Melatonin Series

Science-based melatonin for sleep and antioxidant enhancement

Melatonin is a hormone (*N*-acetyl-5-methoxytryptamine) produced especially at night in the pineal gland. Its secretion is stimulated by darkness and inhibited by light. Melatonin, an indole, is synthesized from tryptophan via serotonin. The suprachiasmatic nuclei (SCN) of the hypothalamus have melatonin receptors, and melatonin may have a direct action on SCN to influence circadian (sleep) rhythms.

ACTIVE INGREDIENTS

TABLETS

Each Melatonin SAP 3 mg tablet contains:
Melatonin ..... 3 mg
Each Melatonin SAP 5 mg tablet contains:
Melatonin ..... 5 mg
Each Melatonin SAP 10 mg tablet contains:
Melatonin ..... 10 mg
These products are non-GMO and vegan friendly.
Contains no: Gluten, soy, wheat, corn, eggs, dairy, yeast, citrus, preservatives, artificial flavour or colour, starch, or sugar.
Melatonin SAP 5 and 10 mg contain 90 tablets per bottle. **Melatonin SAP 3 mg** contains 60 tablets per bottle.

LIQUID

Each Liquid Melatonin SAP spray contains:
Melatonin
(*N*-acetyl-5-methoxytryptamine) ..... 440 mcg
Other ingredients: Ethanol, glycerin, and purified water.
These products are non-GMO and vegan friendly.
Contains no: Gluten, soy, wheat, corn, eggs, dairy, yeast, citrus, preservatives, artificial flavour or colour, starch, or sugar.
Liquid Melatonin SAP contains 50 ml per bottle.

DIRECTIONS FOR USE

TABLETS

3 mg | Adults: Take 1–3 tablets daily at or before bedtime, or as directed by your healthcare practitioner.

5 mg | Adults: Take ½–2 tablets daily or as directed by your healthcare practitioner. Take once a day, at or before bedtime.

10 mg | Adults: Take ½–1 tablet daily or as directed by your healthcare practitioner. Take once a day, at or before bedtime.

For jet lag: Take once a day at bedtime after darkness has fallen, while travelling, and at destination until adaptation to the new daily pattern in occasional short-term use.

LIQUID

Adults: Spray 4–22 times daily under the tongue (4, 11, and 22 sprays provide approximately 1.5, 5, and 10 mg of melatonin, respectively) or as directed by your healthcare practitioner. Sensitivity to melatonin is different from person to person. Take once a day, at or before bedtime. **For jet lag:** Take once a day at bedtime after darkness has fallen, while travelling and at destination, until adaptation to the new daily pattern on occasional short-term use. Consult a healthcare practitioner for use beyond 4 weeks.

INDICATIONS

Multiple human studies have measured the effects of melatonin supplements on sleep in healthy individuals. A wide range of doses have been used, often taken by mouth 30 to 60 minutes prior to sleep time. Most trials have been small, brief in duration, and have not been rigorously designed or reported. However, the weight of scientific evidence does suggest that melatonin decreases the time it takes to fall asleep ("sleep latency"), increases the feeling of "sleepiness," and may increase the duration of sleep.

MULTIFUNCTIONAL PROPERTIES

- Melatonin is also a powerful antioxidant that can easily cross cell membranes and the blood-brain barrier. Unlike other antioxidants, melatonin does not undergo redox cycling, the ability of a molecule to undergo reduction and oxidation repeatedly. Redox cycling may allow other antioxidants (such as vitamin C) to act as prooxidants, counterintuitively promoting free-radical formation.
- Melatonin receptors appear to be important in mechanisms of learning and memory, and melatonin can alter electrophysiological processes associated with memory, such as long-term potentiation (LTP). Melatonin has been shown to prevent the hyperphosphorylation of the tau protein. Hyperphosphorylation of tau protein can result in the formation of neurofibrillary tangles, a pathological feature seen in Alzheimer's disease. Thus, melatonin may be effective for treating Alzheimer's disease.

PURITY, CLEANLINESS, AND STABILITY

All ingredients listed for all **Melatonin SAP** and all **Liquid Melatonin SAP** lot numbers have been tested by a third-party laboratory for identity, potency, and purity.

Scientific Advisory Panel (SAP): adding nutraceutical research to achieve optimum health

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Melatonin is an indoleamine hormone whose precursor is the amino acid tryptophan. Recent research has revealed the many roles it plays in humans. Secreted by the pineal gland, it is also found in peripheral cells and organs. Physiological effects of melatonin include setting the circadian rhythm, seasonal adaptation and pubertal development. It also acts as an antioxidant, interacts with receptors in peripheral organs, and has direct mitochondrial effects. The diverse mechanisms of action render melatonin of extreme importance in the aging and multiple disease processes, especially those associated with oxidative stress. Recent studies have shown the benefits of supplementing melatonin, emphasizing its importance in maintaining health and delaying the progression of certain diseases including sleep disorders, Alzheimer's Disease (AD) and Parkinson's Disease (PD).[1]

INSOMNIA

The pineal gland secretes melatonin, and circulating levels of this hormone are responsible for setting the body's circadian rhythm. In a 24-hour cycle, melatonin production levels peak during sleep when it is dark, and are downregulated by light. This rhythm may be disrupted with exposure to excessive light during dark hours, and/or insufficient amounts of light during the day.

One of the major indications for melatonin is insomnia due to disrupted circadian rhythms or deficient melatonin levels, which naturally decline with age. Studies in those suffering from insomnia show that melatonin supplementation decreases the time it takes to fall asleep (sleep latency), increases the amount of time slept, and improves sleep quality compared to those given placebo.[2, 3, 4] Melatonin supplementation has been shown to be effective for insomnia in children suffering from autism[2] or ADHD[4] and in the elderly.[5] Long-term melatonin treatment was judged to be effective against sleep onset problems in 88% of the cases, but cessation of melatonin led to a relapse of chronic sleep onset disorder.[4] Supplementation of melatonin has also been used to regulate disrupted circadian rhythms in those with jet lag and people who work night shifts.[1]

COMBATING PARKINSON'S, ALZHEIMER'S, AND ISCHEMIC INJURY

Antioxidant and Anti-Inflammatory

Melatonin has a free-radical scavenging ability that produces a cascade effect. Melatonin is oxidized when it reacts with hydrogen peroxide (H_2O_2), reactive oxygen species (ROS), or UV radiation to form a metabolite called *N*-acetyl-*N*-formyl-5-methoxykynuramine (AFMK). ROS stress consumes melatonin at a higher rate than other sources of oxidative stress, leading to higher levels of AFMK. Studies have shown that through the AFMK pathway, one molecule of melatonin can quench 10 molecules of ROS.[6] Various studies have found AFMK formation in cerebrospinal fluid, leukocytes, red blood cells, epithelial cells and keratinocytes.[6] AFMK has further been shown to inhibit lipid peroxidation and oxidative DNA damage, and prevents neuronal cell injury caused by H_2O_2 and amyloid β-peptide.[7]

AFMK inhibits tumour necrosis factor-α (TNF-α) and interleukin-8 (IL8) in neutrophils and peripheral blood mononuclear cells, and inhibits gene expression of cyclo-oxygenase 2 (COX-2).[6] AFMK and its metabolite AMK are effective at inhibiting the synthesis of prostaglandins.[8] When given melatonin, animal models of AD show a decrease in the expression of inflammatory cytokines (TNF-α) in the hippocampus, as well as decreased β-amyloid aggregation.[9] Humans trials also show an increase level of β-amyloid aggregations and CNS inflammation when insulin levels are high.[10]

Melatonin interacts with nitric oxide (NO), a compound important in the regulation of cellular signals in both physiological and pathological processes. NO promotes vasodilation. However, it also has a high affinity for superoxide anion radical (O_2^-), forming peroxynitrite ($ONOO^-$). $ONOO^-$ is generated in times of chronic oxidative stress such as chronic hyperglycemia, hyperlipidemia, tobacco smoking, and prolonged drug use.[11] Pathological effects include endothelial dysfunction leading to vasoconstriction, lipid peroxidation, protein oxidation, and DNA damage. Furthermore, $ONOO^-$ inhibits superoxide dismutase and other antioxidants, which further exacerbates free-radical damage. Melatonin is the only documented antioxidant able to quench $ONOO^-$ in addition to both oxygen- and nitrogen-based reactants, thereby inhibiting the proinflammatory and blocking transcription factors such as nuclear factor kappa B and activator protein 111.

Melatonin regulates the glutathione redox status in isolated brain and hepatic mitochondria, correcting it when it is disrupted by oxidative stress.[11] The antioxidant properties of melatonin make it an appropriate consideration in the treatment of AD and PD. In vitro models of AD have demonstrated the neuroprotective effects of melatonin and it has been shown to limit auto-oxidation of dopamine.[11]

NEURODEGENERATION AND ISCHEMIC INJURY/APOPTOSIS

Neurodegeneration occurs with aging, but is highly exacerbated in diseases such as AD and PD. Excessive apoptosis of cells contributes to the disease process. Melatonin was found to inhibit apoptosis in immune cells and peripheral cells, and in neuronal models of PD and AD. It also was proven to be effective at inhibiting apoptosis in ischemia-reperfusion injury.[12]

Melatonin can also be found in the mitochondria. Melatonin may improve ATP output efficiency via mitigation of oxidative stress, by acting directly on complexes I and IV in the electron transport chain (ETC),[12] while also limiting protein and DNA damage. Glutathione status is of great importance when considering neurodegeneration; melatonin may play a role in the restoration of glutathione levels and the reactivation of the enzymes glutathione peroxidase and superoxide dismutase. The effect of melatonin on GSH homeostasis have also been demonstrated in brain tissue[13] and in gastric mucosa and male testes.[14]

EXCITOTOXICITY

Also impacted by melatonin is the GABA-benzodiazepine receptor complex and NMDA receptor.[12] Excitotoxicity contributes to the pathogenesis of PD and AD. Both in vivo and in vitro studies have found melatonin to have significant antiexcitotoxic effects. Melatonin reduces lipid peroxidation and stabilizes mitochondrial inner membranes, an effect that may improve ETC activity.

TAU PROTEIN AND ALZHEIMER'S DISEASE

Tau-protein regulation plays a vital role in the pathogenesis of AD. Studies suggest that melatonin alters the function of certain protein kinase and phosphatase enzymes, thereby decreasing hyperphosphorylation of the tau protein found in neurofibrillary tangles.[15] Implications of this include neurodegenerative decline. Recent studies have shown melatonin to be effective at inhibiting the hyperphosphorylation of the tau protein.[15]

HYPERHOMOCYSTEINEMIA AND ALZHEIMER'S DISEASE

Hyperhomocyteinemia is a part of the pathogenesis of many disorders involving inflammation and oxidative stress. It is believed to contribute to cardiovascular disease and lipid peroxidation. Increased levels of homocysteine have been found to increase apoptosis in nerve cells, and have been linked to AD.[16] Melatonin has protective actions against hyperhomocysteinemia by reducing oxidative stress, preventing reactive gliosis, inhibiting apoptosis and contributing to the improvement of learning and memory performance.[16]

HYPERINSULINEMIA AND ALZHEIMER'S DISEASE

Results of melatonin as an adjuvant treatment of diabetes mellitus showed benefits in controlling complications of the diabetes mellitus (DM) and lipid profile improvement.[17] Insulin resistance also affects the brain and has been found to increase the risk of age-related impairment and AD. Hyperinsulinemia has an effect on memory, CNS inflammation, and regulation of the β-amyloid peptide, and has also been found to be correlated with hyperphosphorylation of the tau protein.[17, 18]

CANCER

In cancer models, melatonin has been shown to have proapoptotic effects.[12] Alterations in melatonin receptor expression as well as changes in endogenous melatonin production have been shown in breast and prostate cancer, hepatoma and melanoma models.[19]

HORMONES

Melatonin affects the release of gonadatrophins, which suggests its role in fertility treatment. High levels of oxidative stress and low levels of melatonin have been linked to infertility and delayed sexual maturation.[20] Furthermore, evidence of a relationship between light exposure and melatonin secretion and irregular menstrual cycles, menstrual cycle symptoms, and disordered ovarian function have been found.[21] Women with polycystic ovary syndrome seem to be more vulnerable to the influence of light/dark exposure.[20]

Melatonin has been shown to protect against sperm apoptosis via ROS scavenging activities.[22]

A recent study has shown that melatonin crosses the placenta and may be required for a successful pregnancy.[23] It also seems to be involved in correcting the pathophysiology of complications during pregnancy, including those due to abortion, preeclampsia and fetal brain damage.[23]

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For healthcare professional use only.

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INDICATION SPECIFIC DOSAGE SUMMARY BASED ON HUMAN CLINICAL RESEARCH#

#Please note these suggestions are guidelines based on the clinical studies. Evidence for efficacy and safety has been qualitatively (study quality in terms of study design, sample size, appropriate methods of analysis, use of appropriate placebo/control, bias etc) assessed and has been rated using a 5 star ★ rating classification.

(L - Liquid melatonin spray | TI - 3 mg tablet | TII - 5 mg tablet | TIII -10 mg tablet)

Indication	Suggested dosage	Supporting evidence and study outcomes	Study design	Outcome measures/ selection criteria for studies	Safety	Evidence quality rating
Women's Health						
Premenstrual syndrome[1]	TI - 1 per day OR L - 5 sprays per day	Significant increased morning urinary 6-sulfatoxymelatonin (aMt6); reduced objective sleep onset latency and increased stage 2 sleep	Prospective study. (n =5, 3 menstrual cycles); 2 mg of slow-release melatonin 1 h before bedtime	Quantification of ovarian hormones; premenstrual dysphoric disorder (PMDD); sleep onset latency (SOL); circadian parameter assessment	No severe adverse effects reported	★★
PCOS[2,3]	L - 23 sprays per day TI -3 per day TII -2 per day TIII - 1 per day	Significantly reduced hirsutism, serum total testosterone levels; high-sensitivity C-reactive protein, and significantly increased plasma total antioxidant capacity (TAC) levels	Randomized, double-blinded, placebo-controlled study (n=56, 12 weeks); 10 mg of melatonin/day	Hirsutism using a modified Ferriman–Gallwey (mFG) scoring system; evaluation of total testosterone, SHG, and hs-CRP; and plasma samples	No severe adverse effects reported	★★★
	L - 23 sprays per day TI -3 per day TII - 2 per day TIII - 1 per day	Significantly decreased Pittsburgh Sleep Quality Index; Beck Depression Inventory index; Beck Anxiety Inventory index; significantly reduced serum insulin	Randomized, double-blinded, placebo-controlled study (n=58, 12 weeks); 10 mg of melatonin/day	Pittsburgh Sleep Quality Index (PSQI); Beck Depression Inventory index (BDI); Beck Anxiety Inventory index; homeostasis model of assessment-insulin resistance (HOMA-IR)	No severe adverse effects reported	★★★
Perimenopause[4,5]	TI -1 per day OR L - 7 sprays per day	Significant increase in thyroid hormone levels; reduction in luteinizing hormone and follicle-stimulating hormone levels; general improvement in depression symptoms	Randomized, double-blinded, placebo-controlled study (n=79, 6 months); 3 mg of melatonin/day	Basal levels of melatonin in saliva; blood levels of thyroid hormones and luteinizing hormone quantification; Menstrual cyclicity; other psychosomatic and neurovegetative changes	No severe adverse effects reported	★★★
	TI- 1 per day OR L- 7 sprays per day	Significant restoration of imbalance in bone loss; improvement in physical symptoms associated with perimenopause condition	Randomized, double-blinded, placebo-controlled study (n=18, 6 months); 3 mg of melatonin/day	Bone health analysis using Achilles InSight ultrasonometer; N-MID Osteocalcin enzyme-linked immunosorbent assay; serum melatonin levels; Menopause-Specific Quality of Life-Intervention (MENQOL); PSQI	No severe adverse effects reported	★★★
Menopause[6,7]	TI- 1 tablet/day OR L- 7 sprays per day	Significant improvement in sleep quality; including sleep quality and daytime dysfunction	Randomized, double-blinded, placebo-controlled study (n=86, 4 months); 3 mg of melatonin/day	PSQI; Center for Epidemiologic Studies – Depression (CES-D); and the North Central Cancer Treatment Group (NCCTG) hot flash diary	No severe adverse effects reported	★★★★
	TI- ½ to 2 per day OR L- 3-12 sprays per day	Significant improvement in physical symptoms	8 randomized controlled studies (n=812, 3 to 12 months); 1 mg to 5 mg of melatonin/day	Sleep quality; general menopause symptoms; anxiety, depression, and psychosomatic disorder symptoms	No severe adverse effects reported	★★★
Mental Health						
Depression[8,9]	TII- ½ to 5 per day	Significant decrease in depression score, specifically BDI scores	15 randomized controlled studies and 4 randomized crossover studies (n=1178, 10 days to 3.5 years; 2 to 25 mg of melatonin/day	Depressive symptoms measured by the BDI; Hospital Anxiety and Depression Scale (HADS-D); Center for Epidemiologic Studies Depression (CES-D); Major Depression Inventory (MDI); 21-item Hamilton Depression Rating Scale (HDRS-21); Yesavage Geriatric Depression Scale (GDS); Cornell Scale for Depression in Dementia (CSDD); and the 8-item addendum of the Structured Interview Guide for the Hamilton Depression Rating Scale - Seasonal Affective Disorders Version Self-Rating Format (ATYP)	Headaches, daytime sleepiness, dizziness, altered bowel habits, and tachycardia were reported	★★★
	L - 1-13 sprays per day	Significant suppression of LH; increase in cognition; improvement in sleep; relief from hot flashes; improvement in life quality	5 randomized controlled studies and 5 randomized crossover studies (n=486, 2 weeks to 3.5 years; 0.5 to 6 mg of melatonin/day	Depression symptoms measured by CSDD; HDRS 17 and 21; BDI; Delayed sleep phase syndrome (DSPS); Yesavage Geriatric Depression scale	Headaches, daytime sleepiness, dizziness, poor sleep, and fuzzy feelings were reported	★★★
Sleep[10,11,12,13,14]	TI - 1 per day OR L - 5 sprays/day	Significant reduction in PSQI scores; improvement in sleep quality and sleep efficiency; reduced anxiety and fatigue	Randomized, double-blind, placebo-controlled, two-period two-treatment (melatonin and placebo) crossover study (n=33, 4 weeks); 2 mg of prolonged-release melatonin/day	PSQI global scores and sleep onset latency measured by wrist actigraphy; Actigraphy sleep efficiency; Epworth Sleepiness Scale (ESS) and Fatigue Severity Scale (FSS)	No severe adverse effects reported	★★★★
	TI - 1 per day L - 7 sprays per day	Significant improvement in sleep quality	Randomized, double-blind, placebo-controlled, parallel-group study (n=20, 28 days); 3 mg of melatonin/day	PSQI; polysomnography; sleep latency; total sleep time; sleep efficiency; daytime somnolence	No severe adverse effects reported	★★★
	TI - 1 tablet/day TII - ½ per day L - 7 sprays/day	Significant improvement in sleep quality; shortening in sleep onset latency; increased stage 2 sleep	Randomized, double-blind, placebo-controlled, parallel-group study (n=16, 3 weeks); 2.5 mg of melatonin/day	Polysomnography for the analysis of electroencephalography (EEG); left and right electrooculography (EOG); bipolar submental electromyography (EMG); bipolar electrocardiography (ECG); and actigraphy	No severe adverse effects reported	★★★
	L - 1 spray/day	Significant improvement in sleep efficiency; decrease in sleep-related functional impairment, sleep disturbance, insomnia severity, and functional disability	Randomized, double-blind, placebo-controlled study (n=116, 4 weeks); 0.5 mg of fast-release melatonin/day	PSQI, Epworth Sleepiness Scale (ESS); Morningness-Eveningness Questionnaire to assess diurnal preference; Insomnia Severity Index (ISI); The Sheehan Disability Scale (SDS)	No severe adverse effects reported	★★★
	TI - 1 tablet/day OR L - 7 sprays/day	Significant decrease in early wake time and percentage of N2 sleep	Randomized, double-blind, placebo-controlled, parallel study (n=97, 4 weeks); 3 mg of fast-release melatonin/day	PSQI; ESS; Insomnia Severity Index (ISI)	No severe adverse effects reported	★★★

Metabolic Health

Insulin[15]	L - 2 to 22 sprays/day TI -1-3 per day	A slight reduction in fasting insulin levels and reduced insulin resistance	11 randomized controlled studies (n=603, 2 weeks to 1 year); 1 to 10 mg of melatonin/day	Fasting plasma blood glucose levels; HbA1c levels analysis; insulin resistance by HOMA-IR analysis	No severe adverse effects reported	★★★
Coronary heart disease[16]	TII - 2 per day	Significant increase in plasma glutathione levels; a significant decrease in malondialdehyde, protein carbonyl (PCO), and serum high sensitivity C-reactive protein (hs-CRP) levels	Randomized, double-blind, placebo-controlled study (n=60, 12 weeks); 10 mg of melatonin/day	Biomarkers of oxidative stress; other metabolic profiles; blood pressures; mental health parameters	No severe adverse effects reported	★★★
Anthropometric indices[17,18]	TI - 1 per day OR L - 7 sprays/day	Significant reduction in BMI, body weight, and waist circumference	Randomized, double-blind, placebo-controlled study (n=38, 12 weeks); 3 mg of melatonin/day	Anthropometrics; physical activity questionnaire; dietary intake analyses; body melatonin level	No severe adverse effects reported	★★★
	TII - 2 tablets/day TIII -1 per day L - 22 sprays per day	Significant reduction in body weight; a significant increase in the activities of adiponectin and omentin-1 levels and Glutathione peroxidase (GPx)	Randomized, placebo-controlled study (n=30, 30 days); 10 mg of melatonin/day	Anthropometrics; serum concentrations of melatonin; Erythrocytic malondialdehyde (MDA) concentration; activities of Zn/Cu-superoxide dismutase and GPx	No severe adverse effects reported	★★★

Cancer

Cancer[19]	TI - 1 to 6 per day TII - 1 to 4 per day	Reduced stomatitis rate in cancer patients and reduced depression-related symptoms	19 randomized controlled studies (n=2101, 7 days to 1 year); 3 to 20 mg of melatonin/day	PSQI; visual analog scale; sleep quality scale; Athens insomnia scale; BDI; Hamilton Rating Scale for Depression; Hospital Anxiety and Depression Scale; Functional Assessment of Cancer Illness Therapy-Fatigue subscale	No severe adverse effects reported	★★★

Infants-Based

Sleep[20]	L – 1 to 25 sprays per day	Significant improvement in total sleep time and reduction in sleep-onset latency in children with neurodevelopmental delay	Randomized, double-blind, placebo-controlled, parallel study (n=146 ;12 weeks; children aged 3 years to 15 years 8 months. All children started with a 0.5 mg capsule, which was increased through 2 mg, 6 mg, and 12 mg depending on their response to treatment.	Daily sleep diaries; actigraphy; sleep-onset latency (SOL) (time taken to fall asleep), sleep efficiency, Composite Sleep Disturbance Index score, global measure of a child's sleep quality, Aberrant Behaviour Checklist, Family Impact Module of the Pediatric Quality of Life Inventory (PedsQL), the Epworth Sleepiness Scale	No severe adverse effects reported	★★★★
Atopic dermatitis[21,22]	TI - 1 per day L - 3 sprays per day	Significant decrease in SCORAD index; reduced sleep-onset latency	Randomized, double-blind, placebo-controlled, crossover study (n=73, 4 weeks); 3 mg of melatonin/day	Scoring Atopic Dermatitis (SCORAD) index; sleep variables measured by actigraphy, subjective change in sleep and dermatitis, sleep variables measured by polysomnography, nocturnal urinary levels of 6-sulfatoxymelatonin, and serum IgE levels	No severe adverse effects reported	★★★
	L - 6 sprays per day TI - 2 per day	Significant decrease in SCORAD index; significantly improved IgE levels and CSHQ scores	Randomized, double-blind, placebo-controlled study (n=70, 6 weeks); 6 mg of melatonin/day	SCORAD indices; Children's Sleep Habits Questionnaire (CSHQ); pruritus scores, high-sensitivity C-reactive protein (hs-CRP), sleep-onset latency, total sleep time, weight, and BMI	No severe adverse effects reported	★★★

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