production, blood pressure, insulin metabolism, neuromuscular function, etc.,)-- leaving MGs other roles more related to longevity (e.g., CV, cognitive, and muscle long-term health, etc.,-see diagram) compromised including sleep quality – i.e., MG survival actions outweigh its longer-term health functions/contributions (evolutionary triage) – with sleep probably being one of the first systems to suffer – i.e., how important is sleep compared to a heart beating/muscle contracting, energy production, DNA protection and other daily survival needs that MG supports.
    - Available MG will be used for its daily survival functions, depriving the body of MGs ability to support its long-term health functions

MG does not function in a vacuum within any body system including sleep. MG, like all vitamins/minerals (VM), requires other VM to be present for it to positively affect any of its 800 functions

- Any shortage of individual VMs often creates a "domino effect" since they rely on each other to optimize metabolism in the body's myriad pathways – and if even 1-essential VM is completely missing, there is no life*.

Conclusion/takeaway: before adding individual MGS for improving sleep quality, meet ~400-500mg/d through diet and supplement intake that includes a complete MVM containing MG and the other ~20 known under-consumed VMs. From that baseline, if sleep quality is suffering, it is probably unrelated to MG. But supplementation up to (or possibly beyond) the Tolerable Upper Limit Levels (UL) is an option with a qualified professional consent. (Upper limit is set for MGS use only at 350mg/day – i.e., can be added to whatever MG intake comes from diet).

- Lack of this background info has created a rash of MGS promotion on social media platforms – mostly unfounded

* If a human is completely lacking in even one essential vitamin or mineral, they cannot survive; a deficiency in any crucial nutrient can lead to severe health complications and ultimately be fatal depending on the vitamin or mineral missing and the severity of the deficiency.

Rawji et al. Examining the Effects of Supplemental Magnesium on Self-Reported Anxiety and Sleep Quality: A Systematic Review

Summary of Magnesium, mechanisms of action and Its Effects on Sleep from Dietary Sources and Supplements

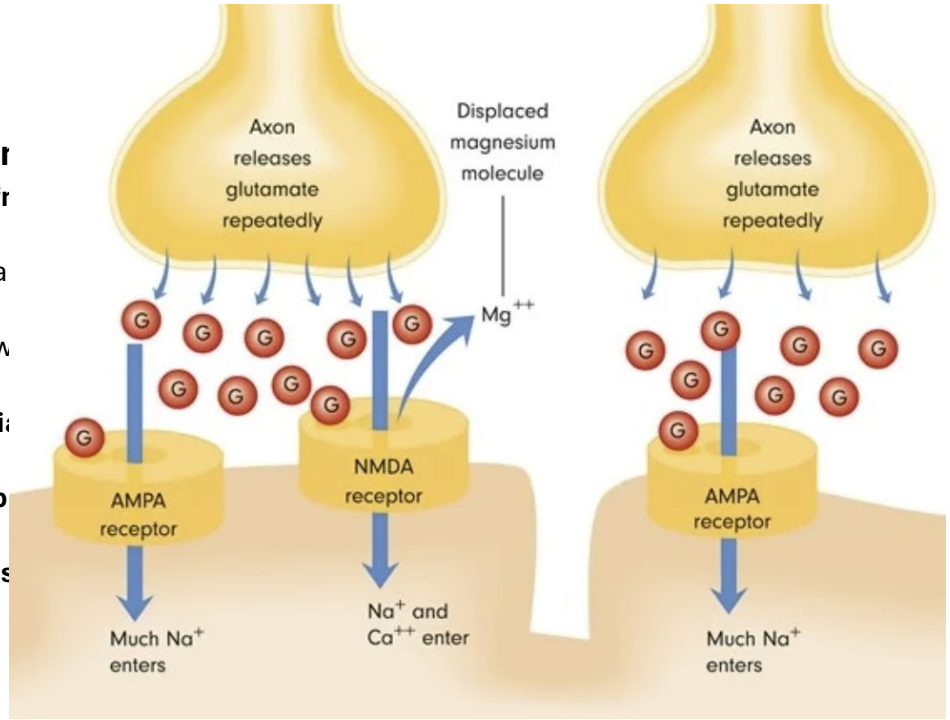
Mechanisms of Action for Sleep and Relaxation

Magnesium plays a crucial role in sleep regulation through multiple biological mechanisms:

1. **NMDA** (N-methyl-D-aspartate) **Receptor* Antagonism**
   - MG acts as a **natural NMDA receptor blocker**, preventing excessive excitatory activity and promoting relaxation in the central nervous system.
2. **GABAergic Modulation**
   - Some studies suggest magnesium may enhance **GABA-A receptor activity**, increasing inhibitory signaling that reduces neural excitability and promotes calmness.
3. **Regulation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis**
   - Magnesium helps **suppress cortisol production**, which in turn reduces stress-related sleep disturbances.
4. **Melatonin and Circadian Rhythm Regulation**
   - Magnesium supports melatonin synthesis and influences **circadian rhythm stability**, leading to improved sleep onset and maintenance.
5. **Muscle Relaxation and Reduction of Restless Limbs**
   - Magnesium reduces muscle tension and is effective in alleviating **restless leg syndrome (RLS)**, contributing to improved sleep quality.

*NMDA receptor allows the binding of the excitatory neurotransmitter glutamate to its site. (Glutamate, an amino acid that acts as a neurotransmitter in the brain. It is the most abundant excitatory neurotransmitter in the CNS)

AMPA-receptors main role is to mediate fast excitatory synaptic transmission



Benefits of MGS Alone for Sleep (only in specific populations and ger

Several studies highlight the **positive effects of magnesium on sleep with doses ranging fr**

- **Improved Sleep Quality:**
  - Studies using **500-729 mg MG daily** demonstrated increased slow-wave sleep a
- **Reduced Sleep Latency:**
  - 250-500mg MGS **shortened the time to fall asleep**, particularly in individuals w
- **Enhanced Melatonin Production:**
  - 250-500mg MGS supports **natural sleep-wake cycles**, helping regulate **circadi**
- **Reduction in Nighttime Awakenings:**
  - 250-500mg MGS in **fewer sleep disturbances and longer uninterrupted sleep**
- **Alleviation of Anxiety-Related Sleep Issues:**
  - Studies show **300-500 mg/day** of magnesium can help **reduce nighttime stres**

Benefits of MGS in support of other compounds for sleep:

- **A melatonin (1.9mg)-magnesium (200mg elemental) supplement**, in a coffee pod format, showed improvements in sleep quality in otherwise healthy individuals with sleep disturbances, however PSQI questionnaire scores still indicated poor quality on average (PSQI > 5).

- **3 months Magnesium (175mg MO), melatonin (1mg), vitamin B complex** supplementation has a beneficial effect in the treatment of insomnia regardless of cause
- **6gm melatonin with 250mg magnesium (MO)** improved sleep quality

Khalid et al. 2024 **Effects of magnesium and potassium supplementation on insomnia and sleep hormones in patients with diabetes mellitus**

- Magnesium (125mg) + potassium (125mg) twice daily (500mg/d total of 250mg each)

Populations That Would Benefit Most from MGS (250-729mg/d)

The effectiveness of magnesium supplementation for sleep improvement is most pronounced in individuals with:

1. **Magnesium Deficiency or Insufficiency**
   - Many people don't consume enough magnesium through diet alone, increasing the risk of **poor sleep quality**.
2. **Older Adults (55+)**
   - Aging reduces magnesium absorption and increases the risk of **sleep fragmentation and insomnia**.
   - Supplementation 250-400mg has been shown to **increase slow-wave sleep and total sleep duration**.
3. **Individuals with High Stress Levels or Anxiety**
   - MG helps regulate the **HPA axis* and cortisol production**, reducing stress-related sleep disturbances.
4. **People with Insomnia and Poor Sleep Quality**
   - Supplementing with 250-500 mg/day has been linked to **improvements in sleep onset latency, efficiency, and duration**.
5. **Individuals with Shift Work or Circadian Rhythm Disruptions**
   - MG can help regulate **melatonin production and support circadian rhythm balance**, assisting those with **jet lag or shift work disorder.**
6. **Those with Restless Leg Syndrome (RLS) or Muscle Tension**
   - MG aids in **muscle relaxation**, making it beneficial for people with **nocturnal cramps or RLS**.

*Hypothalamic-pituitary-adrenal (HPA) axis is a complex endocrine system that plays a crucial role in regulating the body's response to stress

Esquivel et al. 2024-Current Evidence on Common Dietary Supplements for Sleep Quality

With regards to sleep, MG has several essential functions that include; GABA activation (calming neurotransmitter), increases in melatonin production, muscle relaxation, regulation of stress- responses, regulation of calcium levels which promote muscle contraction and relaxation, and anti-anxiety effects. Furthermore, low magnesium status has been associated with chronic inflammatory stress in both animal and human research studies. However, despite its popularity, there are few clinical benefits to MGS in individuals with adequate serum magnesium. There is a potential for MGS in individuals with low serum magnesium to improve sleep quality.

Our world should not be MG deficient/insufficient, therefore the 100mg add from Sleep Aid is safe and appropriate*

- **2 Active: 200mg**
- **1 Woman's: 100mg (b/c most need Ca supp)**
- **2 Over50: 150mg**
- **1 svg SuperBlend: 160mg**
- **1 SuperCalcium: 125mg**
- **2 Sleep Aid: 100mg**

***UL of 350mg from supps is generally disregarded because it's based on a single dose, not spread out as ours would be. Further, the Ca/mg ratio should be protected (2-3:1)**

Final Conclusion/takeaway: Meet ~400-500mg/d through diet and supplement intake that includes a complete MVM containing MG and the other ~20 known under-consumed VMs: dotFIT MVM/Alln1 SuperBlend™ = 100-200mg; Sleep Aid =100mg; diet = 250mg; Daily total is ~450-550mg MG (2-300mg in supps), which would maximize MGs basic role in sleep quality mechanisms, making high dose separate MGS unnecessary and likely ineffective.

MG unique contribution: achieving proper MG intake as described here, offers a unique contribution to the enhancement of all the Sleep Aid's ingredients mechanisms of action related to stress relief, mood, sleep quality and overall health since MG an essential mineral that is active in these myriad pathways and when shorted, all systems suffer. Further, the 100mgs in Sleep Aid offers a potential buffer for people that may need a little extra MG (but still within allowed total supplement range) to maximize MG functions in sleep/calming pathways.

Product Summary

Get relaxed, then fast asleep, quality sleep duration, and wakeup refreshed

What is it

- Formula to promote improved natural sleep quality with instant and controlled release melatonin combined with 5-HTP as the primary active sleep promoting ingredients. The calming herbs Lemon Balm and Hops along with a highly bioavailable form of magnesium are present in complementary amounts to maximize sleep results.

What does it do

Timely increases melatonin (sleep hormone) and serotonin (calming neurotransmitter) levels. The ingredients, have been shown to Improve the overall quality of sleep for persons with common sleep disorders (better sleep efficiency and reduced sleep disturbances) including:

- Enhancing relaxation before bedtime, making it easier to fall and stay asleep
- Increasing total sleep time and shortening the time to fall asleep
- Enhancing sleep efficiency including REM, particularly with higher doses (3-5gm).
- Reducing wakefulness and frequent awakenings.
- Support for insomnia and mitigates jet-lag (adjusting an individual's circadian rhythms)
- Positive support for shift work sleep disorder (e.g., working night shifts, alternating schedules, etc.,)

Who would use it

- Adults with trouble falling and staying sleep including supporting insomnia
- Individuals with shift work or circadian rhythm (24hr internal clock) disruptions. Can help regulate melatonin production and support circadian rhythm balance, assisting those with jet lag or shift work disorder.
    - Formula is b**eneficial for sleep during both nighttime and daytime**, making it useful for those with irregular sleep patterns.
- **Adult's seeking a safe & effective alternative to prescription sleep aids**, which may have adverse effects like increased fall risk, cognitive impairment, and dependency.

Formula to promote improved natural sleep quality with instant and extended-release melatonin combined with 5-HTP as the primary active sleep promoting ingredients. The calming herbs, Lemon Balm and Hops along with a highly bioavailable form of magnesium, are present in complementary amounts to maximize sleep results.

SUGGESTED USE: As a dietary supplement, adults should take 1-2 capsules, 30 minutes before bedtime. Consume with 8 oz. of your favorite beverage.

Supplement Facts

Servings Size: 2 Capsules
Servings Per Container: 60

	Amount Per Serving	% DV
Magnesium (from Magnesium Glycinate, Magnesium Malate and Magnesium Citrate)	100mg	24%
Lemon Balm (Stem and Leaf) Extract	300mg	*
Hops (Flower) Extract	150mg	*
5-HTP	50mg	*
Melatonin (Immediate-Release)	2.5mg	*
Melatonin (Extended-Release)	2.5mg	*

* % Daily Value not established.

120 caps = 2–4-month supply

5-HTP & controlled release melatonin (sleep hormone) to help fall and stay asleep and wakeup refreshed by timely increasing natural melatonin and the body's calming/relaxation neurotransmitters such as serotonin and GABA*

Lemon balm and hops are herbs traditionally used for anxiety, tension/stress, irritability, etc., and insomnia & other sleep disorders. These natural herbs along with a highly bioavailable form magnesium, are complementary and additive to the products effects on sleep quality

Get relaxed, then fast asleep, quality sleep duration, and wakeup refreshed

The ingredients and dosages support:

- **Relaxation before bedtime, making it easier to fall and stay asleep**
- **Increasing total sleep time and shortening the time to fall asleep**
- **Sleep efficiency including REM**
- **Reduction in wakefulness and frequent awakenings.**
- **For insomnia and mitigation of jet-lag (adjusting an individual's circadian rhythms)**
- **Positive support for shift work sleep disorder (e.g., working night shifts, alternating schedules, etc.,)**

Gamma-aminobutyric acid [GABA] is the body's primary **inhibitory neurotransmitter – calming/relaxation effects)**
Serotonin Regulates mood, sleep, appetite, and digestion –called body's natural feel-good chemical and contributes to melatonin production

APPENDIX

Populations That Would Benefit Most from MGS (250-729mg/d)

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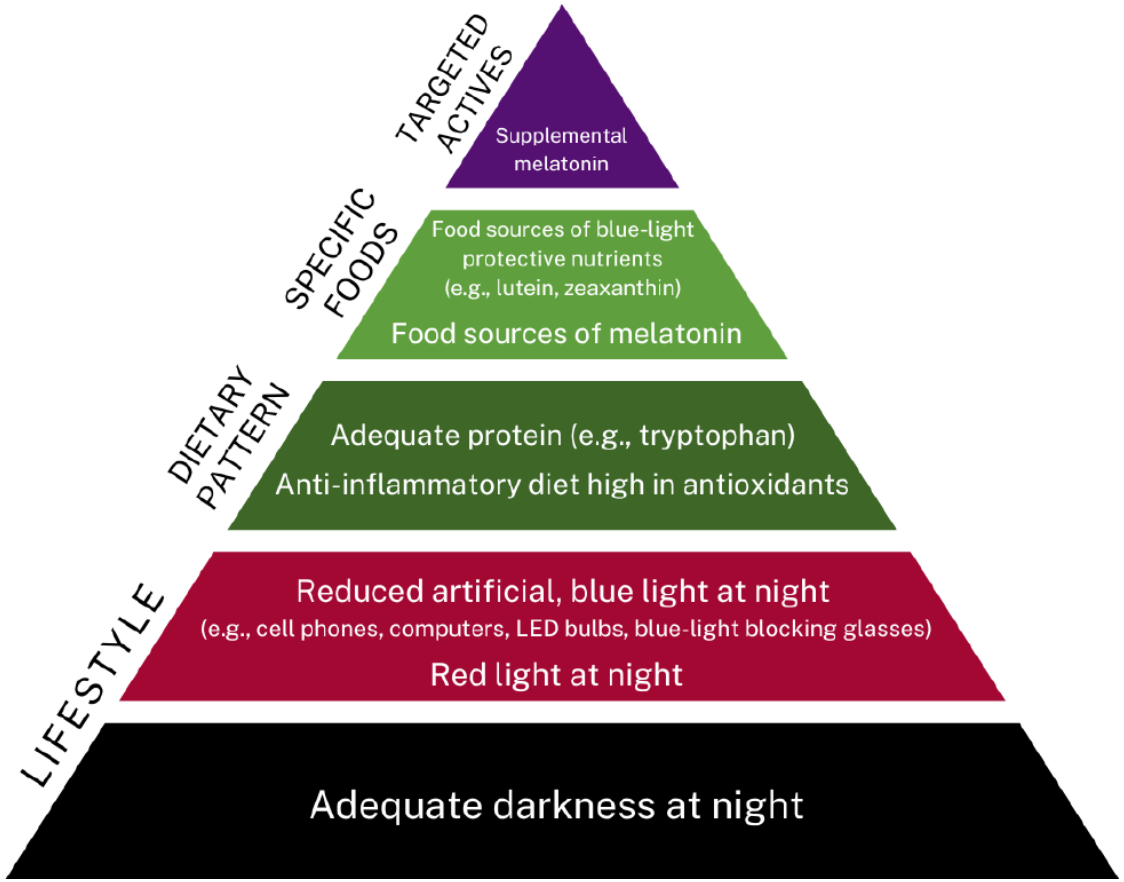


Figure 10. A comprehensive nutrition and lifestyle approach to optimizing melatonin. There are several aspects to ensuring healthy melatonin levels, including lifestyle modifications involving light exposure, selecting specific dietary patterns and foods, and, when required, targeted supplemental sources. Graphic created using Canva.com, accessed 27 July 2022.

Hops contain flavonoids that have sedative and sleep-promoting activities such as α-acid, β-acid, and xanthohumol

The Cherokee's used it for sleep disorders
Hamel P.B., Chiltoskey M.U. In: Cherokee Plants and Their Uses. A 400-Year History. Sylva N.C., editor. Herald Publishing Company; Independence, MA, USA: 1975. p. 72

The use of hops in traditional medicine as a mild sedative arose from the experience of drowsiness and chronic forms of fatigue that the pickers and those who worked with or handled hop inflorescences manifested [82]. An ancient folk remedy is the sleeping drink of fresh hop cones, which are also sealed inside a pillow to be held under the head during the night in order to facilitate sleep. The European Medicine Agency classifies hop herbal preparations as "traditional herbal medicinal products" to be used for the relief of mild symptoms of mental stress and to aid sleep [Lupuli flos. European Medicines Agency. Available online: https://www.ema.europa.eu/en/medicines/herbal/lupuli-flos, accessed on 10 August 2022).

From Drugs.com

Dosing

Hops has been used as a mild sedative or sleep aid, with the dried strobile given in doses of 1.5 to 2 g. An extract combination with valerian, Ze 91019 (ReDormin, Ivel) has been studied at a hops dose of 60mg for insomnia.

Benkherouf et al. Humulone Modulation of $GABA_A$ Receptors and Its Role in Hops Sleep-Promoting Activity

This confirms humulone's mode of action as a positive allosteric modulator of $GABA_A$ receptors, in accordance with the published reports on the enhancement of GABA-induced currents by hops extracts (Aoshima et al., 2006; Sahin et al., 2016)

In conclusion, humulone, a major compound in hops, exhibits sedative/hypnotic effects and acts as a positive allosteric modulator of $GABA_A$ receptors. This supports humulone's substantial role in hops sleep-promoting activity and brings further insight into the probable mode of action for this behavior. Hops flavonoids such as IXN and 6PN may potentiate humulone effects via additive mechanisms on $GABA_A$ receptors. Moreover, the displayed humulone non-competitive synergy with ethanol in $GABA_A$ receptors may contribute to further enhancement in alcohol intoxication with high-hopped beer. Hence, the implication of this on alcohol drinking patterns and reward in humans needs further investigation. Nevertheless, the identification of neuroactive compounds from hops and understanding their interactions advance the development of safe and efficacious remedies for insomnia and sleep disturbances.

The effect of mediterranean diet and chrononutrition on sleep quality: a scoping review

Mediterranean diet demonstrates a more consistent and positive influence on sleep quality compared to chrononutrition

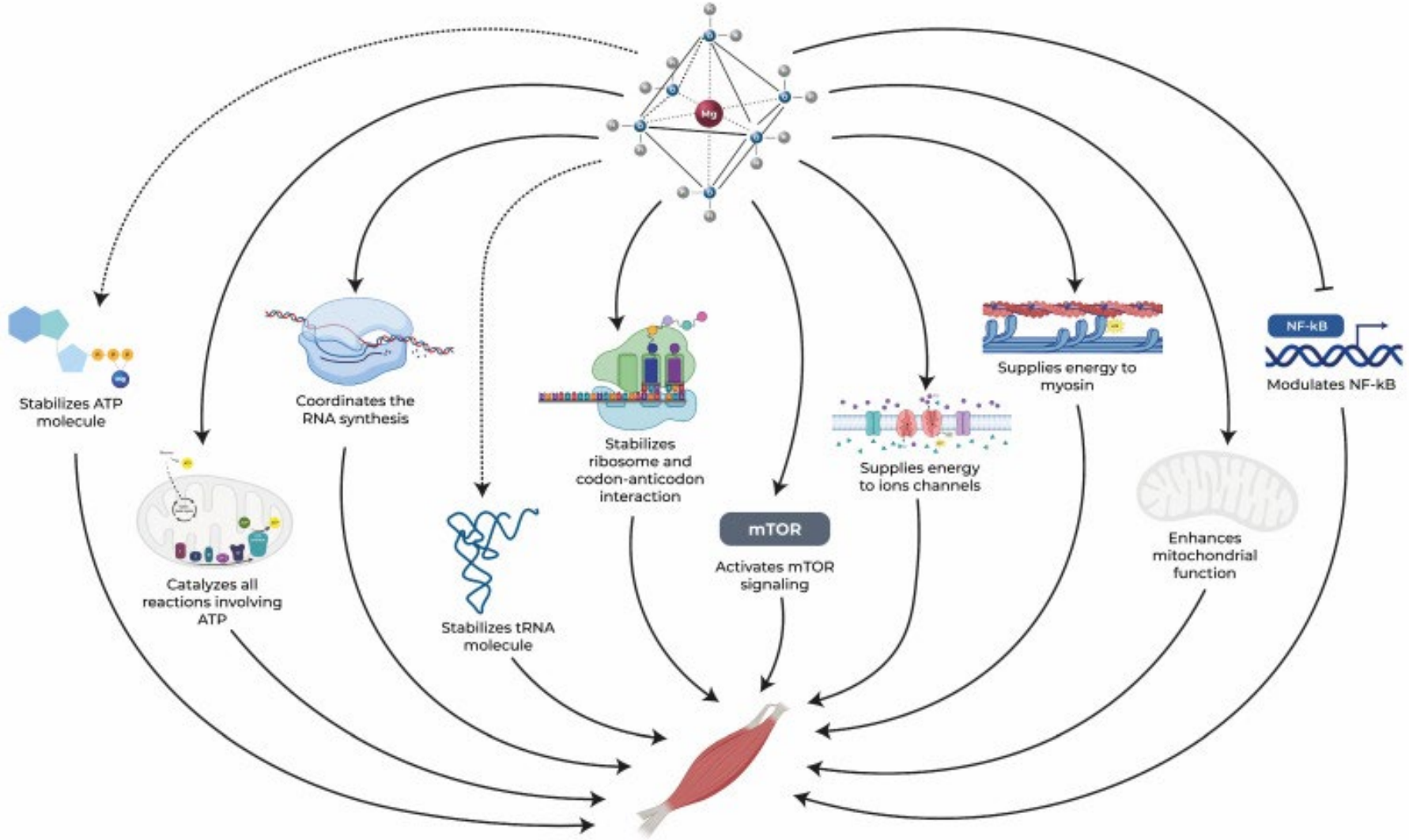
The relationship between food and the circadian clock system, known as *chrononutrition*, explores how the timing of food intake contributes to maintaining health and rapidly resetting our internal clock [5, 15]. Chrononutrition posits that aligning mealtimes with the body's natural rhythms can improve health outcomes [5]. By understanding and applying the principles of chrononutrition, individuals can enhance their metabolic health, potentially prevent chronic diseases, and improve their quality of life [5]. Chrononutrition encompasses a range of dietary methods and terminologies, including time-restricted eating/feeding (TRE/TRF), intermittent fasting (IF), time-based nutrition, and temporal eating/nutrition. In recent years, IF has gained popularity as a viable dietary strategy for weight loss [16]. IF alternates between periods of eating and fasting, with fasting periods typically lasting anywhere from 10 to 24 hours . Similarly, TRE focuses on eating during specific period daily (typically within a 4- to 12-hour window) and abstaining from food for the remainder of the day; this time restricted diet method has gained popularity in recent years [16]. In contrast, Alternate Day Fasting (ADF) involves alternating between a 'fast day,' where intake is limited to 0–600 kcal, and a 'feast day,' where one can eat freely [17].
Meanwhile, chronotype refers to an individual's natural inclination toward being a morning person, evening person, or somewhere in between. This biological predisposition influences daily activity patterns, sleep-wake cycles, and overall energy levels throughout the day. Morning types are early risers who function best in the morning, while evening types are more active and alert later in the day. Intermediate types fall between these two preferences. Chronotype is not only associated with sleep-wake preferences but also impacts lifestyle behaviors, dietary habits, and health outcomes. For instance, one cross-sectional study investigated the association between chronotype and adherence to the MD in middle-aged Italian adults found that evening chronotypes were more likely to follow unhealthy lifestyles, engage in less physical activity, and have lower adherence to the MD compared to morning and intermediate chronotypes [18]. These findings emphasize the importance of incorporating chronotype considerations into dietary and lifestyle interventions to promote healthier behaviors across diverse populations.

Sleep and GABAergic activity

Insomnia and other sleep disorders can have a profound impact on health and quality of life [14]. Common drugs for insomnia can cause side effects such as: nausea, dizziness, daytime fatigue, headache, nightmares and drug dependence [15], thus alternatives such as herbal supplements are being proposed [16]. Rodent study suggested that Ashwagandha can improve sleep duration compared to placebo and decrease sleep latency in caffeine-induced insomnia model. It also impacts sleep architecture, with increased non-rapid eye movement and δ-wave sleep time (known as 'deep sleep phase') [17]. Those effects seem to be associated with the increase in expression of sleep-related gamma-aminobutyric acid (GABA) and its receptors - $GABA_A$, $GABA_B$, 5-hydroxytryptamine receptor also known as serotonin receptor ($5HT_{1A}$) and increase in brain GABA content. Ashwagandha's active compounds are directly binding to $GABA_A$ receptor, because $GABA_A$ receptor antagonists attenuated Ashwagandha's sleep-promoting effects [17].
Above mentioned mechanisms find reliable support in latest scientific data. A recent meta-analysis included 5 randomized controlled trials, combining data of 400 participants, examining effects of Ashwagandha on sleep quantity and quality. Ashwagandha effectively improved overall sleep, compared to placebo, and specific measurements of sleep such as Sleep Quality Scale, sleep onset latency, total sleep time, wake time after sleep onset and sleep efficiency. There was no significant difference in Pittsburgh Sleep Quality Index and total time in bed [18]. Analyzed by participant background, those with insomnia demonstrated larger improvements than those without [16, 19,20,21,22]. Positive effect was also more profound with larger doses (≥ 600 mg/d compared to < 600 mg/d) and longer duration (≥ 8 weeks compared to < 8 weeks) [18]. Three studies that examined mental alertness on rising also showed a positive impact of Ashwagandha [16, 19, 21]. Sleep quality is also shown to be related to stress [23], another target of Ashwagandha supplementation.

Stress and cortisol

According to a systematic review of human trials, amongst many different supplements, Ashwagandha has the most profound effect on hypothalamic-pituitary-adrenal (HPA) axis. This effect on HPA axis, a main regulator of stress response, is evident through lowered morning cortisol levels (a biomarker of stress) following Ashwagandha supplementation [3].
Recent systematic review demonstrated that supplementation with 250–500 mg of Ashwagandha extract, daily for 4 to 13 weeks, significantly decreased morning cortisol levels in adults experiencing higher stress levels [7]. Secondly, improvement in this biomarker finds a reflexion in perceived stress. Multiple studies showed that supplementation with Ashwagandha improves subjective stress measured via Perceived Stress Scale as well as depression and anxiety [6, 11, 22, 24, 25]. However, some studies didn't find any difference between Ashwagandha and placebo with both decreasing stress with similar magnitude [26, 27]. It's worth noting that participants supplemented with Ashwagandha had higher scores of qualities of life [11, 25, 28]. It is hypothesized that some compounds in Ashwagandha (mainly Withaferin A) can directly interact with glucocorticoid receptors in the brain, thus affecting cortisol and stress levels. Other possible mechanisms are associated with GABAergic activity of Ashwagandha and positive impact on sleep quality, which reduce stress [7].



Magnesium exerts an essential role in maintaining muscle health through several pathways. Dotted arrows represent stabilization, solid arrows represent activation, and blunt-end arrows indicate inhibition. ATP: adenosine triphosphate, mTOR: mammalian target of rapamycin, NF-κB: nuclear factor kappa-B, RNA: ribonucleic acid, tRNA: transfer RNA [25,34,35,36,37,38,39,40,41].

Magnesium Distribution in the Human Body [20,21,30,42,43,44].

Location	Magnesium Distribution
Bone	50–60% of total magnesium (24–29 g), with approximately one-third being exchangeable
Soft Tissues (muscles and other organs)	34–39% of total magnesium
Blood	Less than 1% of the body's magnesium
Plasma	60% ionized, 30% bound to albumin, 10% complexed with serum anions (phosphate and citrate)

More than 95% of intracellular magnesium is bound to ATP, proteins, and negatively charged molecules. According to enzymatic databases, current knowledge indicates that magnesium serves as a cofactor in over 600 enzymatic reactions and may act as an activator for an additional 200 enzymes [20,30,31,45]. Consequently, magnesium assumes a fundamental role in cellular homeostasis and organ function, exerting physiological control over several vital metabolic pathways and cellular functions, including its involvement in enzyme-substrate interactions, structural functions, and membrane-related processes [20,21,30].

Magnesium intake recommendations.

Life Stage	PRI (mg)	AR (mg)	UL * (mg)	RDA-DRI (mg)	DRV-AI (mg)
Birth to 6 months	-	-	Nd	30	-
Infants 7–12 months	80	Nd	Nd	75	80
Children 1–3 years	80	65	250	80	170
Children 4–6 years	100	85	250	130	230
Children 7–10 years	150	130	250	240	230
Teen boys 11–18 years	240	170–200	250	410	300
Teen girls 11–18 years	240	170–200	250	360	250
Men	240	170	250	400–420	350
Women	240	170	250	310–320	300
Pregnant	240	170	250	350–400	300
Breastfeeding	240	170	250	310–360	300

Open in a new tab

Population reference intake (PRI), average requirement (AR), recommended dietary allowance (RDA), dietary reference intake (DRI), dietary reference value (DRV), adequate intake (AI), and tolerable upper intake level (UL). * The UL value refers to the intake of magnesium through pharmaceutical or supplements, in addition to the magnesium already present in the diet. Adapted from a previous study [20].

Despite the well-established recommended daily intake guidelines, the average dietary magnesium intake often falls short of meeting these recommendations, with levels significantly lower than the recommended daily intake [21,28]. As a result, subclinical magnesium deficiency is not uncommon in the general population. In fact, nearly two-thirds of Americans consume magnesium in quantities below the RDA, and a similar situation is prevalent in Europe and in Brazil [20,28,54,55]. Notably, although the kidneys help to regulate urinary magnesium excretion to prevent hypomagnesemia, habitual low magnesium intake or excessive losses due to various factors and conditions can eventually culminate in subclinical magnesium deficiency [20].

> In fact, chronic magnesium deficiency is prevalent among the aging population, typically stemming from a reduction in both dietary magnesium intake and intestinal absorption [20,56]. along with the use of multiple medications commonly prescribed to the elderly (including antivirals, antiepileptic drugs, antibiotics, antihistamines, proton pump inhibitors, antacids, and H2 blockers), contribute to magnesium deficits.

Notably, skeletal muscle houses approximately 20% of the body's total magnesium [71]. This essential mineral is intricately associated with various aspects of skeletal muscle function that are negatively impacted in aging subjects. It plays a central role in processes such as protein synthesis, energy production, and muscle contraction while also offering anti-inflammatory and antioxidant benefits, as illustrated in Figure 2 [21,47,72].

Rawji et al. 2024

Examining the Effects of Supplemental Magnesium on Self-Reported Anxiety and Sleep Quality: A Systematic Review

In general, despite notable heterogeneity, the majority of included trials demonstrated at least modest positive results with regard to sleep quality and anxiety across diverse populations. These findings are consistent with animal-based evidence as well as magnesium's known receptor activity in the central nervous system.

Various other forms of magnesium are also readily available commercially, including magnesium glycinate, taurate, sulfate, chloride, malate, threonate, aspartate, citrate, and orotate among others [6]. It is generally believed that organic forms, such as the amino acid chelates above, are absorbed and assimilated by the body more easily versus inorganic forms (e.g., MgO) [6].

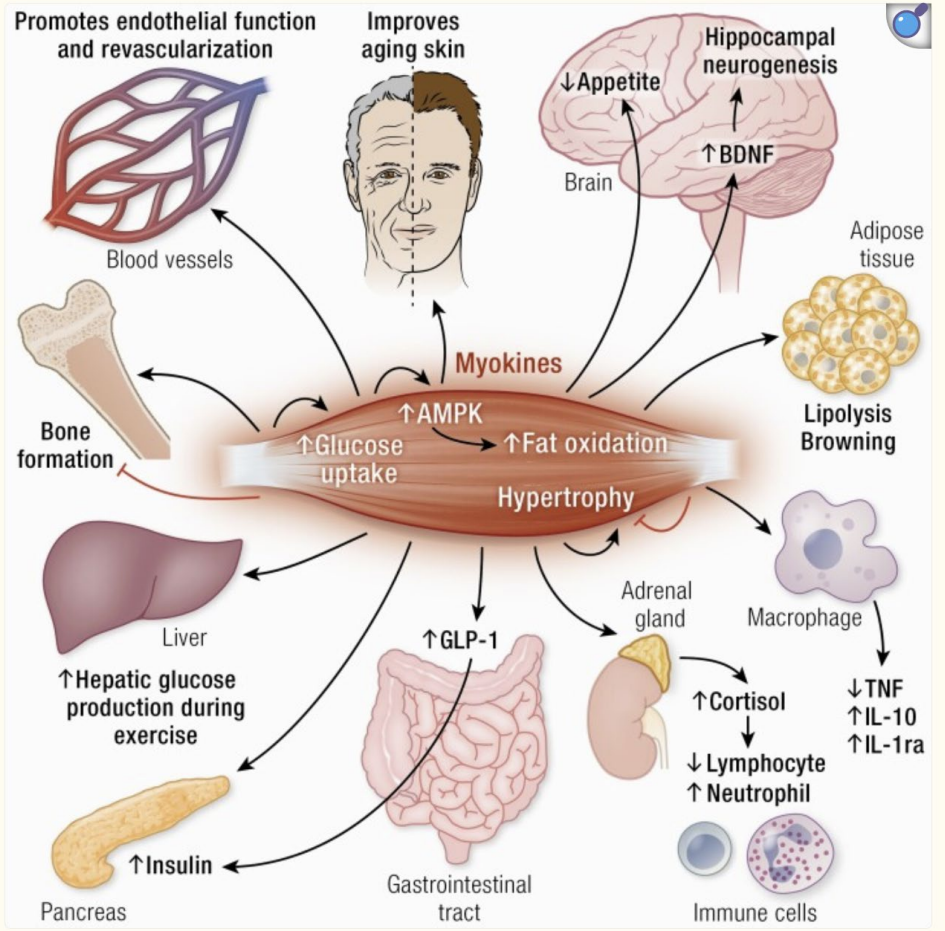
Bioavailability of magnesium food supplements: A systematic review

The aim of this review was to compare the bioavailability of different forms of magnesium and analyze the differences between them.
Results
Inorganic formulations appear to be less bioavailable than organic ones, and the percentage of absorption is dose dependent.
Conclusions
All magnesium dietary supplements can maintain physiological levels in healthy people without prior deficit, although this cannot be assured in older people or those with illnesses or previous subphysiological levels.

6. Pardo MR, Garicano Vilar E, San Mauro Martín I, Camina Martín MA: Bioavailability of magnesium food supplements: a systematic review. Nutrition. 2021, 89:111294. 10.1016/j.nut.2021.111294

Essential Points.

•Myokines are defined as cytokines and other peptides that are produced, expressed and released by muscle fibers and exert either autocrine, paracrine, or endocrine effects
•Myokines mediate communication between muscle and other organs, including brain, adipose tissue, bone, liver, gut, pancreas, vascular bed, and skin, as well as within the muscle itself
•Myokines exert their effects on, for example, cognition, lipid and glucose metabolism, browning of white fat, bone formation, endothelial cell function, hypertrophy, skin structure, and tumor growth
•The myokine IL-6 mediates the exercise-associated anti-inflammatory effects both acutely with each bout of exercise and as a consequence of training adaptation, including reduction in abdominal adiposity.
•The identification of new myokines and their specific roles may lead to novel therapeutic targets
•Myokines can be useful biomarkers for monitoring the type and amount of exercise that are required for the prescription of exercise for people with, for example, cancer, diabetes, or neurodegenerative diseases



No, Heukharang lettuce (Lactuca sativa L.) leaf extract is not considered a hop; hops specifically refer to the dried female flowers of the hop plant (Humulus lupulus), which is a completely different species from lettuce and is primarily used in brewing beer for its bitter flavor and aroma.

Key points to remember:

- **Hop definition:** A hop is a part of the hop plant (Humulus lupulus) used in brewing.
- **Lettuce species:** Heukharang lettuce belongs to the Lactuca sativa species, which is not a hop.

Crosstalk Between Aging, Circadian Rhythm, and Melatonin

Abstract

Circadian rhythms (CRs) are 24-hour periodic oscillations governed by an endogenous circadian pacemaker located in the suprachiasmatic nucleus (SCN), which organizes the physiology and behavior of organisms. Circadian rhythm disruption (CRD) is also indicative of the aging process. In mammals, melatonin is primarily synthesized in the pineal gland and participates in a variety of multifaceted intracellular signaling networks and has been shown to synchronize CRs. Endogenous melatonin synthesis and its release tend to decrease progressively with advancing age. Older individuals experience frequent CR disruption, which hastens the process of aging. A profound understanding of the relationship between CRs and aging has the potential to improve existing treatments and facilitate development of novel chronotherapies that target age-related disorders. This review article aims to examine the circadian regulatory mechanisms in which melatonin plays a key role in signaling. We describe the basic architecture of the molecular circadian clock and its functional decline with age in detail. Furthermore, we discuss the role of melatonin in regulation of the circadian pacemaker and redox homeostasis during aging. Moreover, we also discuss the protective effect of exogenous melatonin supplementation in age-dependent CR disruption, which sheds light on this pleiotropic molecule and how it can be used as an effective chronotherapeutic medicine.

While there are several variables to consider, in general, melatonin is found relatively less in animal foods than in plant foods. Based on published literature, milk and dairy foods, eggs, fish, and meats (beef, lamb, pork) contain some level of melatonin [211]. Conversely, animal foods tend to be better sources of dietary tryptophan than plant foods [249], so the ultimate conversion of these foods into significant quantities of melatonin may need to be considered.

Melatonin has been documented in major plant-derived foods and beverages [211], including vegetables, fruits, nuts, seeds, grains, wine, and beers (see Table 3). Although it can be found throughout most plant parts, melatonin is typically higher in the plant's reproductive organs, especially the seeds [200], most likely to help ensure the plant's survival and protection against environmental stressors

Is Melatonin the "Next Vitamin D"?: A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements

Overall, there are six aspects to consider when selecting a melatonin dietary supplement (see Table 4).

Table 4. Considerations in the selection of a melatonin supplement.

Factor	Details	General Comments
Source	Animal (pineal gland) Chemical synthesis Phytomelatonin Microbial fermentation products (bioengineered)	Synthetic melatonin is the most common form of melatonin on the market but can result in the use of potentially unwanted solvents and substrates in addition to it being environmentally undesirable [210]. Plant-based melatonin presents challenges in concentrating to a viable dose of melatonin. Animal-based melatonin can involve the risk of viral infections. Microbial fermentation products are under development.
Route	Oral intake Oral, immediate release Oral, sustained, time-release Sublingual Intravenous Intramuscular Intranasal Transdermal Anal/Suppository Vaginal delivery	There are a variety of formats available, and each needs to be individualized to the person's needs. Several newer formats are being developed for optimizing delivery, although only oral administration is considered a dietary supplement in the U.S. [260,261].
Delivery	Capsule Tablet Chewable Gummies	A trending format is that of gummies, which is a sweetened gelatinous-type delivery for greater palatability. While it may be the desired delivery form for consumers, there are concerns about the stability of melatonin in such a hygroscopic matrix, the resulting sugar content, the addition of dyes or flavoring agents, and the potential for an overdose of melatonin, especially in the case of children.
Actives	As an isolated compound In combination with other actives In a plant matrix with other phytonutrients	Often, dietary supplements of melatonin will include other nutritional or herbal actives with the intention of synergy or improved efficacy, although, on the whole, these types of preparations have not been effectively studied for interactions.
Quality	Certified Good Manufacturing Practices (cGMP) Third-party testing for heavy metals, and contaminants Packaging integrity to ensure shelf-life and stability.	Not all dietary supplements have the same quality. cGMP and third-party testing can be markers of objective quality measures. Melatonin can degrade in the presence of air and light, so minimizing exposure [262] in oxygen-barrier blister packs would be preferential over open bottle format.
Dose	Physiological dose (0.3–1.0 mg) Supraphysiological dose for occasional use (≥3 mg) Therapeutic dose prescribed by a qualified healthcare practitioner	There is much debate about proper dose levels. Consider safety in addition to efficacy for the clinical condition it is being used for in a patient, as well as the duration of use, whether low dose, short term or high dose, long term.

Kukula-Koch et al. [34] performed cellular assays to determine if superior effects in anti-radical, antioxidant, and anti-inflammatory activities exist in phytomelatonin compared to the synthetic form. Based on these in vitro results using human cell lines, they reported significant benefits with phytomelatonin compared to synthetic melatonin [34]. Phytomelatonin was found to have 646% stronger COX-2 inhibition (see Figure 4), 267–470% more potent free-radical scavenging ability (see Figure 5), and 100% greater efficacy in reducing cellular ROS in a human skin cell line (see Figure 6) when compared to synthetic melatonin, most likely due to the other constituents found in phytomelatonin such as chlorophyll, beta-carotene, lutein, and other protective, antioxidant phytonutrients [values derived from the original data presented in [34].

> The distinct difference between synthetic melatonin and pure phytomelatonin in the true sense would be that the phytomelatonin supplement would exclusively involve the plant material. Melatonin originating solely from the cells of plants, without the other industrial downsides, is highly uncommon

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Lemon balm (*Melissa officinalis*) is a bushy perennial herb in the mint family that has been used in food for over two thousand years. Oral ingestion of lemon balm may help reduce anxiety and depression and improve sleep. Supplementation with lemon balm can also improve blood lipids and blood pressure. When applied to the skin, lemon balm may help with cold sore

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Magnesium distinct chemical properties establish it as a crucial component in the regulation of nearly all biological processes within cells (cofactor in over 600 enzymatic reactions and may act as an activator for an additional 200 enzymes). Therefore, in the absence of adequate magnesium levels, the entire organism is impacted including sleep.

Human intake

Daily intake of dietary magnesium generally falls short of meeting recommendations (FDA recommendation for adults is 420mg/D), with levels significantly lower (268 mg for men and 234 for women). As a result, subclinical magnesium deficiency is not uncommon in the general population in at least two-thirds of Americans (Europe and Brazil). Low magnesium intake affects the sleep quality in certain individuals because the limited availability of MG will be routed to more important enzymatic reactions that are involved with vital daily survival functioning such as maintaining genomic stability, serving as a cofactor for many DNA repair enzymes/DNA protection, ATP production, neuromuscular function, etc., thus shortening amounts that would otherwise satisfy all requirements including MGs contribution to sleep quality. All this considered, the rationale for MG supplementation to improve sleep parameters exists and has fueled the hoopla on social media platforms regarding MG supplementation because benefits would be limited to specific populations. Moreover, magnesium does not function in a vacuum within any body system including sleep. MG requires other vitamins and minerals to be present for it to positively affect any of its 800 functions.

Therefore, before adding a high dose individual magnesium supplement for improving sleep quality, persons should start with meeting recommendations (320-420mgs/d) with diet and a complete multivitamin and mineral formula (MVM), which also contains MG along with the other ~20 known under-consumed vitamins and minerals (VM). From that baseline (American diet supplies ~ Upper limit for supplement use has been set at 350mg/day – i.e., can be added to whatever MG intake comes from diet.

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Magnesium Intakes and Status

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Key points about AMPA receptors:

- **Function:**
When glutamate binds to an AMPA receptor, it opens a channel allowing positively charged ions like sodium and potassium to flow into the neuron, generating an electrical signal.
- **Synaptic plasticity:**
The number and properties of AMPA receptors at a synapse can change based on neuronal activity, contributing to the process of synaptic plasticity, which underlies learning and memory.
- **Structure:**
AMPA receptors are composed of four subunits (GluA1-GluA4) that come together to form a channel.
- **Comparison with NMDA receptors:**
While both are glutamate receptors, AMPA receptors mediate fast synaptic transmission, while NMDA receptors are involved in slower, more sustained responses and are highly permeable to calcium.

AMPA receptors are glutamate-gated ion channels, present in a wide range of neuron types and in glial cells. AMPA-receptors main role is to mediate fast excitatory synaptic transmission, and therefore, they are critical for normal brain function.

Extracellular [Mg^{2+}] is an open channel blocker for NMDA receptors. Membrane depolarization is generally believed to relieve this block via removing magnesium ion to extracellular space

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LB Benefits for Calming and Sleep

1. **Reduces Anxiety and Stress**
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   - Participants experienced **a calming effect**, with improvements in mood and overall emotional well-being.
2. **Improves Sleep Quality and Duration**
   - **Significant improvements in Pittsburgh Sleep Quality Index (PSQI) scores** were observed, indicating **better sleep efficiency and reduced sleep disturbances**.
   - Lemon balm enhances **relaxation before bedtime**, making it easier to **fall asleep and stay asleep**.
3. **Enhances Mood and Emotional Well-being**
   - Supplementation **increased positive affect** (happiness, calmness) and **decreased negative affect** (anger, sadness).
   - Improvements in **mental well-being scores** suggest an overall boost in emotional resilience.
4. **Promotes Cognitive Relaxation**
   - Increased **GABA activity** helps prevent **racing thoughts and cognitive hyperactivity**, which often interfere with sleep.
   - Supports **focus and relaxation** without causing sedation or grogginess.
5. **No Significant Side Effects**
   - The study found **no serious adverse effects** associated with lemon balm supplementation.
   - It is a **safe and well-tolerated natural alternative** to conventional medications for stress and sleep issues

Conclusion

Lemon balm extract is a **powerful natural calming agent** that enhances relaxation, reduces anxiety, and improves sleep quality through its effects on **GABA, serotonin, stress hormones, and neuroprotection**. The clinical trial supports its use as a **safe and effective supplement for individuals experiencing emotional distress and sleep disturbances**, making it a promising alternative to pharmaceutical sleep aids.

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   - Participants experienced **a calming effect**, with improvements in mood and overall emotional well-being.
2. **Improves Sleep Quality and Duration**
   - **Significant improvements in Pittsburgh Sleep Quality Index (PSQI) scores** were observed, indicating **better sleep efficiency and reduced sleep disturbances**.
   - Lemon balm enhances **relaxation before bedtime**, making it easier to **fall asleep and stay asleep**.
3. **Enhances Mood and Emotional Well-being**
   - Supplementation **increased positive affect** (happiness, calmness) and **decreased negative affect** (anger, sadness).
   - Improvements in **mental well-being scores** suggest an overall boost in emotional resilience.
4. **Promotes Cognitive Relaxation**
   - Increased **GABA activity** helps prevent **racing thoughts and cognitive hyperactivity**, which often interfere with sleep.
   - Supports **focus and relaxation** without causing sedation or grogginess.
5. **No Significant Side Effects**
   - The study found **no serious adverse effects** associated with lemon balm supplementation.
   - It is a **safe and well-tolerated natural alternative** to conventional medications for stress and sleep issues

Conclusion

Lemon balm extract is a **powerful natural calming agent** that enhances relaxation, reduces anxiety, and improves sleep quality through its effects on **GABA, serotonin, stress hormones, and neuroprotection**. The clinical trial supports its use as a **safe and effective supplement for individuals experiencing emotional distress and sleep disturbances**, making it a promising alternative to pharmaceutical sleep aids.