

Is Melatonin the “Next Vitamin D”?

**Deanna Minich, PhD, CNS, IFMCP,
Chief Science Officer, Symphony Natural Health**

Disclaimers & Disclosures

Disclaimer

This presentation contains ***educational material only*** and is not intended to take the place of advice from your own physician(s) or to be a means of diagnosing or treating an illness.

Disclosure of Financial Relationships

- **Chief Science Officer** (independent contractor), Symphony Natural Health, manufacturer of Herbatonin[®], a phytomelatonin made from alfalfa, rice, and chlorella.
- **Speaker:** Metagenics, Genova Diagnostics, others
- **Educator:** University of Western States, Institute for Functional Medicine, Institute for Brain Potential
- **Stock options/Stockholder:** Genexa Health

Off-Label Usage

- None

Objectives

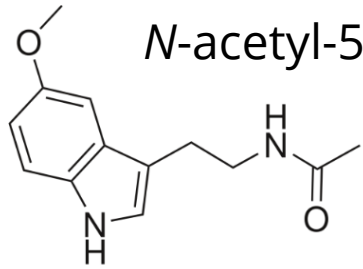
- Understand the similarities and differences between melatonin and vitamin D
- Identify dietary and supplemental sources of melatonin
- Cite the scientific evidence to support the role of melatonin beyond sleep benefits
- Apply concepts learned into clinical practice by understanding clinical uses and dosing

Why does it seem that melatonin is always in the news?

Too much of a good thing?

Misinformation continues to grow, raising uncertainty and more questions on uses, dosing, sources, forms, safety, and quality.

- Children overdosing on melatonin gummies
- Melatonin supplements not hitting label claims
- Melatonin is a “hormone”!
- Melatonin causing issues with gut inflammation?
- If you take melatonin, your body stops making it.
- Melatonin causes nightmares.



N-acetyl-5-hydroxytryptamine

Melatonin:
An ancient molecule turned into one of the most popular modern-day supplements

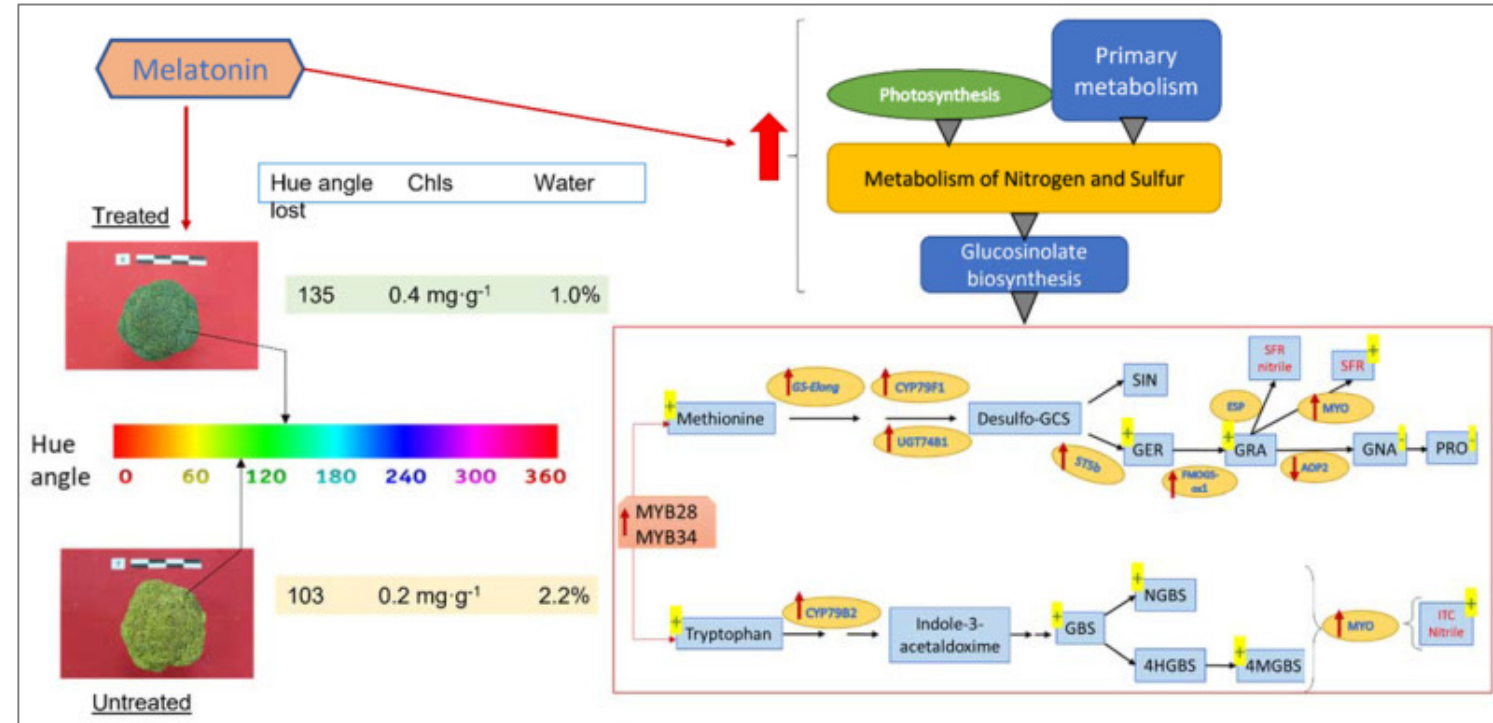


Image credit: Hernández-Ruiz, J.; Ruiz-Cano, D.; Giraldo-Acosta, M.; Cano, A.; Arnao, M.B. Melatonin in *Brassicaceae*: Role in Postharvest and Interesting Phytochemicals. *Molecules* **2022**, *27*, 1523. <https://doi.org/10.3390/molecules27051523CC-BY4.0>.

Review of the Science & Clinical Application of Melatonin

Review

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

Deanna M. Minich ^{1,*}, Melanie Henning ², Catherine Darley ³, Mona Fahoum ⁴, Corey B. Schuler ^{5,6} and James Frame ^{7,8}

- ¹ Department of Human Nutrition and Functional Medicine, University of Western States, Portland, OR 97213, USA
- ² Department of Sports and Performance Psychology, University of the Rockies, Denver, CO 80202, USA
- ³ College of Naturopathic Medicine, National University of Natural Medicine, Portland, OR 97201, USA
- ⁴ School of Naturopathic Medicine, Bastyr University, Kenmore, WA 98028, USA
- ⁵ School of Nutrition, Sonoran University of Health Sciences, Tempe, AZ 85282, USA
- ⁶ Department of Online Education, Northeast College of Health Sciences, Seneca Falls, NY 13148, USA
- ⁷ Natural Health International Pty., Ltd., Sydney, NSW 2000, Australia
- ⁸ Symphony Natural Health, Inc., West Valley City, UT 84119, USA

Abstract: Melatonin has become a popular dietary supplement, most known as a chronobiotic, and for establishing healthy sleep. Research over the last decade into cancer, Alzheimer’s disease, multiple sclerosis, fertility, PCOS, and many other conditions, combined with the COVID-19 pandemic, has led to greater awareness of melatonin because of its ability to act as a potent antioxidant, immune active agent, and mitochondrial regulator. There are distinct similarities between melatonin and vitamin D in the depth and breadth of their impact on health. Both act as hormones, affect multiple systems through their immune-modulating, anti-inflammatory functions, are found in the skin, and are responsive to sunlight and darkness. In fact, there may be similarities between the widespread concern about vitamin D deficiency as a “sunlight deficiency” and reduced melatonin secretion as a result of “darkness deficiency” from overexposure to artificial blue light. The trend toward greater use of melatonin supplements has resulted in concern about its safety, especially higher doses, long-term use, and application in certain populations (e.g., children). This review aims to evaluate the recent data on melatonin’s mechanisms, its clinical uses beyond sleep, safety concerns, and a thorough summary of therapeutic considerations concerning dietary supplementation, including the different formats available (animal, synthetic, and phytomelatonin), dosing, timing, contraindications, and nutrient combinations.

Keywords: melatonin; phytomelatonin; vitamin D; sleep; circadian rhythm; antioxidant; blue light; chronobiotic; chrononutrition; darkness deficiency

1. Introduction

Due to the interest in immune health prompted by the pandemic and its lasting effects on mental health and sleep disturbances, melatonin (*N*-acetyl-5-methoxytryptamine) has become a popular topic of media discussion as well as a research interest, with several publications steadily rising every year. In conjunction with the plethora of scientific discoveries, there has been heightened awareness by consumers and health practitioners for its use as a sleep aid and immune health, most likely resulting in the more than doubling of melatonin dietary supplement sales in the U.S. to USD 821 million in 2020 compared with 2017 [1].

With its surge in popularity, concern about low levels, and correspondingly high dietary supplement sales, it has been generally suggested that melatonin is the “next vitamin D.” Aside from the trends, there are several scientific reasons for this comparison.



Citation: Minich, D.M.; Henning, M.; Darley, C.; Fahoum, M.; Schuler, C.B.; Frame, J. Is Melatonin the “Next Vitamin D”? A Review of Emerging Science: Clinical Uses, Safety, and Dietary Supplements. *Nutrients* **2022**, *14*, 3934. <https://doi.org/10.3390/nu14193934>

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Comment

Comment on Minich et al. Is Melatonin the “Next Vitamin D”? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients* **2022**, *14*, 3934

Ryszard Pluta 

Department of Pathophysiology, Medical University of Lublin, 20090 Lublin, Poland; pluta@imdik.pn.pl or pluta2018@wp.pl



Citation: Pluta, R. Comment on Minich et al. Is Melatonin the “Next Vitamin D”? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients* **2022**, *14*, 3934. <https://doi.org/10.3390/nu15061506>

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I read an article by Minich D.M. et al. [1] with great interest that suggests melatonin as the “next vitamin D”. The authors claim that there are clear similarities between melatonin and vitamin D in their health effects, focusing on the data on melatonin’s mechanisms of action. The article does not provide a clear answer to the question posed in the title. In conclusion, the authors claim that “overall, melatonin is an intriguing compound, not unlike vitamin D, which is pleiotropic in activity and responsive to light-dark cycles” [1]. This study provides an opportunity to discuss the possible effects of natural substances, such as melatonin, in the prevention and/or treatment of neurodegenerative diseases such as post-ischemic brain [2] and Alzheimer’s disease [3]. In this extensive and interesting analysis, I noticed that the authors presented the effect of melatonin on the modification of amyloid, tau protein, and neurotransmission in the brain in a very limited way; although the authors gently touch on this problem, the changes of which are significant in post-ischemic neurodegeneration [2] and in Alzheimer’s disease [3].

There is evidence that melatonin enhances the function of α -secretase and promotes the non-amyloidogenic pathway [4]. Melatonin inhibits the β -secretase function and the expression of the amyloid protein precursor, which affects the production of amyloid [3,4]. It also modulates the activity of the genes of the above proteins [5]. Melatonin inhibits the formation of amyloid oligomers and reduces their toxicity [5]. It interacts directly with amyloid and inhibits its aggregation [6]. Melatonin modifies the secondary structure of amyloid and promotes the conversion of the β -sheet into a random coil, which inhibits amyloid oligomerization and aggregation [3,4].

Research supports melatonin’s ability to prevent, reduce, or remove amyloid plaques from the brain, which is associated with improved spatial learning and memory [7]. A clinical trial has shown that the elimination of amyloid from the brain during sleep is significantly increased compared to the waking brain [8].

Moreover, the ability of melatonin to inhibit the hyperphosphorylation of the tau protein has been well documented in vitro and in vivo studies [4,7]. In a transgenic model of Alzheimer’s disease, melatonin has been shown to lower levels of hyperphosphorylated tau protein, and exercise further reduces levels of amyloid oligomers [5]. In addition, a study of mice injected with β -amyloid peptide 1–42 into the brain to induce Alzheimer’s disease showed that they had decreased hyperphosphorylated tau protein following the administration of melatonin, resulting in improved neuronal viability [9]. Inhibition of the melatonin synthesizing enzyme 5-hydroxyindole-O-methyltransferase has also been shown to result in tau protein hyperphosphorylation and spatial memory impairment, which were reversible with melatonin administration [7].

Melatonin has been shown to influence the neurotransmission of the cholinergic and glutamatergic systems [7,10].

All these studies suggest that melatonin may be effective in preventing the pathology of amyloid and tau protein and modulating the metabolism of the amyloid protein precursor. I have doubts about the suggestion that melatonin is the “next vitamin D”. Does

Reply

Reply to Pluta, R. Comment on “Minich et al. Is Melatonin the “Next Vitamin D”? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients* **2022**, *14*, 3934”

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Citation: Minich, D.M.; Henning, M.; Darley, C.; Fahoum, M.; Schuler, C.B.; Frame, J. Reply to Pluta, R. Comment on “Minich et al. Is Melatonin the “Next Vitamin D”? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients* **2022**, *14*, 3934”. <https://doi.org/10.3390/nu15061507>

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We would like to thank Dr. Pluta for his thoughtful comments [1] on our review article [2] questioning whether melatonin is the “next vitamin D”. Specifically, Dr. Pluta detailed several aspects of melatonin’s functions in brain health and in neurodegenerative processes related to Alzheimer’s disease. From the research he presented, towards the end of these comments, he summarized: “All these studies suggest that melatonin may be effective in preventing the pathology of amyloid and tau protein and modulating the metabolism of the amyloid protein precursor. I have doubts about the suggestion that melatonin is “next vitamin D” [sic]. Does vitamin D have the therapeutic properties described above for melatonin?”

As we stated in our article, there are several similarities between melatonin and vitamin D: “Both act as hormones, affect multiple systems through their immune-modulating, anti-inflammatory functions, are found in the skin, and are responsive to sunlight and darkness. In fact, there may be similarities between the widespread concern about vitamin D deficiency as a “sunlight deficiency” and reduced melatonin secretion as a result of “darkness deficiency” from overexposure to artificial blue light”. In other words, the two have overlapping functions and complementary activities related to light exposure. Additionally, both compounds decline endogenously with age [3,4]. They are associated with increases in age-associated conditions such as cancer [5,6], cognitive impairment/dementia [7–9], autoimmune diseases [10–12], and even cardiovascular disease [13,14], thereby indicating that there may be an increased need state throughout the lifespan. Thus, we suggested that melatonin may even be a necessary “nutrient” similar to vitamin D.

Our suggestion is not that one replaces the other, but that there may be some similarities in function. Furthermore, our intention in this review article was to provide a survey of multiple areas of clinical concern related to how melatonin and vitamin D may be involved in foundational mechanisms associated with a broad spectrum of disease pathologies, including their (1) anti-inflammatory activities [15]; (2) antioxidant potential [16]; and (3) mitochondrial regulation [17].

What Dr. Pluta seems to be asking is how vitamin D compares with melatonin in relation to amyloid and tau protein pathology. In his comment, he cited several studies indicating melatonin’s proficiency in accomplishing many functions related to amyloid metabolism and inhibiting the tau protein’s hyperphosphorylation. While these are important hallmarks of dementia, we would like to offer a fundamental mechanistic view of neurodegenerative diseases involving the three aforementioned mechanisms.

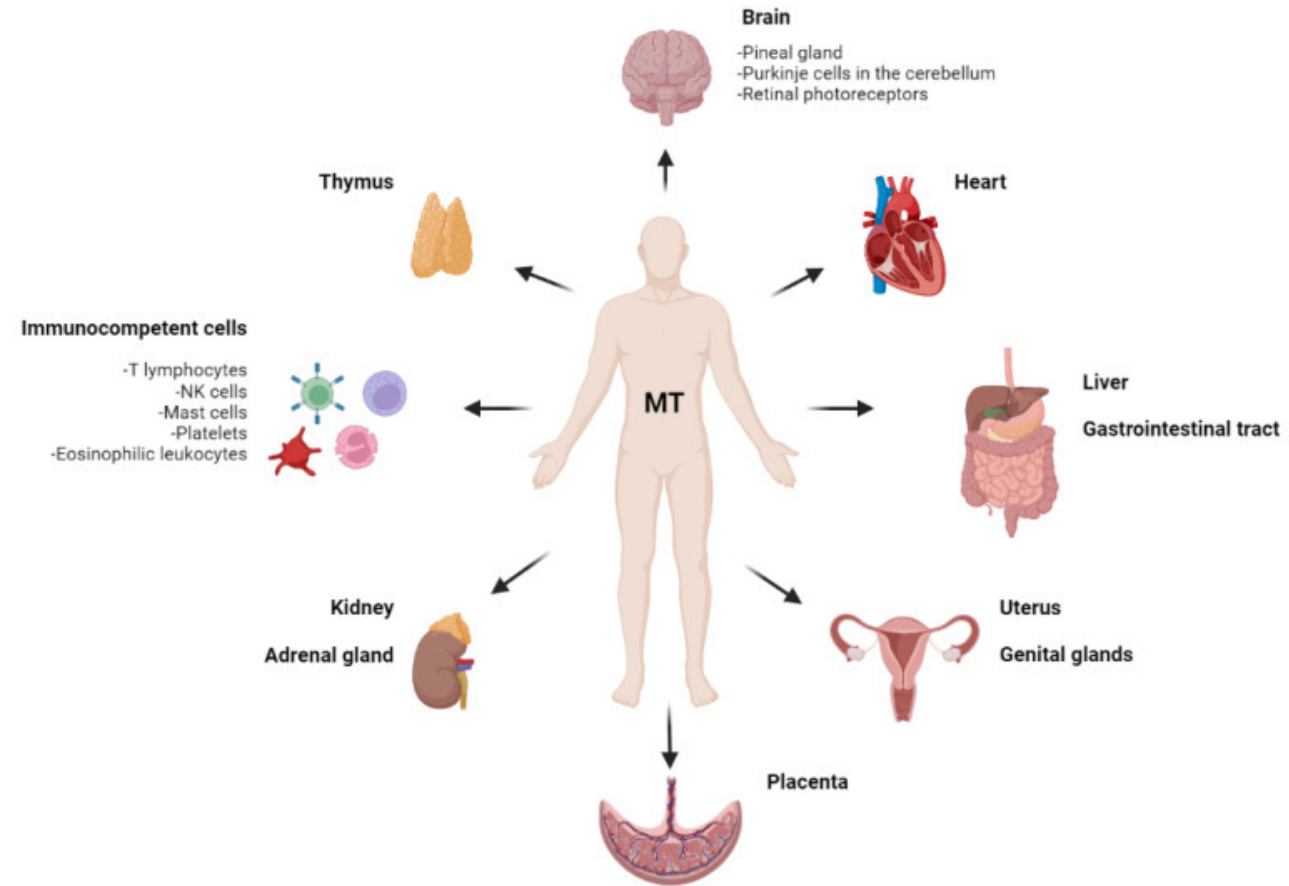
Melatonin: Where is it found?

Widespread in the body: brain, retina, skin, liver, kidney, thyroid, thymus, skeletal muscle, and reproductive system among others.

Present in almost all body fluids, including amniotic fluid, breast milk, cerebrospinal fluid, feces, synovial fluid, saliva, and urine.

Cells have melatonin receptors in the membrane, known as MT1 and MT2, and three nuclear receptors, ROR-alpha, -beta and -gamma.

Two main organs produce melatonin: the pineal gland and the gut.



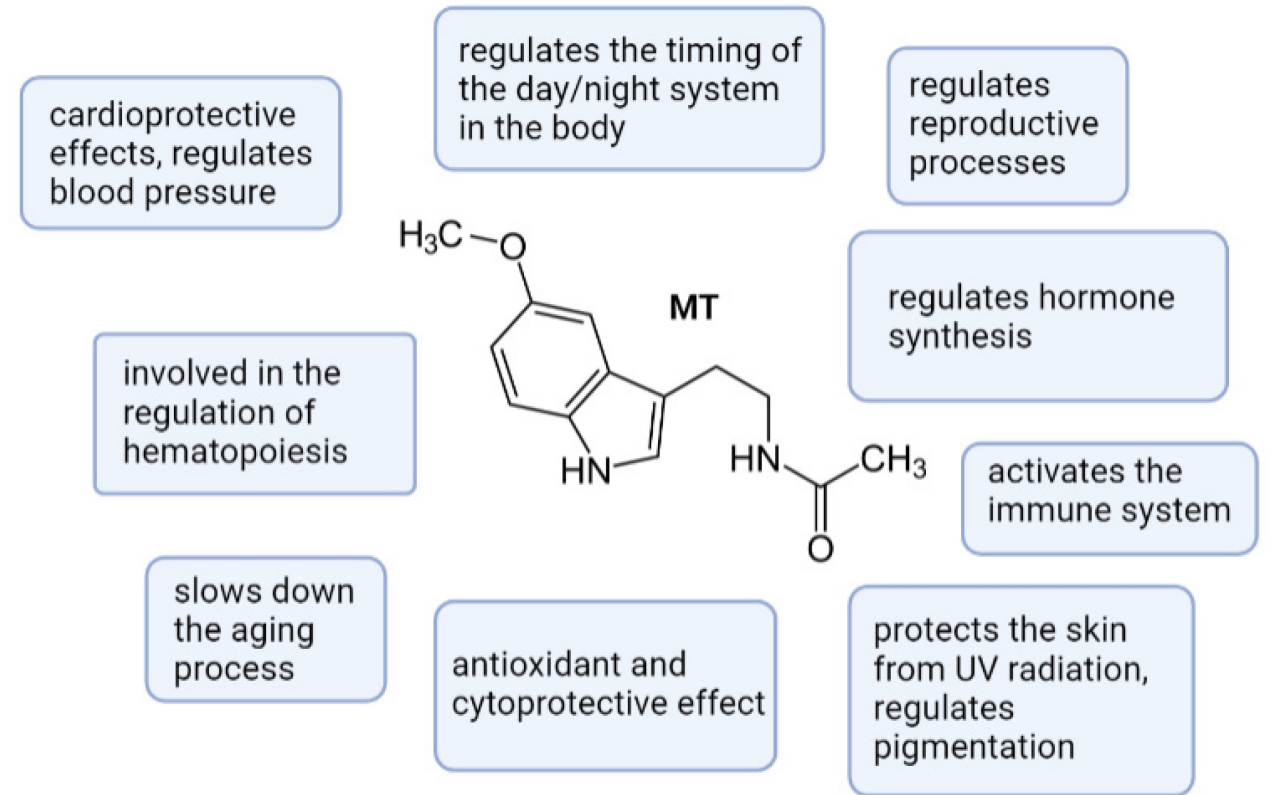
Kvetnoy I, Ivanov D, Mironova E, Evsyukova I, Nasyrov R, Kvetnaia T, Polyakova V. Melatonin as the Cornerstone of Neuroimmunoendocrinology. *Int J Mol Sci.* 2022 Feb 6;23(3):1835. doi: 10.3390/ijms23031835. PMID: 35163757; PMCID: PMC8836571.

Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients.* 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539. PMID: [35956837](https://pubmed.ncbi.nlm.nih.gov/35956837/)

Functions translate into physiology:

Melatonin plays a role in these processes

- Temperature
- Sleep/wake cycle
- Cortisol secretion
- Blood pressure
- Cell proliferation
- Immune system activity
- Gut microbiome regulation
- Neurotrophic factor & protector: promotes neuronal differentiation, proliferation, and neuronal survival in newly formed neurons; role in neuroglymphatic fluid



Kvetnoy I, Ivanov D, Mironova E, Evsyukova I, Nasyrov R, Kvetnaia T, Polyakova V. Melatonin as the Cornerstone of Neuroimmunoendocrinology. *Int J Mol Sci.* 2022 Feb 6;23(3):1835. doi: 10.3390/ijms23031835. PMID: 35163757; PMCID: PMC8836571. CC-BY 4.0

Low Melatonin is Associated with Different Conditions

Without apparent SCN degeneration:

- Aging
- Dementia
- Some mood disorders
 - Schizophrenia
 - Obsessive-compulsive disorder
- Severe pain
 - Fibromyalgia
- Certain types of cancer
- Insulin resistance
- Type 2 diabetes
- Migraine
- Sleep disturbance

Dysfunctional signal transduction through receptors:

- Parkinson's disease
- Alzheimer's disease

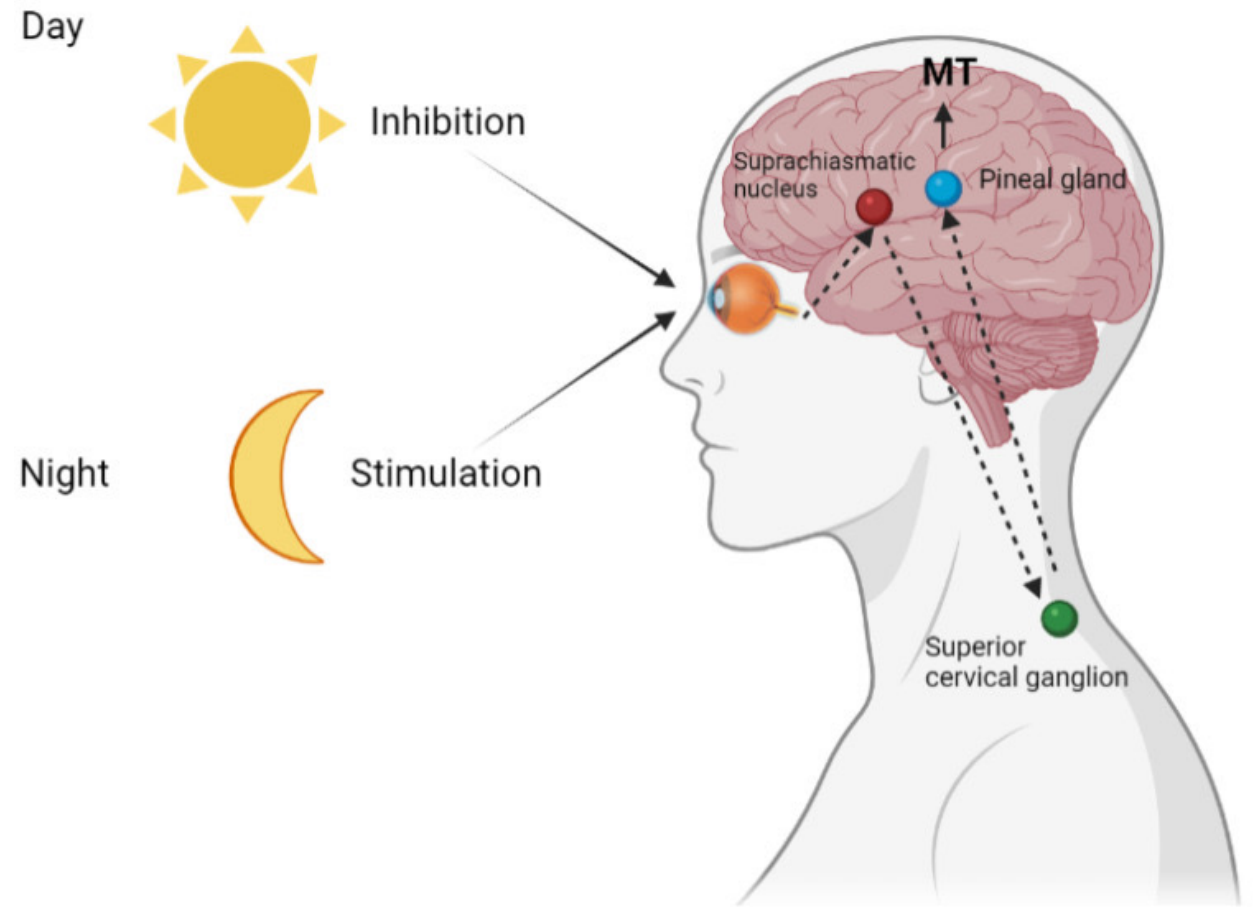
Possible involvement of gene variants:

- Type 2 diabetes
- Rheumatoid arthritis
- Adolescent idiopathic scoliosis
- PCOS

Hardeland R. Neurobiology, pathophysiology, and treatment of melatonin deficiency and dysfunction. *ScientificWorldJournal*. 2012;2012:640389. doi: 10.1100/2012/640389. Epub 2012 May 2. PMID: 22629173; PMCID: PMC3354573.

Melatonin as hormone: Melatonin is produced by the pineal gland to help modulate circadian rhythm

It can help with falling asleep faster, but
not necessarily staying asleep longer.

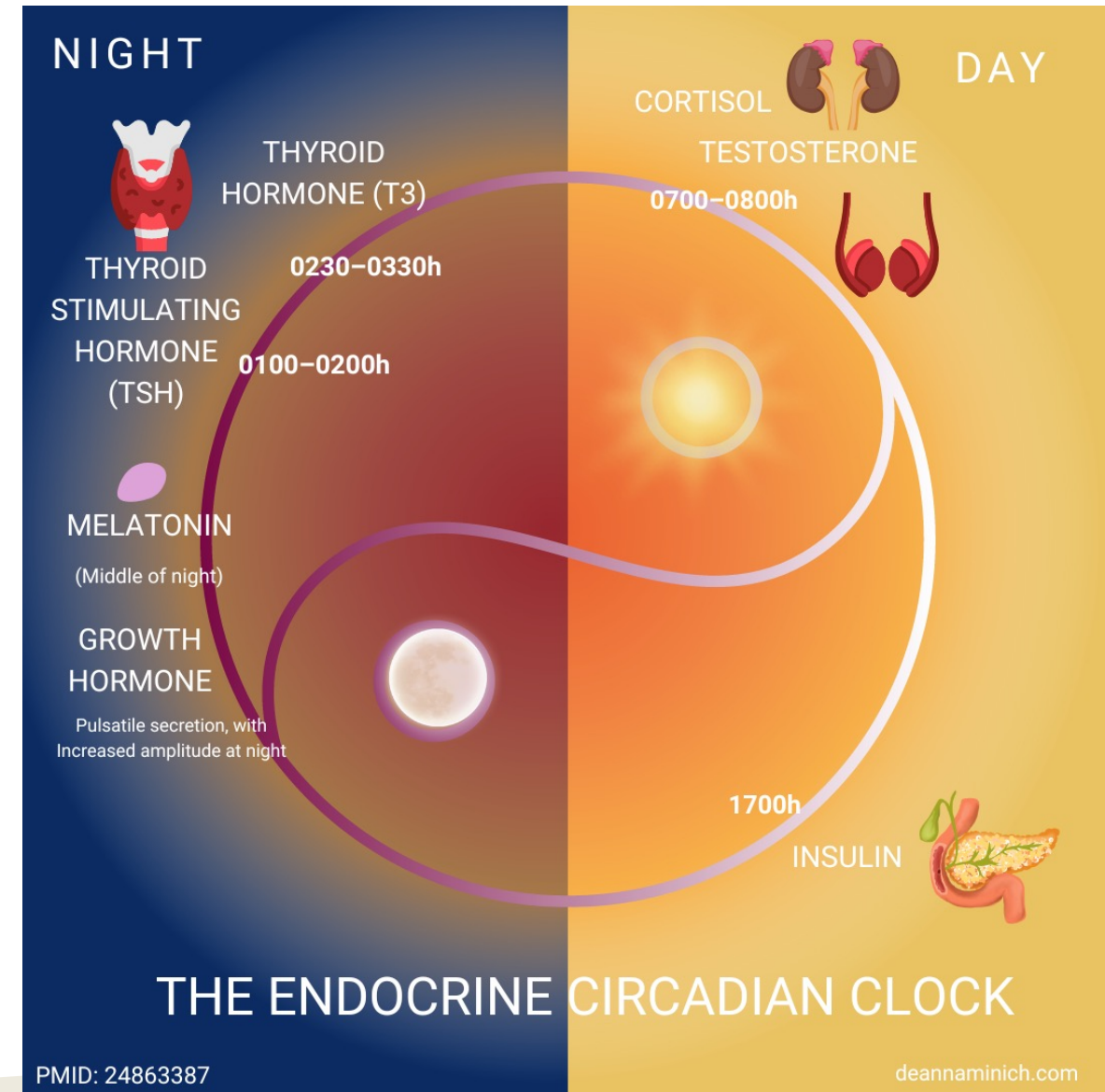


Kvetnoy I, Ivanov D, Mironova E, Evsyukova I, Nasyrov R, Kvetnaia T, Polyakova V. Melatonin as the Cornerstone of Neuroimmunoendocrinology. *Int J Mol Sci.* 2022 Feb 6;23(3):1835. doi: 10.3390/ijms23031835. PMID: 35163757; PMCID: PMC8836571. CC-BY 4.0

The Circadian Clock: Connector to Hormonal Communication

- An animal study identified that there was heightened CLOCK gene activity at time preceding dawn and dusk (“transcriptional rush hours”)
- ~ 7% to 13% of a cell’s transcriptome is under circadian control [PMID: **24863387**]
- Liver has one of the highest levels of circadian genes (>3000).
- “Chronotherapeutics”

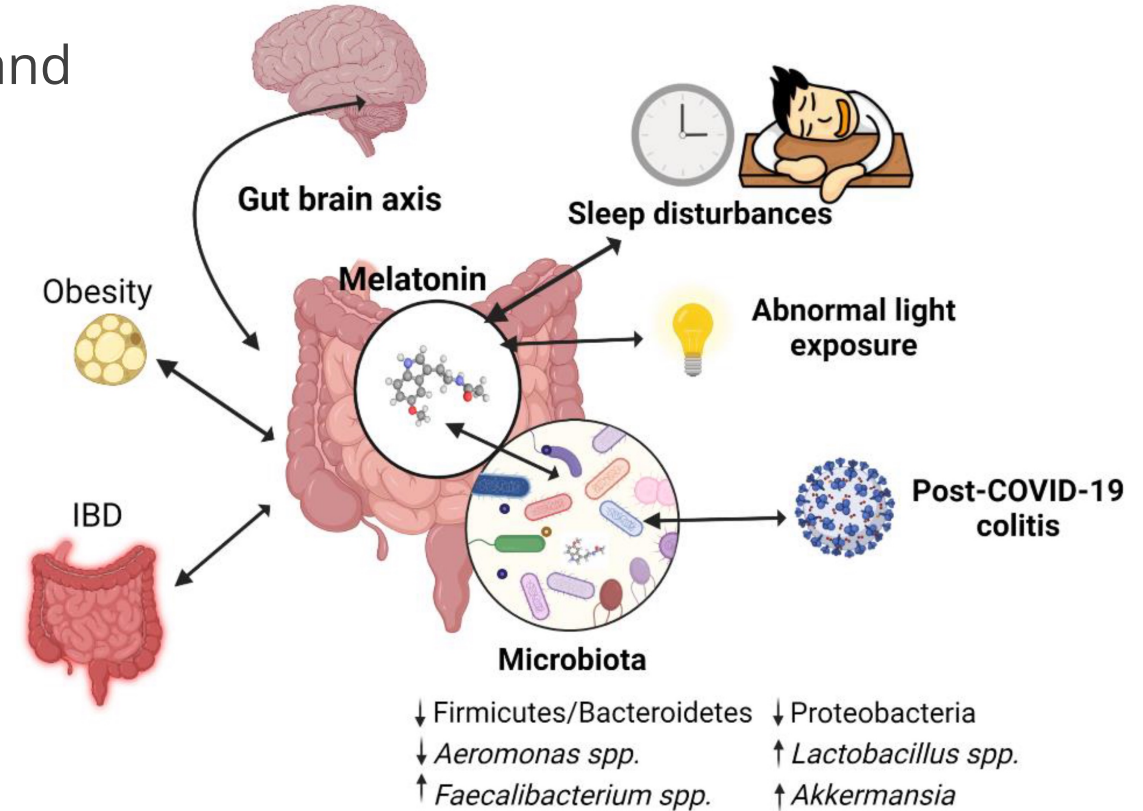
Zhang R, Lahens NF, Ballance HI, Hughes ME, Hogenesch JB. A circadian gene expression atlas in mammals: implications for biology and medicine. Proc Natl Acad Sci U S A. 2014 Nov 11;111(45):16219-24. doi: 10.1073/pnas.1408886111. Epub 2014 Oct 27. PMID: 25349387; PMCID: PMC4234565.



The gastrointestinal tract:

One of the greatest concentrations of extra-pineal melatonin

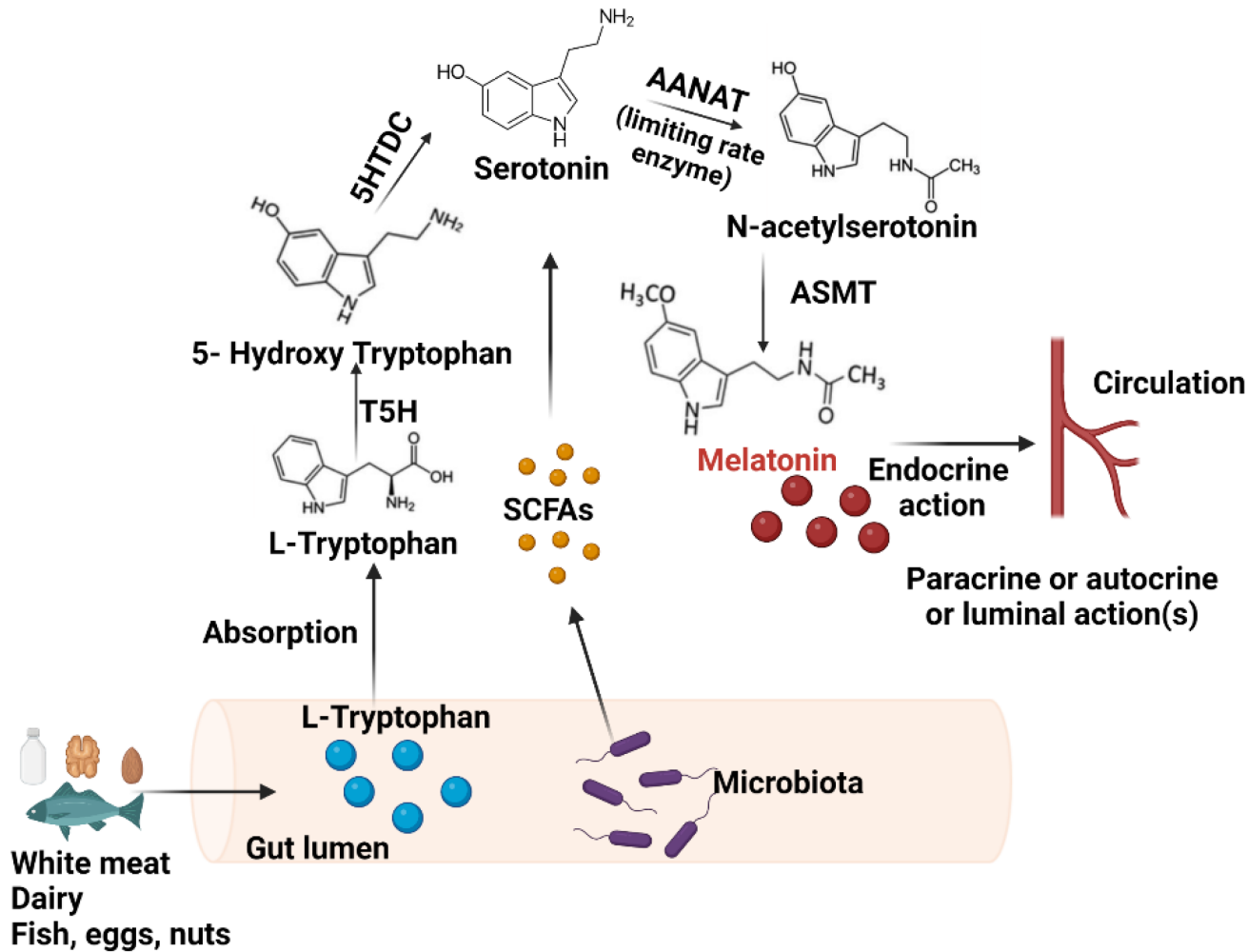
- 400-times-higher concentration than the pineal gland
- Melatonin has been documented in every compartment of the gastrointestinal tract (GIT):
 - Lumen
 - Mucosa
 - Muscularis
- And in every segment:
 - Esophagus to rectum
- Possible functions:
 - Immunity
 - Gastrointestinal secretion
 - Intestinal motility
 - Gut microbiome modulation



Ilesanu, M.I.; Zahiu, C.D.M.; Dogaru, I.-A.; Chitimus, D.M.; Pircalabioru, G.G.; Voiculescu, S.E.; Isac, S.; Galos, F.; Pavel, B.; O'Mahony, S.M.; Zagrean, A.-M. Melatonin–Microbiome Two-Sided Interaction in Dysbiosis-Associated Conditions. *Antioxidants* **2022**, *11*, 2244. <https://doi.org/10.3390/antiox11112244>. CC-BY.

The gastrointestinal tract:

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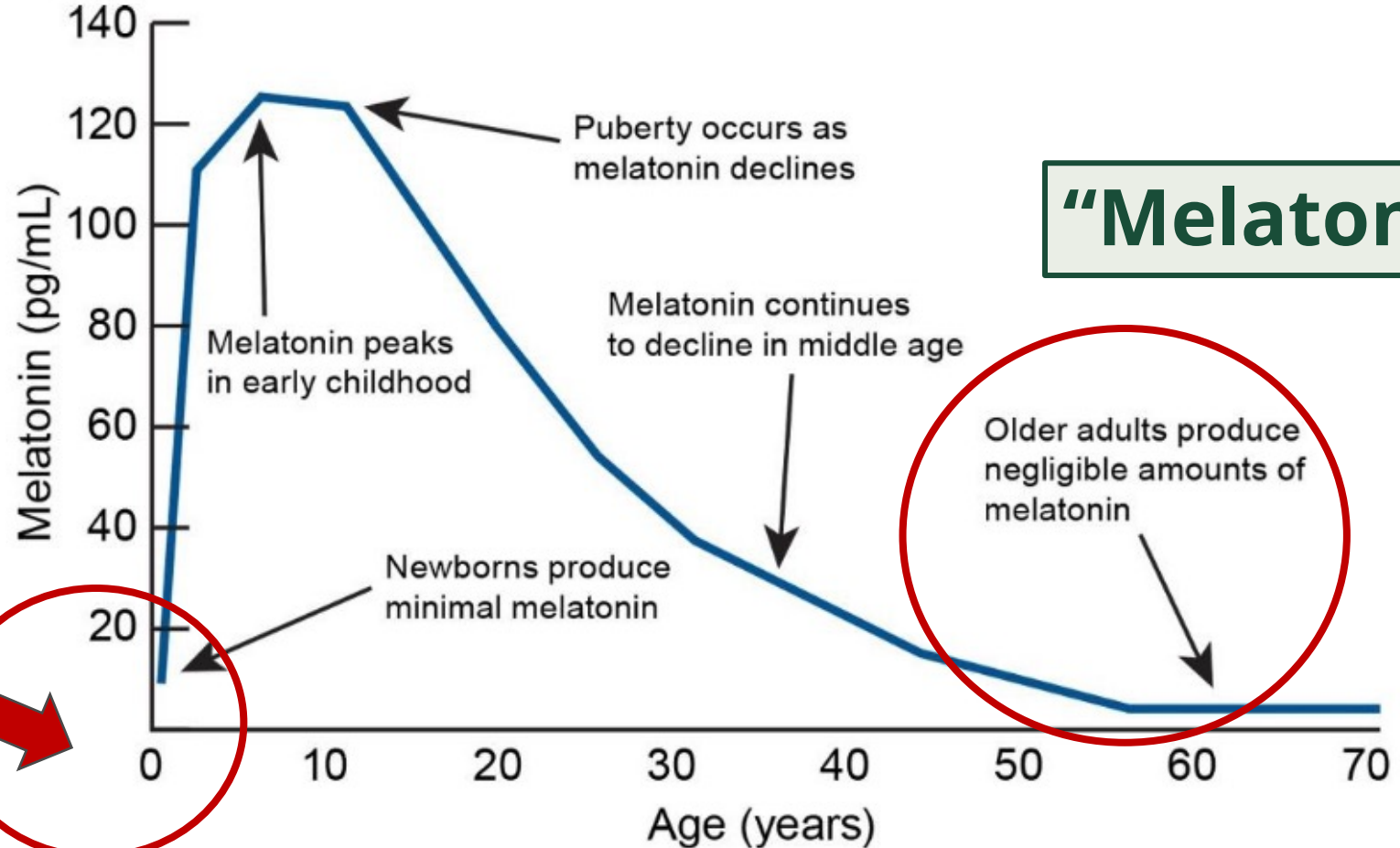
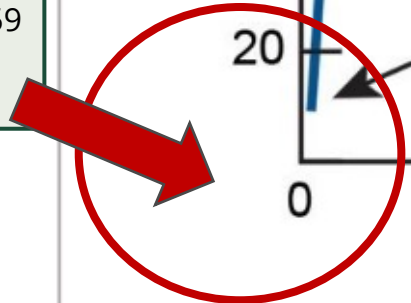
“SCFAs produced in the intestinal lumen stimulate the ECs to release serotonin and enhance MT production.”

Iesanu, M.I.; Zahiu, C.D.M.; Dogaru, I.-A.; Chitimus, D.M.; Pircalabioru, G.G.; Voiculescu, S.E.; Isac, S.; Galos, F.; Pavel, B.; O'Mahony, S.M.; Zagrean, A.-M. Melatonin–Microbiome Two-Sided Interaction in Dysbiosis-Associated Conditions. *Antioxidants* **2022**, *11*, 2244. <https://doi.org/10.3390/antiox11112244>. CC-BY.

The Functional Medicine “Melatonin Timeline”

“Maternal melatonin”

Li F, Lai J, Ma F, Cai Y, Li S, Feng Z, Lu Z, Liu X, Ke Q, Hao H, Xiao X. Maternal melatonin supplementation shapes gut microbiota and protects against inflammation in early life. *Int Immunopharmacol.* 2023 May 29;120:110359. doi: 10.1016/j.intimp.2023.110359 . Epub ahead of print. PMID: 37257272.



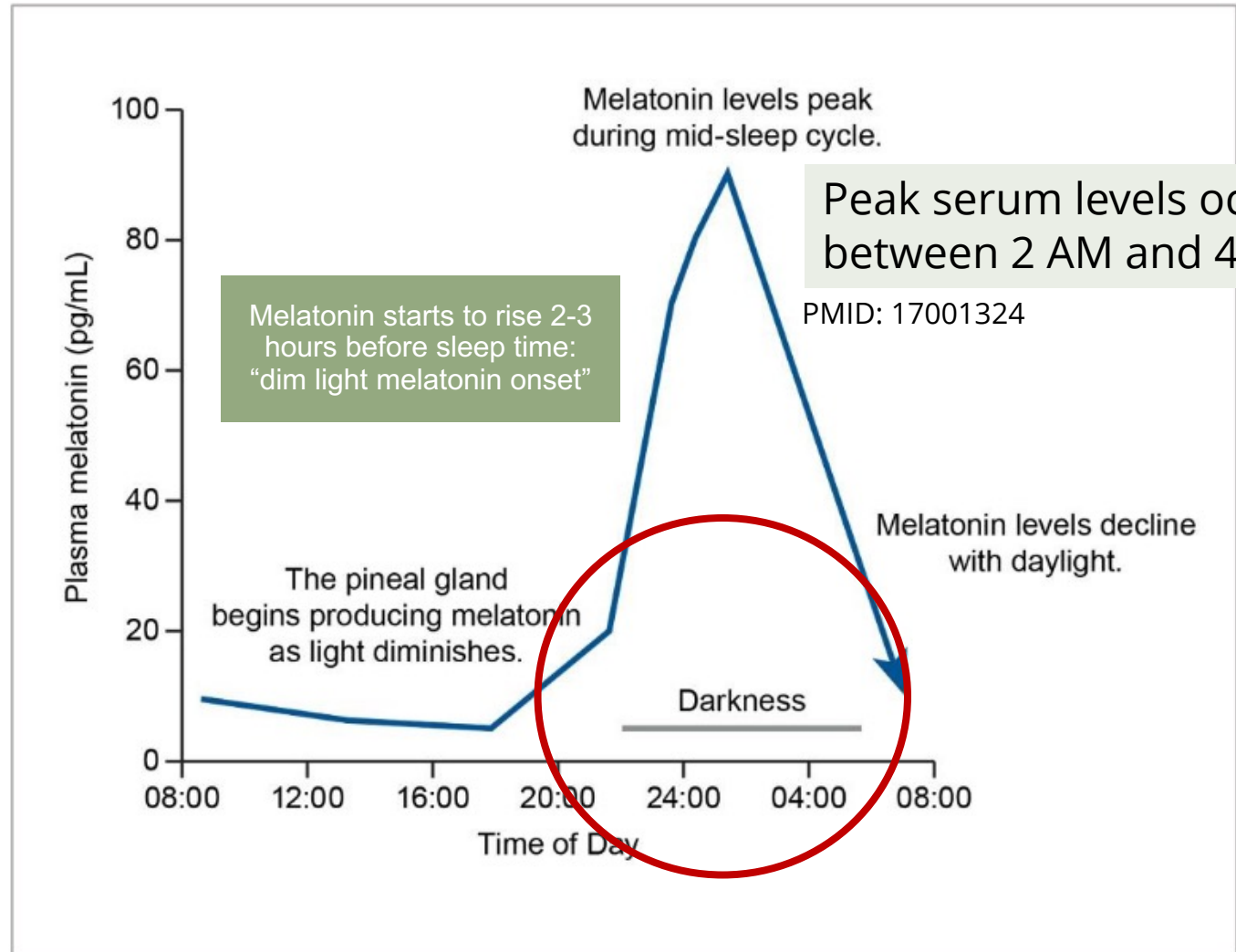
“Melatoninpause”

Graphic modified from:

Grivas T.B., Sawidou O.D. Melatonin the “light of night” in human biology and adolescent idiopathic scoliosis. *Scoliosis.* 2007;2:6. doi: 10.1186/1748-7161-2-6.

Diurnal production of melatonin:

Melatonin as the “darkness hormone”



Graphic modified from:

Grivas T.B., Savvidou O.D. Melatonin the “light of night” in human biology and adolescent idiopathic scoliosis. *Scoliosis*. 2007;2:6. doi: 10.1186/1748-7161-2-6.

Both Day & Night Needed for Healthy Melatonin

- Before electric lighting, humans were exposed to high-intensity (>300 lux) and dim (<30 lux) light during the day and night, respectively.
- Currently, most people exposed to electric light during the day and night.
- Morning or afternoon bright light exposure have been shown in studies to increase nocturnal melatonin levels.
- Early bright light can also advance the onset of melatonin.
- LED and other bulbs can suppress melatonin by over 50%.
 - One study showed that 30 lux at night suppressed endogenous melatonin by >50% [PMID: **31138694**].
- Candlelight has negligible suppressive effect on melatonin levels.

References: PMID: **28245865**; PMID: **9121707**; PMID: **31138694**; PMID: **11507175**

Light Exposure Recommendations

Daytime light recommendations for indoor environments

- 250 lux, preferably daylight, or blue-enriched light
- Try to work in front of a window with natural light if indoors (4479 lux vs. 200 lux; average outdoor lux 10-20k)

Evening light recommendations for residential and other indoor environments

- For 3 hours before bed, use 10 lux, minimal blue light
- Use dimmers and reduced intensity LED bulbs (warmer hue)

Nighttime light recommendations for the sleep environment

- Maximum 1 lux, but up to 10 lux if there needs to be activity
- Use an app to assess to know that you've got the right amount of light

Brown TM, Brainard GC, Cajochen C, Czeisler CA, Hanifin JP, Lockley SW, et al. (2022) Recommendations for daytime, evening, and nighttime indoor light exposure to best support physiology, sleep, and wakefulness in healthy adults. PLoS Biol 20(3): e3001571.

Artificial light at night (ALAN): An overlooked endocrine disruptor

Ouyang JQ, Davies S, Dominoni D. Hormonally mediated effects of artificial light at night on behavior and fitness: linking endocrine mechanisms with function. *J Exp Biol.* 2018 Mar 15;221(Pt 6):jeb156893. doi: 10.1242/jeb.156893. PMID: 29545373; PMCID: PMC5897701.

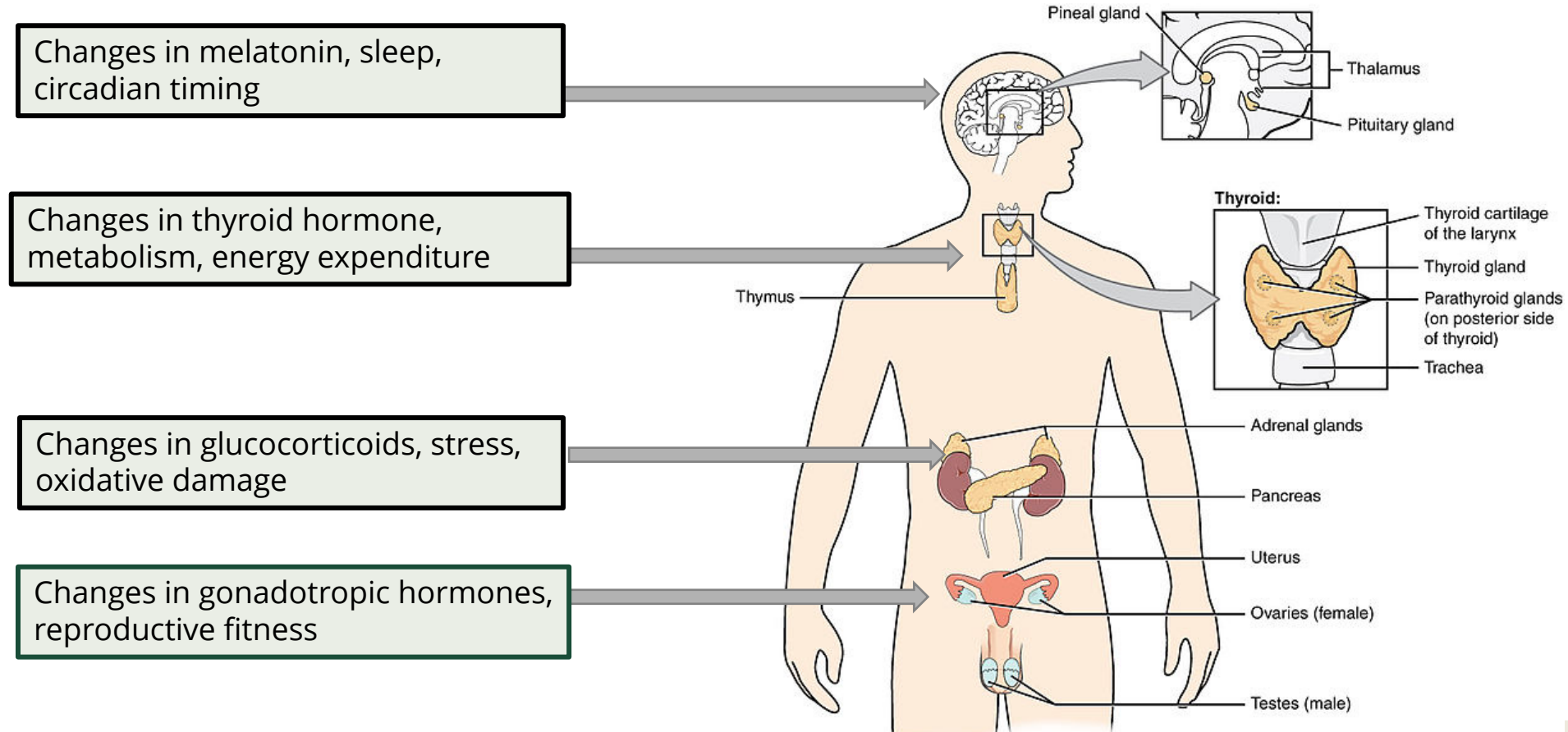


Image Credit: Illustration from Anatomy & Physiology, OpenStax College, Connexions Web site. <http://cnx.org/content/col11496/1.6/>, Jun 19, 2013. CC BY 3.0.

<https://creativecommons.org/licenses/by/3.0/> https://commons.wikimedia.org/wiki/File:1801_The_Endocrine_System.jpg#/media/File:1801_The_Endocrine_System.jpg

Eye Color Can Change Sensitivity to Light at Night Effects on Melatonin

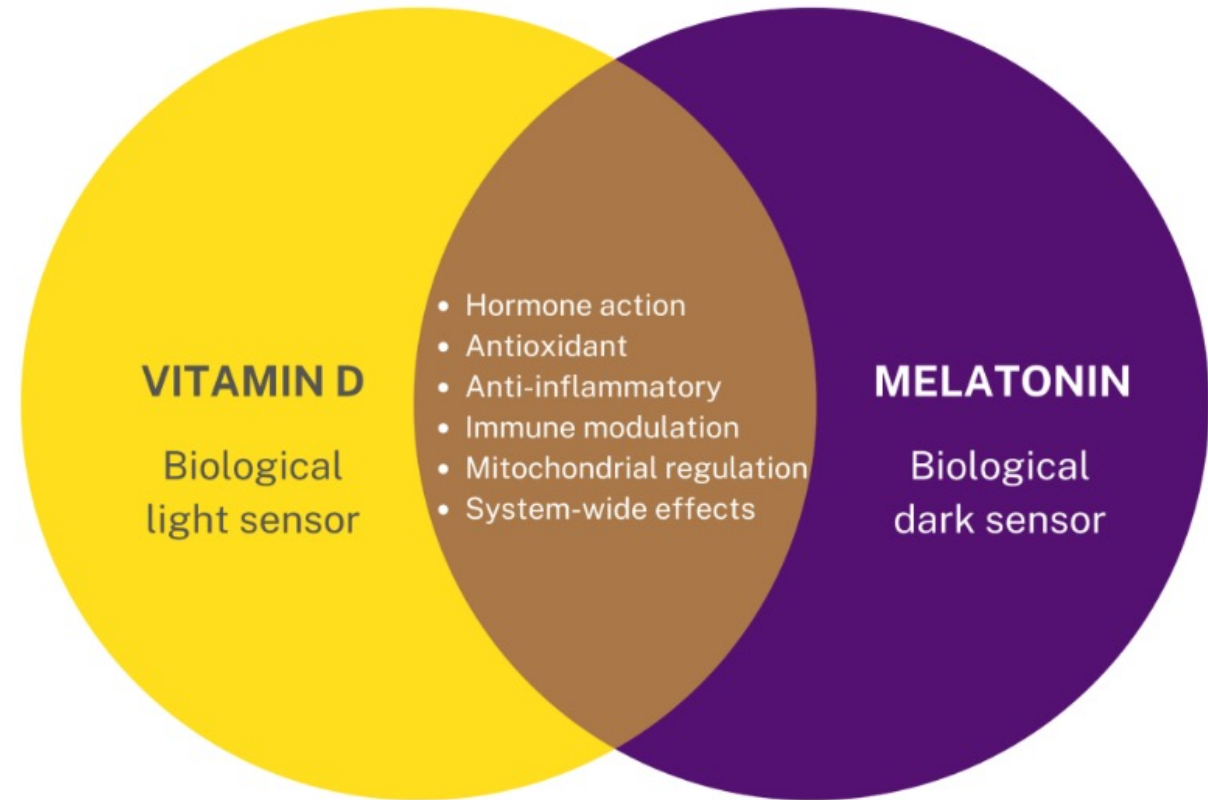
- Those with light-colored eyes will be more susceptible (~17%) to the suppressive effects of blue light at night on endogenous melatonin synthesis compared with those who have dark-colored eyes [1].
- However, those with light-colored eyes are less prone to Seasonal Affective Disorder (SAD) [2].

References:

1. Higuchi S, Motohashi Y, Ishibashi K, Maeda T. Influence of eye colors of Caucasians and Asians on suppression of melatonin secretion by light. *Am J Physiol Regul Integr Comp Physiol*. 2007 Jun;292(6):R2352-6. doi: 10.1152/ajpregu.00355.2006. Epub 2007 Mar 1. PMID: 17332164.
2. Goel N, Terman M, Terman JS. Depressive symptomatology differentiates subgroups of patients with seasonal affective disorder. *Depress Anxiety*. 2002;15(1):34-41. doi: 10.1002/da.1083. PMID: 11816051.

We've long come to know about sunlight deficiency.

Do we also have a "darkness deficiency"?



Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*. 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.

How do you know if your patients have darkness deficiency?



DO YOU HAVE DARKNESS DEFICIENCY?

Darkness Deficiency is a term defined in the [scientific literature](#) that relates to the overabundance of artificial light at night in one's environment, disrupting the circadian rhythm balance of hormones, such as melatonin.

Directions: Answer each question using your typical daily routine as a reference of what you are doing or have done over the past month.

HOME

Are you in well-lit rooms in your home between dusk and dawn?

Weekly: 5 or more days (2 points) / 2-4 days (1 point) / 0-1 day (0 points)

Are you on your computer, iPad, or other electronic devices after 7 PM without any blue-light blocking filter?

Weekly: 5 or more days (2 points) / 2-4 days (1 point) / 0-1 day (0 points)

Do you watch television in the evening after 7 PM?

Weekly: 5 or more days (2 points) / 2-4 days (1 point) / 0-1 day (0 points)

BEDROOM (OR WHERE YOU SLEEP)

Are you using your smartphone or another electronic device (s) while in bed before going to sleep?

Weekly: 5 or more days (2 points) / 2-4 days (1 point) / 0-1 day (0 points)

Do you read books in bed before going to sleep?

Weekly: 5 or more days (2 points) / 2-4 days (1 point) / 0-1 day (0 points)

Do you keep lights in your bedroom on when you are sleeping, even just a night light?

Weekly: 5 or more days (2 points) / 2-4 days (1 point) / 0-1 day (0 points)

Do you have an LED alarm clock next to your bed?

Weekly: 5 or more days (2 points) / 2-4 days (1 point) / 0-1 day (0 points)

Do you have appliances in your bedroom that emit light throughout the night (e.g., smoke alarm, air filter)?

Weekly: 5 or more days (2 points) / 2-4 days (1 point) / 0-1 day (0 points)

Does your bedroom get light from outside at night (e.g., streetlights, moonlight)?

Weekly: 5 or more days (2 points) / 2-4 days (1 point) / 0-1 day (0 points)

WORK & OTHER ACTIVITIES

Do you drive or travel after 7 PM in an airplane, train, or bus for extended periods (over 45 mins)?

Weekly: 5 or more days (2 points) / 2-4 days (1 point) / 0-1 day (0 points)

Do you do shift work (i.e., working in the evening, sleeping during the day)?

Weekly: 5 or more days (2 points) / 2-4 days (1 point) / 0-1 day (0 points)

Do you spend more than 2 hours in well-lit areas after 7 PM (e.g., a shopping mall, sporting events, gym)?

Weekly: 5 or more days (2 points) / 2-4 days (1 point) / 0-1 day (0 points)



Overall Scoring:

Highly Darkness Deficient:	19-24
Somewhat Darkness Deficient:	13-18
Only Mildly Darkness Deficient:	7-12
Darkness Sufficient:	1-6

What you can do to become "darkness sufficient":

- Ensure your sleeping room is entirely dark (use heavy blinds or curtains) or use an eye mask while sleeping
- Wear blue-light-blocking glasses if on devices in the evening
- Turn off, or at least minimize, artificial lighting 3 hours before bedtime
- Use blue-light blocking screens on devices (available as apps)
- Choose red light when possible
- Choose lighting that can be dimmed (either automatically on a timer or manually)
- Cover up or unplug brightly lit appliances
- Keep a regular sleep-wake schedule that shifts slightly with the seasons

What lights are acceptable at night:

- Fire in fireplace
- Candles
- Red lights (red rather than blue-enriched bulbs)
- Salt lamps

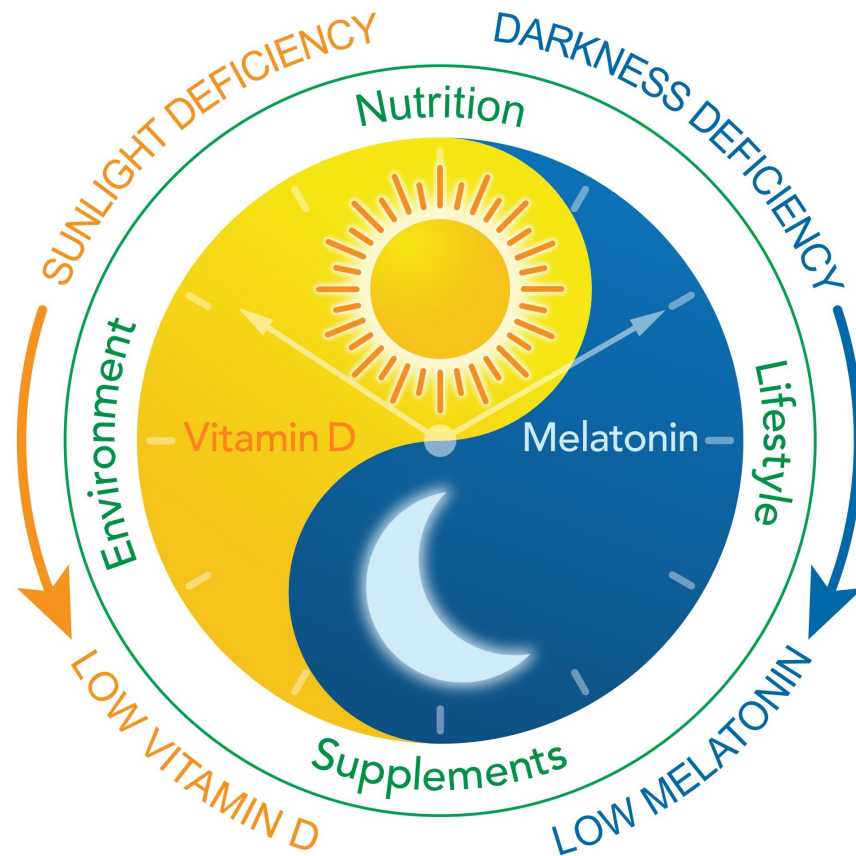
References:

1. Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*. 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.
2. Gooley JJ, Chamberlain K, Smith KA, Khalsa SB, Rajaratnam SM, Van Reen E, Zeitzer JM, Czeisler CA, Lockley SW. Exposure to room light before bedtime suppresses melatonin onset and shortens melatonin duration in humans. *J Clin Endocrinol Metab*. 2011 Mar;96(3):E463-72. doi: 10.1210/jc.2010-2098. Epub 2010 Dec 30. PMID: 21193540; PMCID: PMC3047226.
3. Brown TM, Brainard GC, Cajochen C, Czeisler CA, Hanifin JP, et al. Recommendations for daytime, evening, and nighttime indoor light exposure to best support physiology, sleep, and wakefulness in healthy adults. *PLOS Biology* 2022;20(3).
4. Stothard ER, McHill AW, Depner CM, Birks BR, Moehrlan TM, Ritchie HK, Guzzetti JR, Chinoy ED, LeBourgeois MK, Axelsson J, Wright KP Jr. Circadian Entrainment to the Natural Light-Dark Cycle across Seasons and the Weekend. *Curr Biol*. 2017 Feb 20;27(4):508-513. doi: 10.1016/j.cub.2016.12.041. Epub 2017 Feb 2. PMID: 28162893; PMCID: PMC5335920.

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Melatonin and vitamin D:

Connection through the circadian cycle



The "circadian system," which, in humans, includes the genes responsive to the 24-h cycle (about 3,000 genes), their output, and the cascade of their signals.

PMID: 21193540, PMID: 33304237

Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*. 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.

Comparison between vitamin D & melatonin:

Are they both essential nutrients?

Feature	Vitamin D	Melatonin
Basic functions	Considered to act as a hormone; Antioxidant; Anti-inflammatory compound; Mitochondrial regulator	Hormone; Antioxidant; Anti-inflammatory compound; Mitochondrial regulator
Bodily systems	All	All
Relationship with light	Light (UV) is needed for synthesis.	Darkness is needed for synthesis.
Synthesis	Synthesized in the skin, activated by liver and kidney	Synthesized in the skin and many other tissues; Produced by pineal gland and gut (enterochromaffin cells)
Seasonal variation	Yes	Yes [28]
Chemical nature	Lipid-soluble	Amphiphilic
Transport	Crosses blood–brain barrier	Crosses blood–brain barrier
Nutritional status	Greater risk of insufficiency and/or deficiency with increasing age	Greater risk of insufficiency and/or deficiency with increasing age
Obtained from dietary sources	Yes	Yes
Biological need may change depending on lifestyle	Yes	Yes

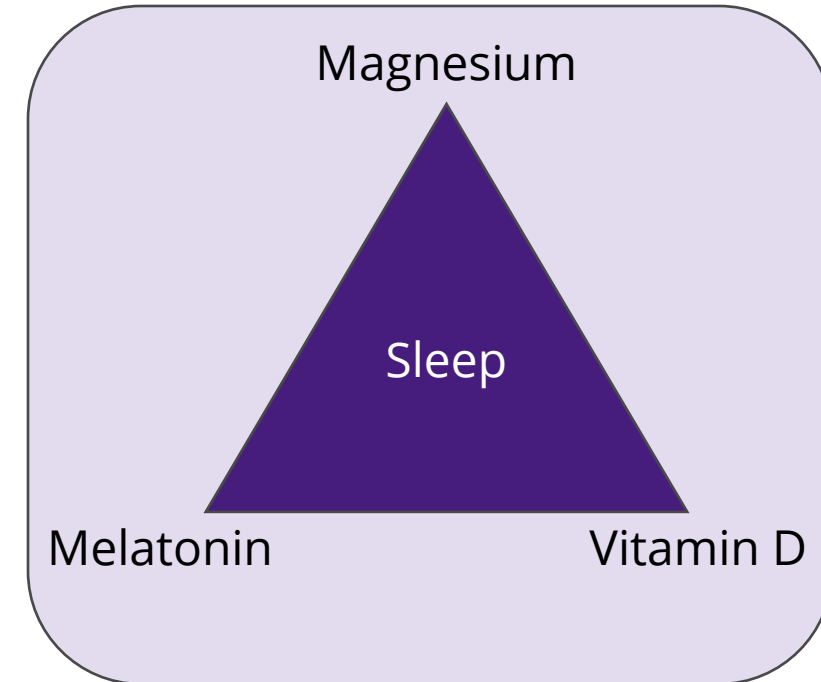
Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*. 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.

Vitamin D, melatonin, and sleep:

What is the connection?

- N=79 women (18-49 yo)
- Blood samples (vitamin D and melatonin)
- Sleep questionnaire (Pittsburgh Sleep Quality Index, PSQI)
- Results showed:
 - A majority of the women were either vitamin D deficient (64.6%) or insufficient (21.5%).
 - Higher melatonin levels were associated with reduced risk for vitamin D deficiency.
 - There was a positive correlation between serum melatonin and 25-OH vitamin D3.

Takeaway: Vitamin D levels are correlated with melatonin levels, and there may be a connection between them and sleep disorders.



İncedal Sonkaya Z, Yazgan B, Kurtgöz A, Demir AD, İncedal Irgat S. Examination of correlations between vitamin D and melatonin levels with sleep among women aged 18-49 years. Cent Eur J Public Health. 2023 Mar;31(1):19-24. doi: 10.21101/cejph.a7324. PMID: 37086416.

It's too simple to limit melatonin to being a hormone:

Melatonin is the ultimate “multi-tasker”.

“Melatonin has recently been reclassified as a multitasking molecule, and not exclusively a hormone, due to the finding about the existence of essential enzymes for its synthesis and the presence of melatonin receptors in many tissues and, also, the discovery of its antioxidant and generalized anti-inflammatory properties.”

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8226101/>

The six main functions of melatonin:

1. Amphiphilic antioxidant
2. Anti-inflammatory agent
3. Nerve growth factor and potential active in glymphatic flux
4. Liquid-liquid phase separation related to viral replication
5. Chronobiotic
6. Mitochondrial regulator

The six main functions of melatonin:

When you know how it works, you can understand how to apply it clinically

1. Amphiphilic Antioxidant:

- One of the most potent, ubiquitous, and unique antioxidants [1, 2]
 - One molecule of melatonin and its metabolites can scavenge up to 10 free radicals
 - Twice as effective as vitamin E; 5x more potent than glutathione at neutralizing hydroxyl radicals [6].
 - Has both water- and fat-soluble properties, making it accessible throughout the body and able to perform several levels of antioxidant activity
- It can prevent, scavenge, and repair oxidative stress.
- It may lead to the production of more antioxidants, like glutathione, as shown in animal studies [3, 4].
- Superoxide dismutase, glutathione peroxidase, and glutathione reductase are stimulated by melatonin [5]
- Melatonin is unique in that it is a hormone that can flex to being an antioxidant. Other hormones not known to have this effect [6].

1. PMID: 17198536. 2. PMID: 36235587 3. <https://pubmed.ncbi.nlm.nih.gov/16816830/>. 4. <https://doi.org/10.3390/antiox10121885>; 5. PMID: [34177952](https://pubmed.ncbi.nlm.nih.gov/34177952/) 6. Reiter R. and Robinson J. Melatonin. Bantam Publishers, 1995.

The six main functions of melatonin:

When you know how it works, you can understand how to apply it clinically

Oxidative stress reduction at nighttime

It appears that pineal gland-derived melatonin is highest at night (about 2-4 AM; PMID: [35956837](#)), which is also when some of the oxidative stress enzymes are also high and subject to circadian influence:

- Superoxide dismutase (SOD)
- Catalase (CAT)
- Glutathione reductase (R-GSSG)
- Glutathione (GSH)

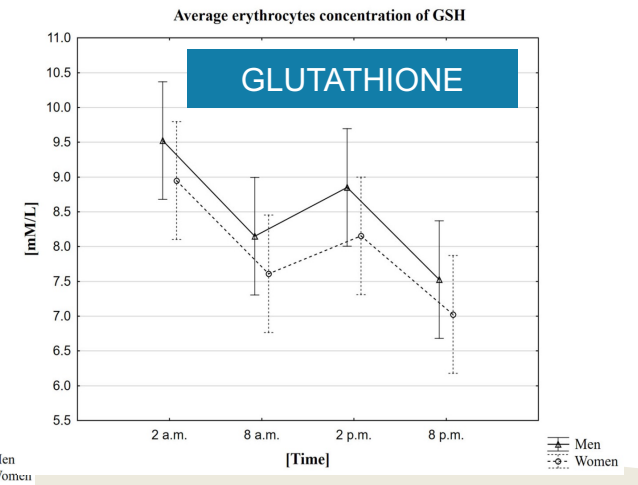
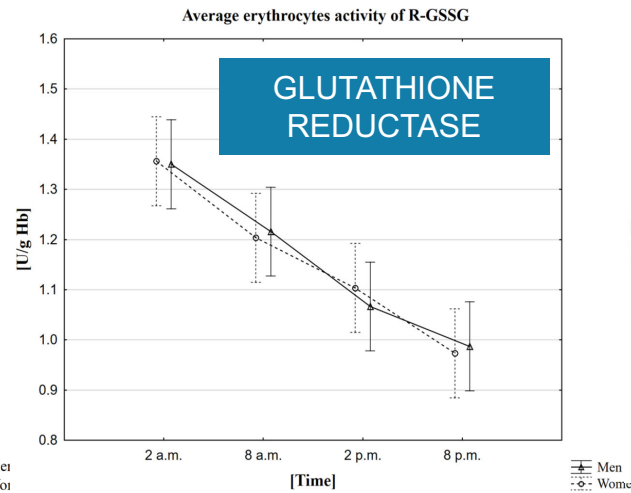
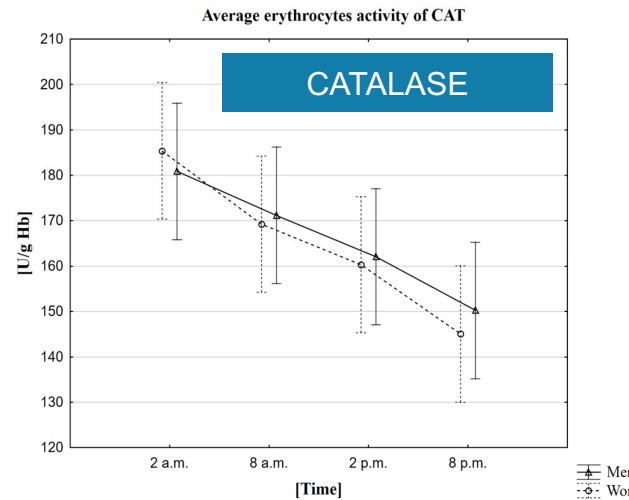
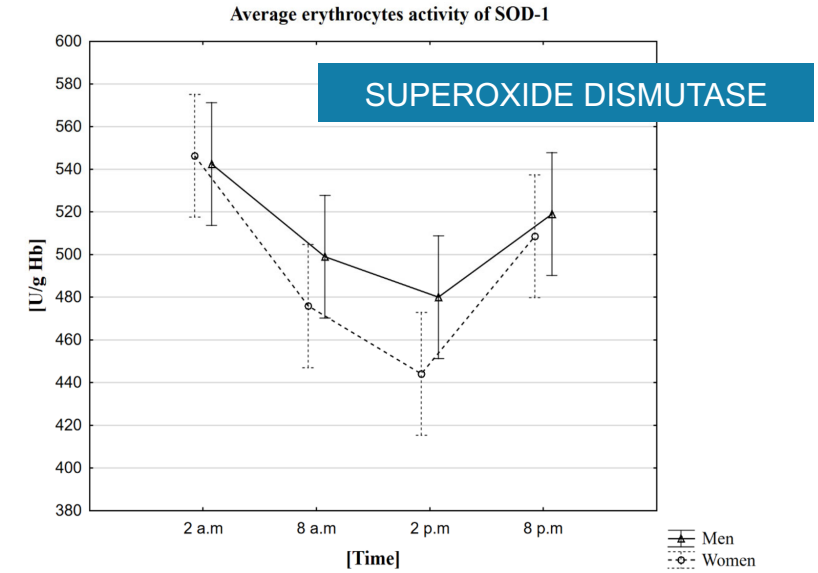
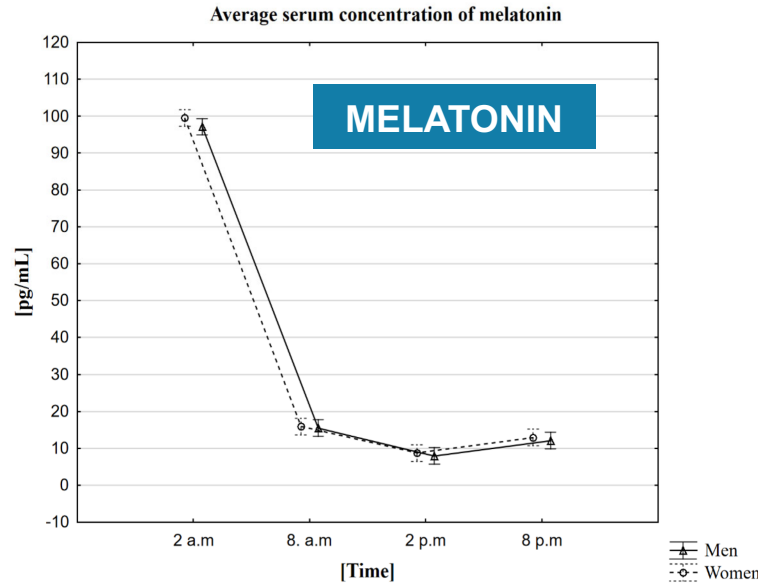
“The highest activity of these enzymes and the highest concentration of GSH at night are most likely related to the intensification of processes leading to the removal of free radicals during sleep, which in turn leads to the inhibition of oxidative stress in the organism.”

Budkowska M, Cecerska-Heryć E, Marcinowska Z, Siennicka A, Dołęgowska B. The Influence of Circadian Rhythm on the Activity of Oxidative Stress Enzymes. Int J Mol Sci. 2022 Nov 17;23(22):14275. doi: 10.3390/ijms232214275. PMID: 36430753.

Nighttime is repair time.

Adrenaline and cortisol are the “get up and go” hormones.

Melatonin is the “rest and rejuvenate” hormone.



Connecting the East-West Dots

- 2-4 AM peak “clean-up time”
- High antioxidant activity
- High melatonin
- Shift into REM sleep
- Dream state
- In TCM, liver-lung time (high CLOCK gene oscillating organs)

Time	Organ System
03:00 – 05:00	Lungs
05:00 – 07:00	Large Intestine
07:00 – 09:00	Stomach
09:00 – 11:00	Spleen
11:00 – 13:00	Heart
13:00 – 15:00	Small Intestine
15:00 – 17:00	Bladder
17:00 – 19:00	Kidneys
19:00 – 21:00	Pericardium
21:00 – 23:00	Triple Warmer
23:00 – 01:00	Gallbladder
01:00 – 03:00	Liver

Adapted from Samuels, N. (2000). Chronotherapy in traditional chinese medicine. *The American Journal of Chinese Medicine*, 28(03n04), 419–423. <https://doi.org/10.1142/s0192415x00000490>.

The six main functions of melatonin:

When you know how it works, you can understand how to apply it clinically

2. Anti-inflammatory

- Its anti-inflammatory properties further support many body systems, especially the immune system, such as with the cytokine storm, and its potential role in phase separation.
- Inhibitory role on the NLRP3 inflammasome
- Supplemental use for COVID and long-COVID

PMID: 36235587; PMID: 33651308. PMID: 36358996

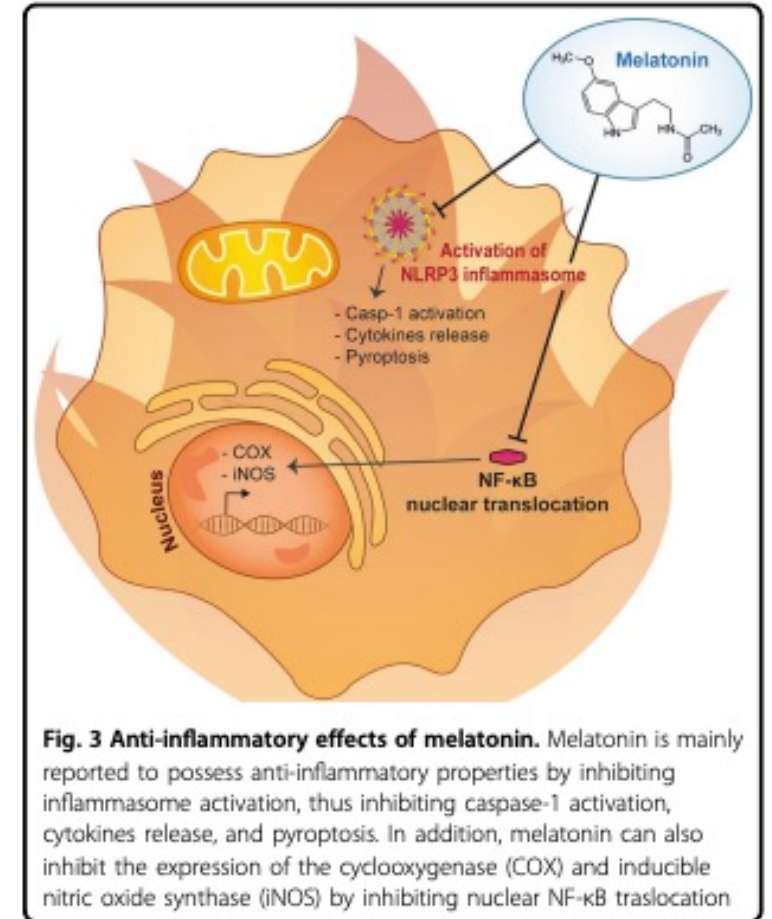


Image credit: Tarocco A, Caroccia N, Morciano G, et al. Melatonin as a master regulator of cell death and inflammation: molecular mechanisms and clinical implications for newborn care. *Cell Death Dis.* 2019;10(4):317. Published 2019 Apr 8. doi:10.1038/s41419-019-1556-7. [CC-BY 4.0](#).

The six main functions of melatonin:

When you know how it works, you can understand how to apply it clinically

3. Neuroprotective: Nerve growth factor

- Improved cognitive deficits in obese mice and increased BDNF; PMID: 35858673
- Supplementation of 3 mg positively influencing BDNF and sleep in obese children; PMID: 36634691.
- Systematic review/meta-analysis indicated improved depression but *no effect* on BDNF; PMID: 36049659
- Might be protective against arsenic-induced neurotoxicity: PMID: 36871878



Review

Melatonin: A Neurotrophic Factor?

Armida Miranda-Riestra¹, Rosa Estrada-Reyes², Erandis D. Torres-Sanchez³, Silvia Carreño-García⁴, Genaro Gabriel Ortiz^{3,5,*} and Gloria Benítez-King^{1,*}

¹ Laboratorio de Neurofarmacología, Subdirección de Investigaciones Clínicas, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Calzada México-Xochimilco 101, San Lorenzo Huipulco, Talpan 14370, Mexico City, Mexico

² Laboratorio de Fitofarmacología, Dirección de Investigaciones en Neurociencias, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Calzada México-Xochimilco 101, San Lorenzo Huipulco, Talpan 14370, Mexico City, Mexico

“Recent research has supported that melatonin contributes to neuronal survival, proliferation, and differentiation, such as dendritogenesis and axogenesis, and its processes are similar to those caused by Nerve Growth Factor, Brain-Derived Neurotrophic Factor, Neurotrophin-3, and Neurotrophin-4/5.”

Miranda-Riestra A, Estrada-Reyes R, Torres-Sanchez ED, Carreño-García S, Ortiz GG, Benítez-King G. Melatonin: A Neurotrophic Factor? *Molecules*. 2022 Nov 10;27(22):7742. doi: 10.3390/molecules27227742. PMID: 36431847; PMCID: PMC9698771.

Er, Carreño-García, S, Ortiz, GG, Benítez-King, G. Melatonin: A Neurotrophic Factor? *Molecules* 2022, 27, 7742. <https://doi.org/10.3390/molecules27227742>

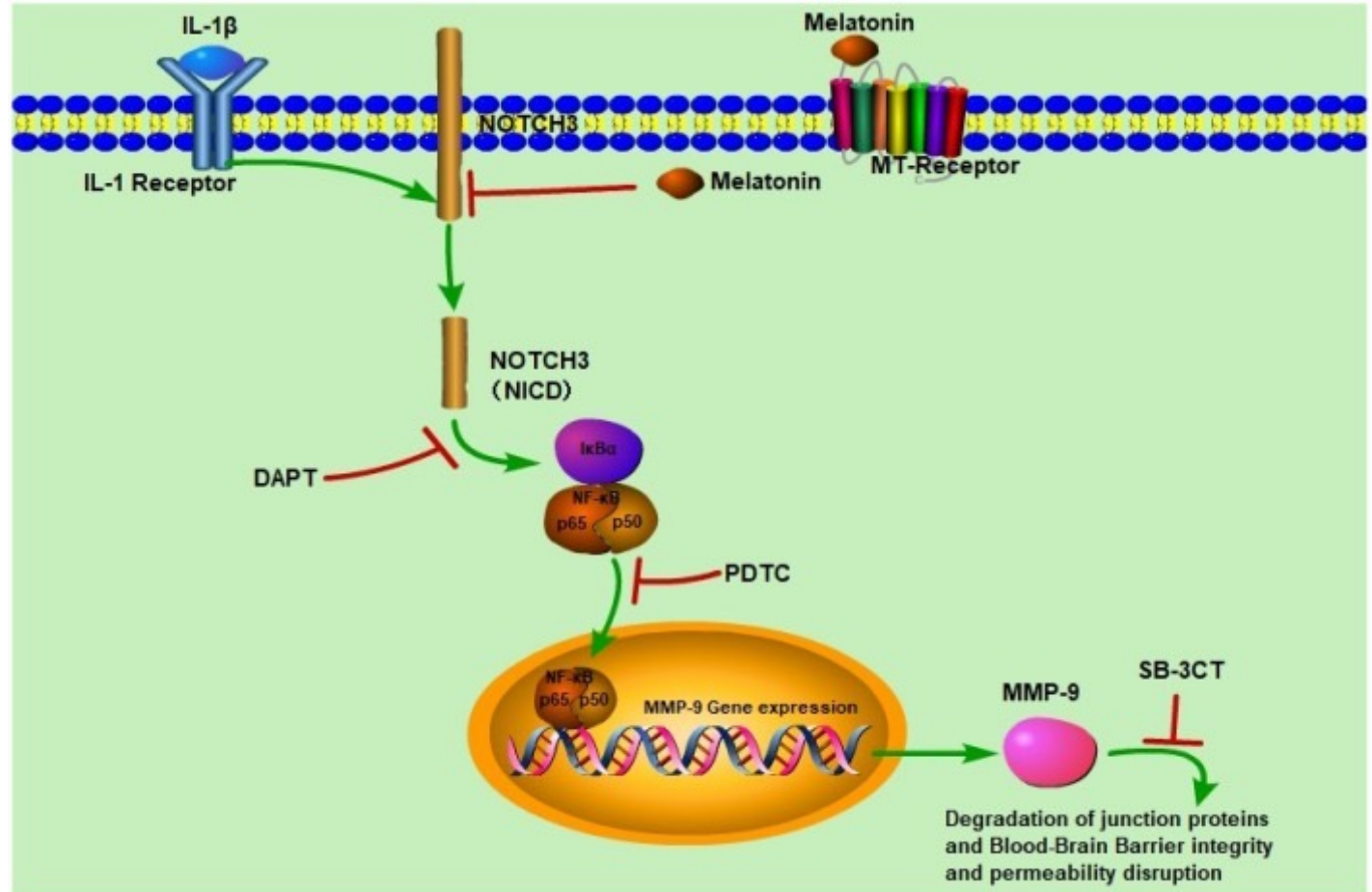
Factor, Neurotrophin-3, and Neurotrophin-4/5. Furthermore, this indolamine has apoptotic and anti-inflammatory actions in specific brain regions akin to those exerted by neurotrophic factors. This review presents evidence suggesting melatonin's role as a neurotrophic factor, describes the signaling pathways involved in these processes, and, lastly, highlights the therapeutic implications involved.

Neurotrophic-like characteristics of melatonin

MEL Neurotrophic-like Characteristics
MEL has membrane receptors coupled to G protein
MEL promotes neuronal differentiation, proliferation, and neuronal survival in newly formed neurons
MEL participates in mature brain neuroplasticity and neurodevelopment by stimulating second messenger cascades (Ca ²⁺ , CaMKII, Trk receptors)
Exerts antidepressant and anxiolytic-like effects associated to increased neurogenesis
Adjuvant in antidepressant treatments due to its synergistic effect with other molecules administered as antidepressant such as SSRIs (fluoxetine, citalopram) or ketamine
MEL can be used as neuroprotector in diseases whose treatments cause toxicity
MEL has anti-inflammatory properties and restorative effects in toxin-induced rodent models of persistent/chronic and neuropathic pain and spinal cord injury
MEL protects and maintains immune cells in non-neuronal places, like NTFs does
MEL can change the reorganization of the cytoskeleton
Promotes neuron's maturation, neuritogenesis, dendritic growth, and axogenesis. MEL also increases the complexity of the dendrite trees in crucial brain regions affected in neurodegenerative diseases.
Free radical scavenging properties of MEL equip it with antioxidant and neuroprotective effects. MEL modulates the production of other antioxidant molecules

Chart from: Miranda-Riestra A, Estrada-Reyes R, Torres-Sanchez ED, Carreño-García S, Ortiz GG, Benítez-King G. Melatonin: A Neurotrophic Factor? *Molecules*. 2022 Nov 10;27(22):7742. doi: 10.3390/molecules27227742. PMID: 36431847; PMCID: PMC9698771. CC-BY 4.0

Melatonin decreases permeability of the blood-brain barrier as shown in preclinical (cell + animal) studies



Qin W, Li J, Zhu R, Gao S, Fan J, Xia M, Zhao RC, Zhang J. Melatonin protects blood-brain barrier integrity and permeability by inhibiting matrix metalloproteinase-9 via the NOTCH3/NF- κ B pathway. *Aging (Albany NY)*. 2019 Dec 7;11(23):11391-11415. doi: 10.18632/aging.102537. Epub 2019 Dec 7. PMID: 31811815; PMCID: PMC6932927. CC-BY 3.0.

How sleep helps remove neurotoxins:

The glymphatic fluid exchange

- There is exchange and transport of metabolites through the glymphatic fluid.
- The glymphatic fluid refers to the area where the cerebral spinal fluid (CSF) and interstitial fluid (ISF) come together by the cerebral blood vessels [1]:
 - The CSF is active by arteries, the ISF deposits by the veins [1].
- Amyloid-beta is increased during wakefulness [1].
- Research suggests that clearance of amyloid-beta and hyperphosphorylated tau proteins (two hallmarks of Alzheimer's disease) can occur during sleep, especially slow-wave sleep [1, 2, 3]
- **Melatonin** may be an important molecule for this process [4].

1. PMID: 24136970; 2. PMID: 29279202; 3. PMID: 33134185; 4. PMID: 35316766; 5. PMID: 36917314

The brain detoxifies during sleep

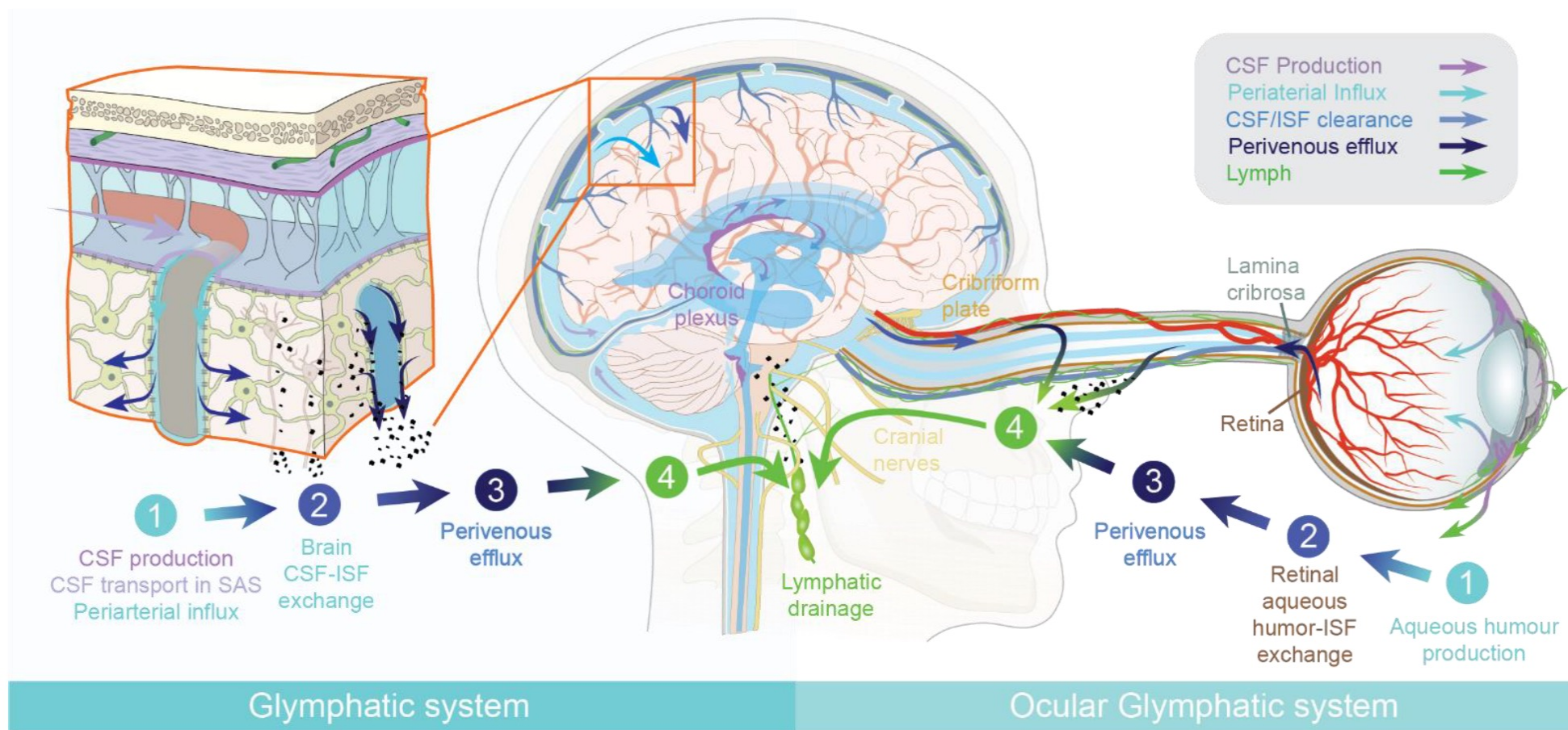


Image Credit: Mogensen, F.L.-H.; Delle, C.; Nedergaard, M. The Glymphatic System (En)during Inflammation. *Int. J. Mol. Sci.* 2021, 22, 7491. <https://doi.org/10.3390/ijms22147491>. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license. CC BY 4.0.

Inflammation impedes glymphatic function and flux

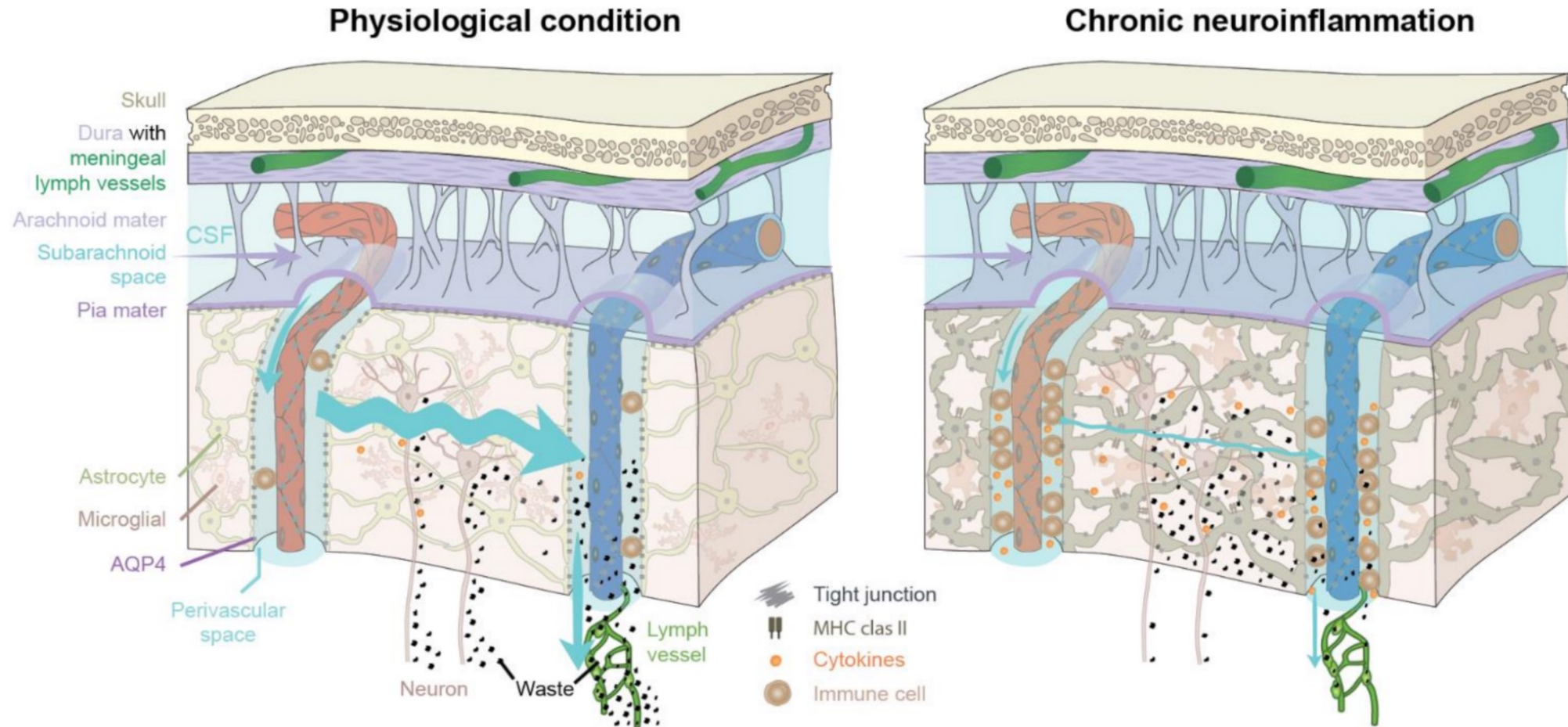


Image Credit: Mogensen, F.L.-H.; Delle, C.; Nedergaard, M. The Glymphatic System (En)during Inflammation. *Int. J. Mol. Sci.* 2021, 22, 7491. <https://doi.org/10.3390/ijms22147491>. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license. CC BY 4.0

The six main functions of melatonin:

When you know how it works, you can understand how to apply it clinically

4. Liquid-liquid phase separation (LLPS) related to viral replication

- Within the cell there are membrane-bound organelles (like the mitochondria) and areas of the cell that are phase separated from the membrane, like islands. They are referred to as liquid-like membrane-less organelles, or MLOs.
- These MLOs self-organizing, ordered, and disordered liquid particles come together to perform functions like assisting in the generation of energy (ATP), stress response, gene expression, and even viral replication.
- In some cases, the MLOs may become dysfunctional and result in the aggregation of proteins like amyloid and tau, thereby being implicated in neurodegenerative conditions.
- Preliminary research compiled by Loh and Reiter suggests that melatonin application in the early stages of infection, specific to SARS-CoV2, may help to prevent the formation of these viral “factories” through LLPS, thereby blocking several of their outputs to try to overtake the transcriptomic features of the cell.
- This is still an emerging area, and not much clinical research has been done, but the clinical conditions affected through the mitochondria, oxidative stress, and immune markers have been shown to benefit from melatonin (e.g., cancer, autoimmune conditions, neurodegenerative conditions).

<https://www.phytomelatonin.com/viral-defense-and-phase-separation>; Loh D, Reiter RJ. Melatonin: Regulation of Viral Phase Separation and Epitranscriptomics in Post-Acute Sequelae of COVID-19. Int J Mol Sci. 2022 Jul 23;23(15):8122. doi: 10.3390/ijms23158122. PMID: 35897696; PMCID: PMC9368024.

Loh D, Reiter RJ. Light, Water, and Melatonin: The Synergistic Regulation of Phase Separation in Dementia. *Int J Mol Sci.* 2023 Mar 19;24(6):5835. doi: 10.3390/ijms24065835. PMID: 36982909; PMCID: PMC10054283.



Review

Light, Water, and Melatonin: The Synergistic Regulation of Phase Separation in Dementia

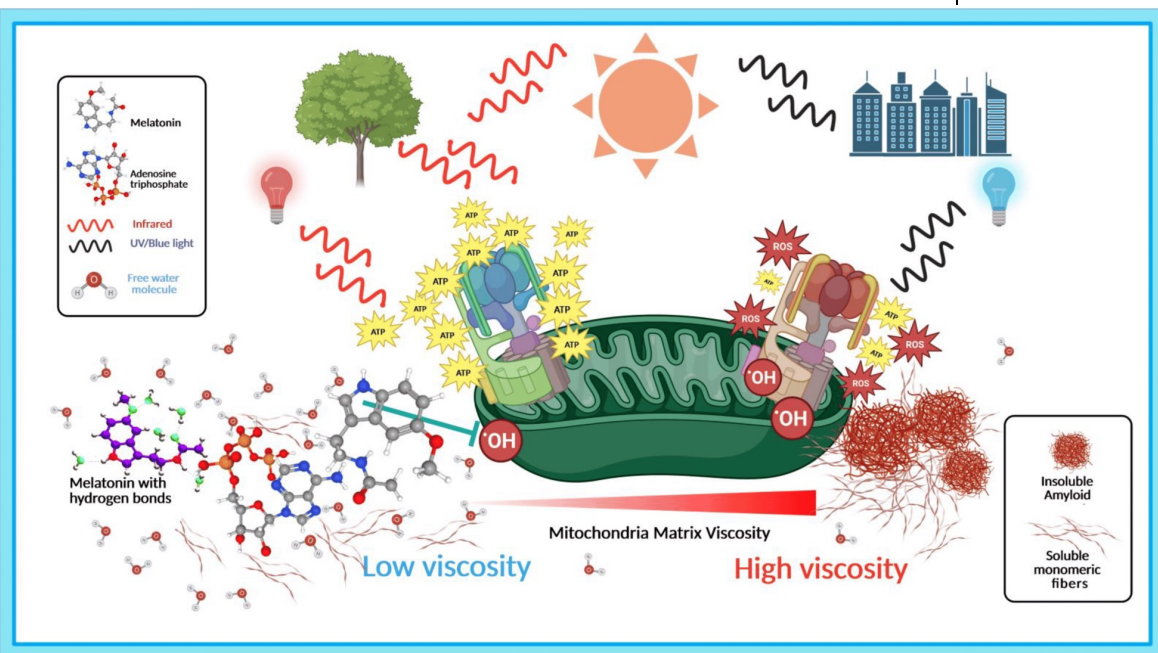
Doris Loh ¹ and Russel J. Reiter ^{2,*}

¹ Independent Researcher, Marble Falls, TX 78654, USA

² Department of Cell Systems and Anatomy, UT Health San Antonio, San Antonio, TX 78229, USA

* Correspondence: reiter@uthscsa.edu

Abstract: The swift rise in acceptance of molecular principles defining phase separation by a broad array of scientific disciplines is shadowed by increasing discoveries linking phase separation to pathological aggregations associated with numerous neurodegenerative disorders, including Alzheimer's disease, that contribute to dementia. Phase separation is powered by multivalent macromolecular interactions. Importantly, the release of water molecules from protein hydration shells into bulk creates entropic gains that promote phase separation and the subsequent generation of insoluble cytotoxic aggregates that drive healthy brain cells into diseased states. Higher viscosity in interfacial waters and limited hydration in interiors of biomolecular condensates facilitate phase separation. Light, water, and melatonin constitute an ancient synergy that ensures adequate protein hydration to prevent aberrant phase separation. The 670 nm visible red wavelength found in sunlight and employed in photobiomodulation reduces interfacial and mitochondrial matrix viscosity to enhance ATP production via increasing ATP synthase motor efficiency. Melatonin is a potent antioxidant that lowers viscosity to increase ATP by scavenging excess reactive oxygen species and free radicals. Reduced viscosity by light and melatonin elevates the availability of free water molecules that allow melatonin to adopt favorable conformations that enhance intrinsic features, including binding interactions with adenosine that reinforces the adenosine moiety effect of ATP responsible for preventing water removal that causes hydrophobic collapse and aggregation in phase separation. Precise recalibration of interspecies melatonin dosages that account for differences in metabolic rates and bioavailability will ensure the efficacious reinstatement of the once-powerful ancient synergy between light, water, and melatonin in a modern world.



Reiter, R.J. Light

The six main functions of melatonin:

When you know how it works, you can understand how to apply it clinically

5. Chronobiotic

- Influences the phase and/or the period of the circadian clock
- Helps to entrain circadian rhythm when there is internal desynchronization such as in blindness or aging or external disruption such as with shift-work or jetlag
- Lowers core body temperature (*think night sweats in perimenopausal women)
- Can be used to advance or delay the sleep phase
- Shown in animals to modify the circadian rhythm of gut bacteria to change their production of SCFAs [PMID: 37057339]

Fischer S, Smolnik R, Herms M, Born J, Fehm HL. Melatonin acutely improves the neuroendocrine architecture of sleep in blind individuals. *J Clin Endocrinol Metab.* 2003 Nov;88(11):5315-20. doi: 10.1210/jc.2003-030540. PMID: 14602767. Pevet P, Challet E, Felder-Schmittbuhl MP. Melatonin and the circadian system: Keys for health with a focus on sleep. *Handb Clin Neurol.* 2021;179:331-343. doi: 10.1016/B978-0-12-819975-6.00021-2. PMID: 34225973. Pfeffer M, Korf HW, Wicht H. Synchronizing effects of melatonin on diurnal and circadian rhythms. *Gen Comp Endocrinol.* 2018 Mar 1;258:215-221. doi: 10.1016/j.ygcen.2017.05.013. Epub 2017 May 19. PMID: 28533170.

Phase Response Curves

- **Phase advance:** Set the circadian clock earlier
 - Take melatonin 2-4 hours before DLMO
- **Phase delay:** Set the circadian clock later
 - Take melatonin within 4 hours before waking

When 0.5 mg and 3.0 mg melatonin were compared, 3.0 mg was more substantial in its ability to shift the phase response curve; however, if the soporific effect of melatonin is to be avoided, then using lower dose would be best.

Burgess HJ, Revell VL, Molina TA, Eastman CI. Human phase response curves to three days of daily melatonin: 0.5 mg versus 3.0 mg. *J Clin Endocrinol Metab.* 2010 Jul;95(7):3325-31. doi: 10.1210/jc.2009-2590. Epub 2010 Apr 21. PMID: 20410229; PMCID: PMC2928909.

The six main functions of melatonin:

When you know how it works, you can understand how to apply it clinically

6. Mitochondrial regulator and role in autophagy/mitophagy

As a result of its potency in metabolic areas of the body, more recognition has been given to melatonin's role in cancer, mitochondrial health, and aging.

“Mitochondria can take up pineal-derived or exogenously administered melatonin from the circulation, but they also have the ability to intrinsically produce it ([49–51](#)). Mitochondria are believed to have evolved when melatonin-producing bacteria were engulfed by early eukaryotes ([21](#), [26](#)). When confronted with melatonin from the blood, the mitochondria concentrate it against a gradient ([52](#)).”

Novais AA, Chuffa LGA, Zuccari DAPC, Reiter RJ. Exosomes and Melatonin: Where Their Destinies Intersect. Front Immunol. 2021 Jun 11;12:692022. doi: 10.3389/fimmu.2021.692022. PMID: 34177952; PMCID: PMC8226101.

Melatonin & Metabolism

“There is also evidence that melatonin supplementation not only modulates body weight and metabolic parameters but also has the ability to reverse the metabolic perturbations caused by chronodisruption.”

Ahluwalia, M.K. Chrononutrition—When We Eat Is of the Essence in Tackling Obesity. *Nutrients* **2022**, *14*, 5080. <https://doi.org/10.3390/nu14235080>

The spectrum of clinical uses for melatonin

Body System	Possible Clinical Uses
Central Nervous System	<ul style="list-style-type: none"> Circadian rhythm modulation Sleep-wake disorders Sleep disturbance Cognitive conditions such as dementia Migraines and headache Tinnitus Attention-Deficit Hyperactivity Disorder (ADHD) Autism Eye disorders (e.g., glaucoma)
Cardiovascular System	<ul style="list-style-type: none"> Hypercholesterolemia Hypertension/high systolic blood pressure Metabolic syndrome Endothelial dysfunction Glycemic balance (varying effects due to differing response in MTNR1B G-risk allele carriers)
Reproductive System	<ul style="list-style-type: none"> Preeclampsia Fertility As an adjunct to care for endometriosis Polycystic Ovarian Syndrome (PCOS)
Gastrointestinal System	<ul style="list-style-type: none"> Gastroesophageal Reflux Disease (GERD) Ulcers Irritable Bowel Syndrome (IBS)
Immune System	<ul style="list-style-type: none"> Autoimmune conditions (Multiple sclerosis, Hashimoto's thyroiditis) Coronavirus Disease (COVID-19) Oxidative stress from athletic performance stress Oxidative stress from excessive environmental toxin load Cancer; chemopreventive and as an adjunct to treatment depending on the cancer type and individual
Musculoskeletal System	<ul style="list-style-type: none"> Osteopenia

Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*. 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.

Sources of Melatonin: Foods

- Minute amounts of melatonin is widespread in both animal and plant foods; the chemical structure in both is bioidentical to what is in humans.
- Common sources include vegetables, fruits, nuts, seeds, grains, wine, and beers
- There is a high degree of variability due to many factors such as cultivars, growing conditions, germination, harvesting, and processing (e.g., roasting, drying).

Category	Select Types (Listed in Alphabetical Order)
Vegetables	Several types: Asparagus, beetroot, cabbage, carrot, corn, ginger root, purslane, spinach, taro
Fruits	Several types: Apple, banana, cherries (sweet, tart), cucumber, grapes, kiwifruit, peppers, pineapple, pomegranate, strawberries, tomatoes
Nuts	Almonds, pistachios, walnuts
Seeds	Anise, celery, coriander, fennel, fenugreek, flax, green cardamom, mustard (black, white), poppy, sunflower; Raw and germinated seeds of alfalfa, broccoli, lentil, mung bean, onion, red cabbage, and radish
Grains	Barley, oat, rice, wheat
Beans & Legumes	Kidney beans (sprouts), soybeans
Herbs & Spices	Black pepper, feverfew, sage, St. John's wort, select Chinese medicinal herbs
Oils	Argan oil, extra virgin olive oil, grapeseed oil, linseed oil, primrose oil, sesame oil, soybean oil, sunflower oil, walnut oil, wheat germ oil
Beverages	Beer, coffee, grape juice, orange juice, wine

Levels consumed within the typical diet do not significantly contribute to circulating levels. - PMID: **17001324**

Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*. 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.

It would take large quantities of food to get a physiological dose (0.3 mg) of melatonin*

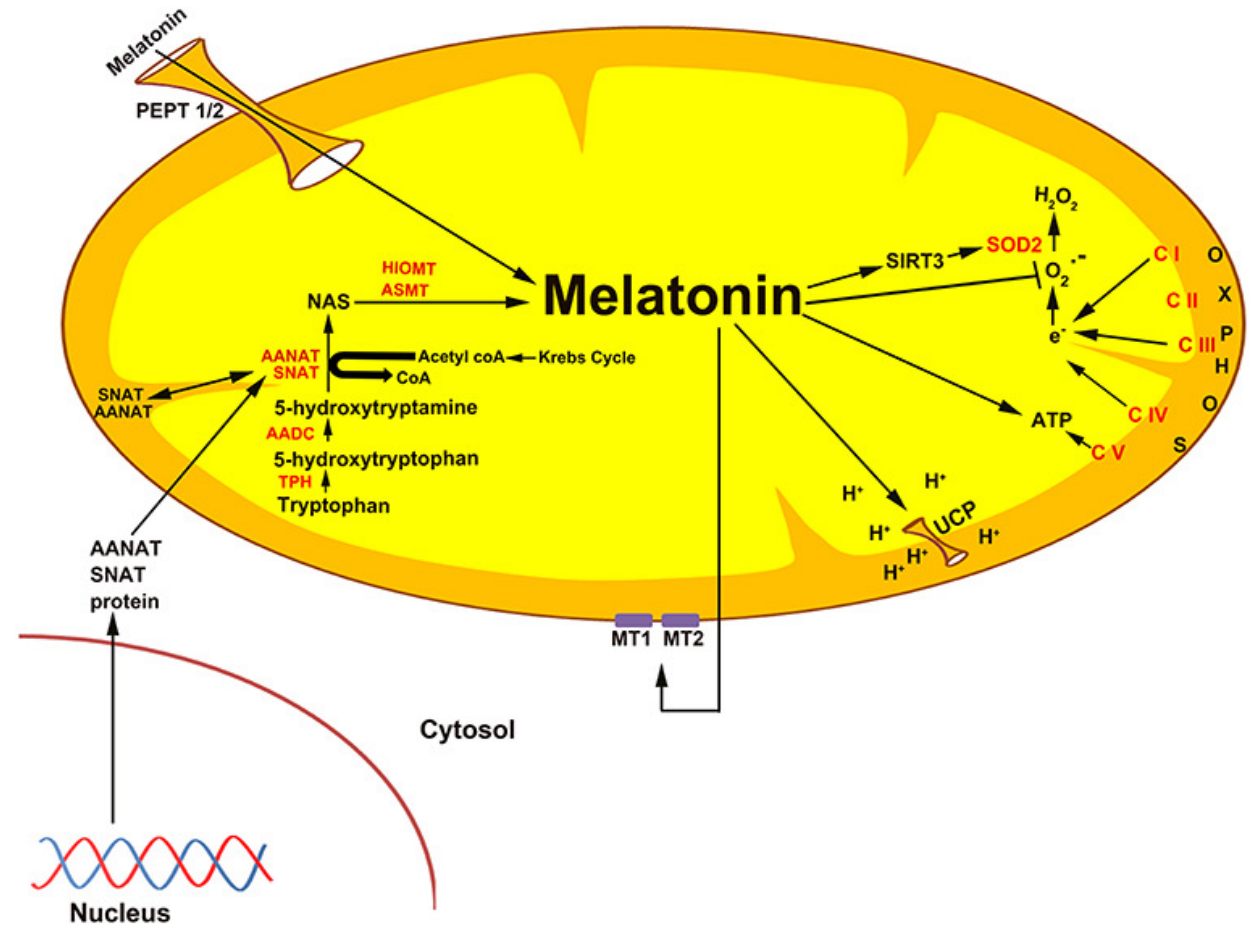
Food	Quantity
Tart cherries	2,718 fresh cherries
Shelled walnuts	About 857 cups
Milk	Over 85 eight-ounce glasses of cow's milk
Strawberries	Over 2000 fresh medium strawberries
Fuji apples	A little more than 11 medium-sized Fuji apples
Grapes	15,000 grapes
Pistachios	Over 1500 raw pistachios*
Tomatoes	About 20 whole tomatoes
Mushrooms	60 fresh mushrooms

*There is a high degree of variability due to many factors: method of analysis, cultivars, growing conditions, germination, harvesting, & processing (e.g., roasting, drying).

Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*. 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.

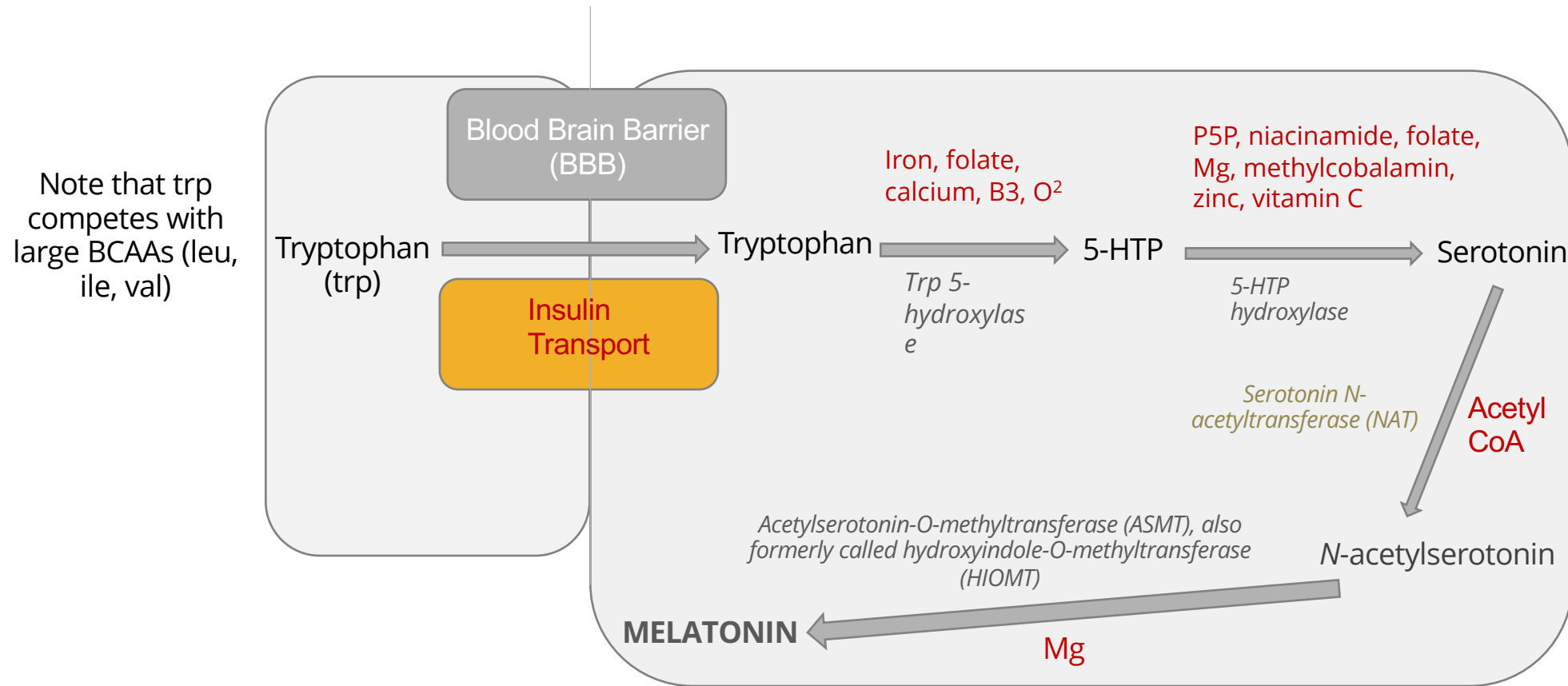
Melatonin is made from tryptophan

- Melatonin is made from tryptophan; plants can make their own tryptophan.
- The conversion of tryptophan to melatonin requires several steps, all with varying degrees of efficiency (e.g., includes methyltransferases).



Zhao D, Yu Y, Shen Y, Liu Q, Zhao Z, Sharma R and Reiter RJ (2019) Melatonin Synthesis and Function: Evolutionary History in Animals and Plants. *Front. Endocrinol.* 10:249. doi: 10.3389/fendo.2019.00249. <https://creativecommons.org/licenses/by/4.0/>

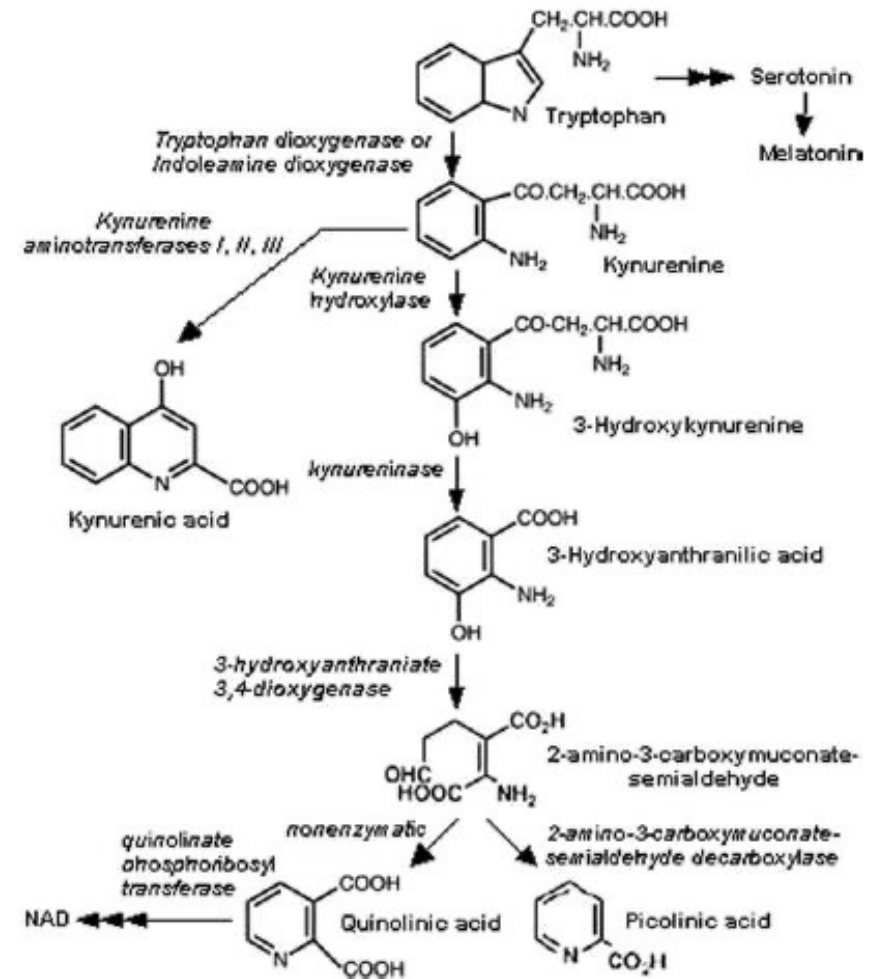
What about just eating more foods that contain tryptophan?



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Kynurenine Pathway

- 95% of tryptophan goes to kynurenine
- 5% goes to serotonin and melatonin
- The kynurenic pathway is essential to convert tryptophan into nicotinamide adenine dinucleotide (NAD⁺) for cellular energy



[KP pathway - Kynurenine pathway - Wikipedia](#)

Kynurenine Pathway – Energy & Stress

- Low levels of melatonin may upregulate the kynurenine pathway, along with the aryl hydrocarbon receptor (AhR) on the outer mitochondrial membrane¹
- The AhR is responsible for modulating²:
 - Mitochondrial metabolism
 - Melatonergic pathways
 - Acetyl-coenzyme A
 - COX-2 prostaglandin
 - When triggered, endogenous pineal melatonin is suppressed
- In depression kynurenine levels in the brain are high. It is then converted to either kynurenic acid with its neuroprotective properties, or quinolinic acid, a neurotoxin³
- Exercise increases throughout put to the serotonin-melatonin pathway, impacting mood and cognition¹

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Melatonin supplements:

General Overview

- Only oral administration is considered a dietary supplement in the USA
 - Immediate release
 - Sustained, time-release (consider coating agents)
 - Capsule
 - Tablet
 - Chewable
 - Gummies
- Variety of other routes to deliver melatonin: sublingual, intravenous, intramuscular, intranasal, transdermal, suppository (anal, vaginal)
- Note quality (cGMP, third party testing for contaminants)
- Packaging integrity due to degradation with air and light

Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*. 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.

What about chewables and gummies?

- Alternate formats are trending.
- Gummies account for ~50% of all melatonin supplements on Amazon.
- Concerns about gummies include:
 - The stability of the hygroscopic matrix
 - The potential for an overdose by children
 - Inclusion of other undesirable agents (e.g., sugars, dyes, and flavors)
- Chewables have similar issues.
- In general, people have pill fatigue and are seeking alternate formats.

Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*. 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.

Melatonin supplements:

Dosing Considerations

- General clinical recommendation to follow suit with other hormones: **the lowest dose for the shortest duration**
- Side effects (e.g., grogginess, headaches, vivid dreams) in some cases, which may be due to several factors, including ones listed below:
 - Presence of other actives in the supplement which may be synergistic or antagonistic
 - Personalized kinetics/metabolism via cytochrome enzymes like CYP1A2
 - Half-life of melatonin is short at 45-60 minutes.
 - Time of administration to delay or forward the phase-response curve
 - Lifestyle practices (e.g., sleep hygiene, stress regulation/cortisol)
 - Seasonal shifts (e.g., daylight savings, less/more darkness through the year)

Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*. 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.

Melatonin supplements:

Dose Levels

- More is not always better.
- Physiological dose (0.3 -1 mg) for more maintenance, such as with shift work and aging
 - Higher dose (3 mg) has been shown to cause plasma elevations of melatonin in morning hours in addition to hypothermia.
- Supraphysiological doses (≥ 3 mg) for specific clinical conditions such as jetlag, symptomatic relief from chemotherapy, etc.
 - *Should be evaluated by a qualified healthcare practitioner*

Zhdanova IV, Wurtman RJ, Regan MM, Taylor JA, Shi JP, Leclair OU. Melatonin treatment for age-related insomnia. J Clin Endocrinol Metab. 2001 Oct;86(10):4727-30. doi: 10.1210/jcem.86.10.7901. PMID: 11600532.

Vural EM, van Munster BC, de Rooij SE. Optimal dosages for melatonin supplementation therapy in older adults: a systematic review of current literature. Drugs Aging. 2014 Jun;31(6):441-51. doi: 10.1007/s40266-014-0178-0. PMID: 24802882.

Melatonin supplements:

Dose Levels

- Lowest possible dose (0.3 mg to a maximum of 1-2 mg) of immediate-release formulation melatonin advised for older adults
- 1 hour before bedtime

Vural EM, van Munster BC, de Rooij SE. Optimal dosages for melatonin supplementation therapy in older adults: a systematic review of current literature. *Drugs Aging*. 2014 Jun;31(6):441-51. doi: 10.1007/s40266-014-0178-0. PMID: 24802882.

Melatonin Supplementation:

Summary of Dose Levels

Clinical Indication	Goal	Dosing Strategy
Overall health: cellular health, healthy inflammatory response, antioxidant, mitochondrial regulator	Replenishment for levels lost with aging	Physiological dose- 0.3 - 1 mg on a daily level
Aggressive clinical use: under supervision	Assisting in management of select health conditions	10 mg or greater, short-term
Shift work and jetlag	Realignment of the circadian rhythm	0.5 - 6 mg
General sleep support	Assisting with sleep patterns	0.3 - 0.6 mg

Dosing of Melatonin: Summary of Research Findings

Condition	Dose(s)	Reference(s)*
MCI/Alzheimer's Disease	2.5 mg – 10 mg**	1
Parkinson's Disease	2-50 mg**	2
Diabetes	3 and 10 mg	3, 4
Hypertension	1 and 5 mg	3, 5
Bone Health	1- 5 mg	6-9
Eye Health (glaucoma and macular degeneration)	2-20 mg	10-11
Multiple Sclerosis	3- 25 mg	12
COVID***	3 or 6 mg (7-14 days)	13
Cancer	10-50 mg	3, 14-16
Thyroid Health	3 mg	17

* See slide for list of references; ** Major outcome measures were for sleep. *** Most studies on COVID are MOA or trials are in process

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Melatonin supplements:

Can I take melatonin long-term?

- Oral melatonin is considered a safe product that is well-tolerated for general use in adults and children, with adverse effects rarely reported in the literature ¹⁻³.
- There are currently more than 40 studies on the use of melatonin in various health conditions showing the safety of **up to 8-10 mg** for 6 months to 2 years when used appropriately ².
- Increased likelihood of adverse events occurring when melatonin is dosed 10 mg or higher ^{4, 5}.

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Melatonin supplements:

What about higher doses?

- “The **potential therapeutic value** of melatonin has been suggested by a limited number of clinical trials generally employing melatonin in the **2-10 mg/day** range. However, from **animal studies** the **cytoprotective** effects of melatonin need higher doses to become apparent (**i.e. in the 100 mg/day range**). Hence, controlled studies employing melatonin doses in this range are urgently needed.”¹
- Pharmacokinetic studies have used higher doses, including 80-100 mg in humans to **assess safety and adverse effects**²⁻⁵

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Does taking melatonin result in decreased production in the body?

- Research studies have shown that melatonin from supplementation **does not** impact endogenous production [1-4].
- Three decades' worth of clinical trials using high-dose melatonin supplements in cancer patients has not documented this effect.
- High-dose long-term use of melatonin could potentially reduce sensitivity of receptor sites and create a need for higher doses of melatonin [5].
 - The caveat is that there may be a threshold in reducing sensitivity once receptor sites are saturated.
- Exogenous melatonin may help increase the cell's production of melatonin, at least in cancer cells, by removing metabolic blocks to its synthesis [6].

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Supplemental sources:

Terms to be aware of

- Plant-based
- Natural
- Vegan
- Vegetarian
- Herbal

Did you know?

The bioavailability of melatonin in females is double that of males, i.e., $16.8 \pm 12.7\%$ vs. $8.6 \pm 3.9\%$, respectively.

Fourtillan JB, Brisson AM, Gobin P, Ingrand I, Decourt JP, Girault J. Bioavailability of melatonin in humans after day-time administration of D(7) melatonin. *Biopharm Drug Dispos.* 2000 Jan;21(1):15-22. doi: 10.1002/1099-081x(200001)21:1<15::aid-bdd215>3.0.co;2-h. PMID: 11038434.

Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients.* 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.

Supplemental sources:

Naturally-derived and chemically-processed

- Historically, melatonin derived from the pineal gland of animals until viral infections/prions became a concern
- A majority (~99%) of melatonin supplements are now synthetically made through a multi-chemical step process commonly involving a starter compound followed by subsequent reactions using petrochemical-derived chemicals like acetone, ethanol, and cold petroleum ether.
- Plant-based melatonin supplements may also involve chemicals needed for extraction.
- Newer horizon of bioengineered melatonin from microorganisms

Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*. 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.

Risk of contaminants in synthetically-produced melatonin¹

- 1,2,3,4-tetrahydro- β -carboline-3-carboxylic acid
- 3-(phenylamino)alanine
- 1,1'-ethylidenebis-(tryptophan) (so-called peak E)
- 2-(3-indolylmethyl)-tryptophan
- formaldehyde-melatonin
- formaldehyde-melatonin condensation products
- hydroxymelatonin isomers
- 5-hydroxy-tryptamine derivatives
- 5-methoxy-tryptamine derivatives
- *N*-acetyl- and diacetyl-indole derivatives
- 1,3-diphthalimidopropane
- hydroxy-bromo-propylphthalimide
- chloropropylphthalimide

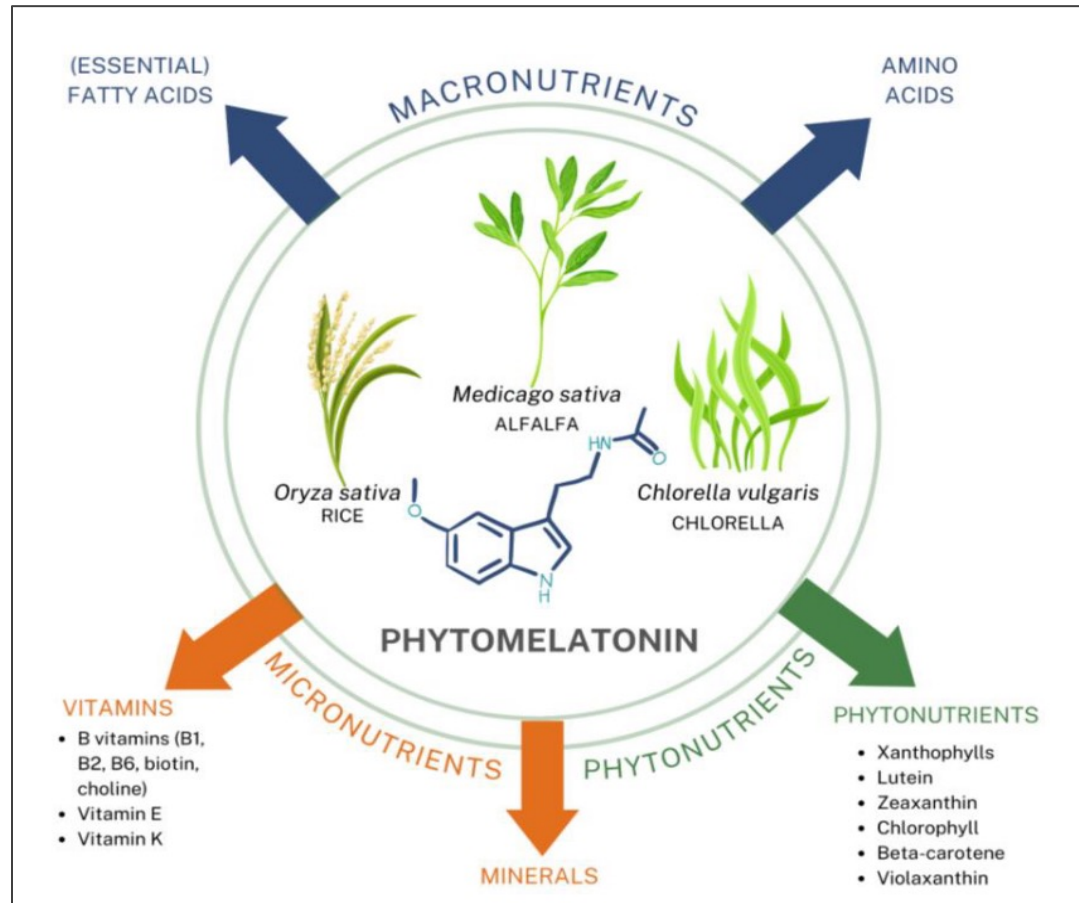
Canadian researchers analyzed 31 melatonin supplements and noted²:

- The melatonin content in the products ranged from 17% to 478% of label claim
- There was substantial variation in batches by as much as 465%.
- Finally, 8 out of 30 supplements tested contained serotonin.

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Phytomelatonin:

Bioidentical melatonin in the plant cell matrices from rice, alfalfa, chlorella



Article

Is Phytomelatonin Complex Better Than Synthetic Melatonin? The Assessment of the Antiradical and Anti-Inflammatory Properties

Wirginia Kukula-Koch ^{1,*}, Dominik Szwajgier ², Katarzyna Gawel-Beben ³, Marcelina Strzpek-Gomółka ³, Kazimierz Głowniak ³ and Henry O. Meissner ⁴

- ¹ Department of Pharmacognosy with Garden of Medicinal Plants, Medicinal University in Lublin, 1 Chodźki Str., 20-093 Lublin, Poland
 - ² Department of Biotechnology, Microbiology and Human Nutrition, University of Life Sciences, 8 Skromna Str., 20-704 Lublin, Poland; dominik.szwajgier@up.lublin.pl
 - ³ Department of Cosmetology, University of Information Technology and Management in Rzeszów, 2 Sucharskiego Str., 35-225 Rzeszów, Poland; kagawel@wsiz.rzeszow.pl (K.G.-B.); mstrzpek@wsiz.rzeszow.pl (M.S.-G.); kglowniak@wsiz.rzeszow.pl (K.G.)
 - ⁴ Therapeutic Research, TTD International Pty Ltd., 39 Leopard Ave., Gold Coast 4221, Australia; dr.meissner@ttintl.com.au
- * Correspondence: virginia.kukula@gmail.com



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Abstract: This work aims to assess the recently established anti-inflammatory and antioxidant potential of melatonin of plant origin extracted from the plant matrix as a phytomelatonin complex (PHT-MLT), and compare its activity with synthetic melatonin (SNT-MLT) when used on its own or with vitamin C. For this purpose, a COX-2 enzyme inhibitory activity test, an antiradical activity in vitro and on cell lines assays, was performed on both PHT-MLT and SNT-MLT products. COX-2 inhibitory activity of PHT-MLT was found to be ca. 6.5 times stronger than that of SNT-MLT (43.3% and 6.7% enzyme inhibition, equivalent to the activity of acetylsalicylic acid in conc. 30.3 ± 0.2 and 12.0 ± 0.3 mg/mL, respectively). Higher antiradical potential and COX-2 inhibitory properties of PHT-MLT could be explained by the presence of additional naturally occurring constituents in alfalfa, chlorella, and rice, which were clearly visible on the HPLC-ESI-QTOF-MS fingerprint. The antiradical properties of PHT-MLT determined in the DPPH test (IC₅₀ of 21.6 ± 1 mg of powder/mL) were found to originate from the presence of other metabolites in the 50% EtOH extract while SNT-MLT was found to be inactive under the applied testing conditions. However, the antioxidant studies on HaCaT keratinocytes stimulated with H₂O₂ revealed a noticeable activity in all samples. The presence of PHT-MLT (12.5, 25 and 50 µg/mL) and vitamin C (12.5, 25 and 50 µg/mL) in the H₂O₂-pretreated HaCaT keratinocytes protected the cells from generating reactive oxygen species. This observation confirms that MLT-containing samples affect the intracellular production of enzymes and neutralize the free radicals. Presented results indicated that MLT-containing products in combination with Vitamin C dosage are worth to be considered as a preventive alternative in the therapy of various diseases in the etiopathogenesis, of which radical and inflammatory mechanisms play an important role.

Keywords: synthetic melatonin; phytomelatonin complex; COX-2 inhibition; antiradical potential; DPPH; *Medicago sativa*; *Chlorella vulgaris*; *Oryza sativa*; HaCaT cells

1. Introduction

Melatonin has been identified as “uncommonly effective” in reducing oxidative stress under a host of clinical circumstances [1]. This biogenic amine—a derivative of tryptamine (*N*-acetyl-5-methoxytryptamine)—was first isolated from the pineal gland of animals and later from humans [2,3]. It was identified as a hormone primarily responsible for regulating circadian rhythm and blood pressure. Numerous scientific publications confirm

Phytomelatonin outperforms synthetic melatonin in cell assays

- Anti-inflammatory activity (COX-2)
- Free radical scavenging activity (DPPH%)
- Cellular health (ROS in skin cell line)

	Antioxidant potential	Anti-Radical Activity	Cellular Health	Anti-inflammatory
Measurement	ORAC	DPPH	ROS	COX-2
% Improvement over synthetic melatonin	300%	Up to 470%	100%	646%

Kukula-Koch W, Szwajgier D, Gaweł-Bęben K, Strzępek-Gomółka M, Głowniak K, Meissner HO. Is Phytomelatonin Complex Better Than Synthetic Melatonin? The Assessment of the Antiradical and Anti-Inflammatory Properties. *Molecules*. 2021 Oct 8;26(19):6087. doi: 10.3390/molecules26196087. PMID: 34641628; PMCID: PMC8512846.

Better reduction of inflammation by phytomelatonin compared with synthetic melatonin

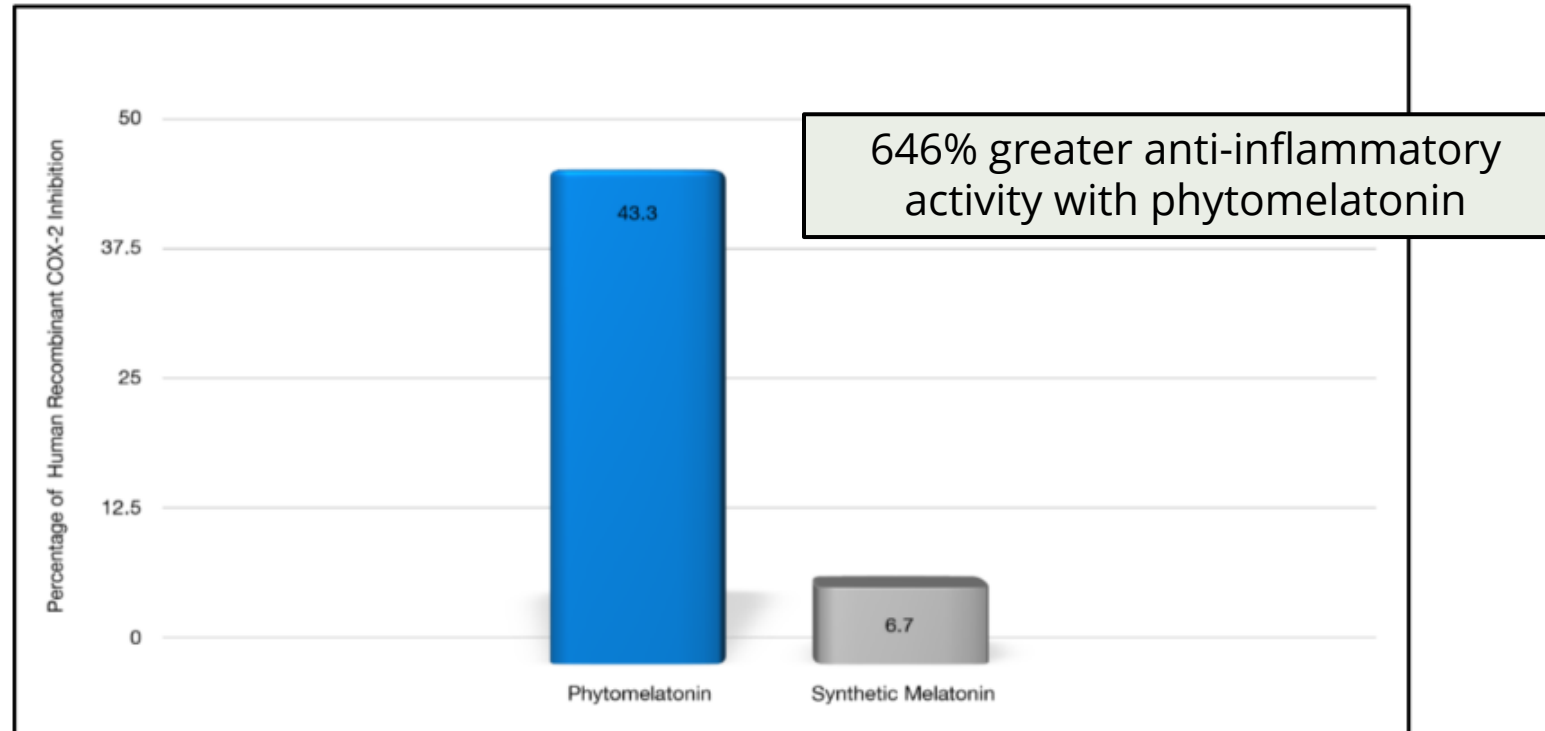


Figure 4. Inhibition of inflammation by phytomelatonin (blue bar) and synthetic melatonin (gray bar). Data are expressed as a percentage of human recombinant COX-2 inhibition. Amounts used for each were 0.030 mL (5 mg/mL). Values are derived from the original data presented in [34].

Kukula-Koch W, Szwajgier D, Gawel-Beben K, Strzypek-Gomolka M, Glowniak K, Meissner HO. Is Phytomelatonin Complex Better Than Synthetic Melatonin? The Assessment of the Antiradical and Anti-Inflammatory Properties. *Molecules*. 2021 Oct 8;26(19):6087. doi: 10.3390/molecules26196087. PMID: 34641628; PMCID: PMC8512846.

Better free radical scavenging (DPPH%) by phytomelatonin compared with synthetic melatonin

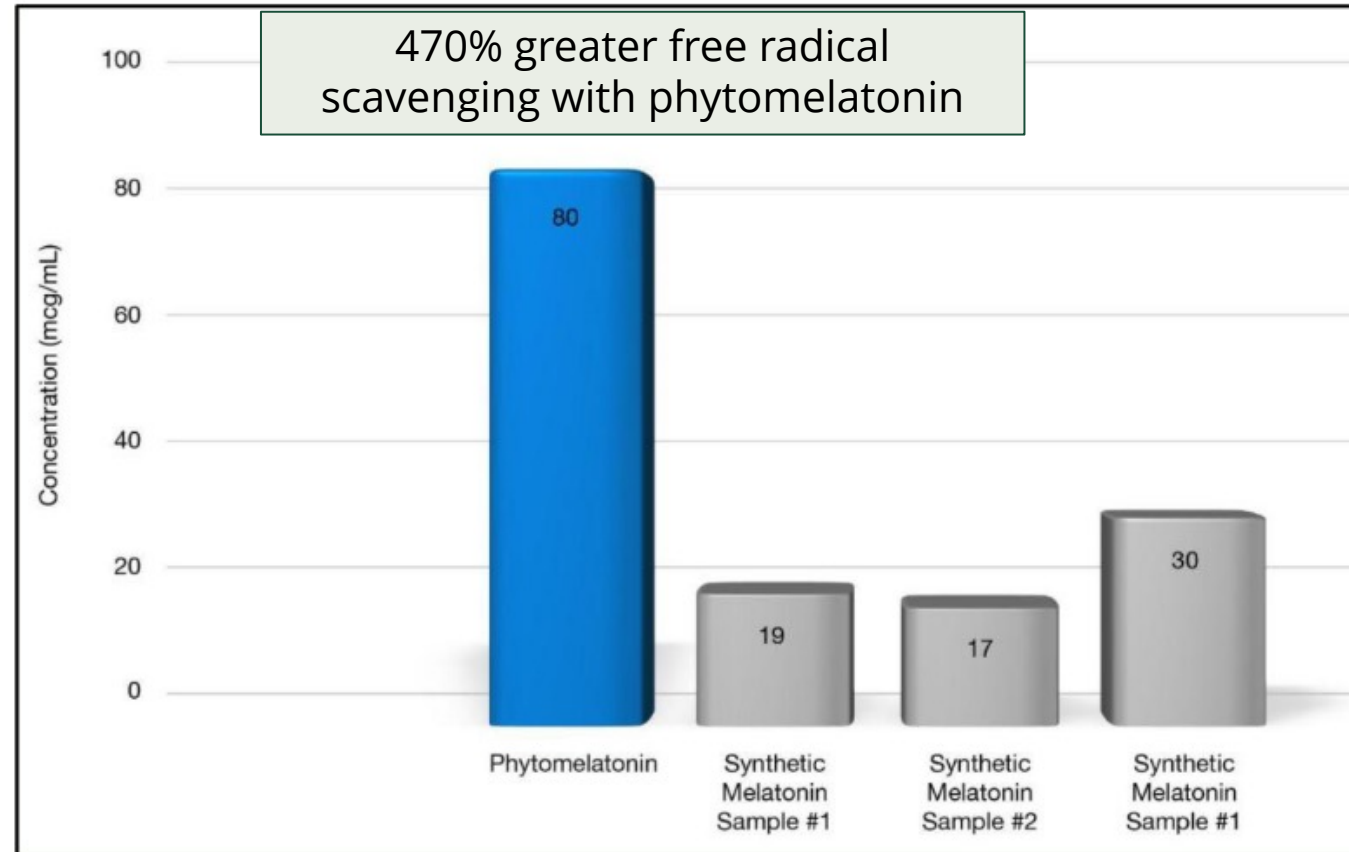


Figure 5. Free Radical Scavenging Percentage (DPPH%) by phytomelatonin (blue bar) and three synthetic melatonins (gray bars). Data are expressed as mcg/mL. Values are derived from the original data presented in [34].

Improved ROS levels with phytomelatonin compared with synthetic melatonin

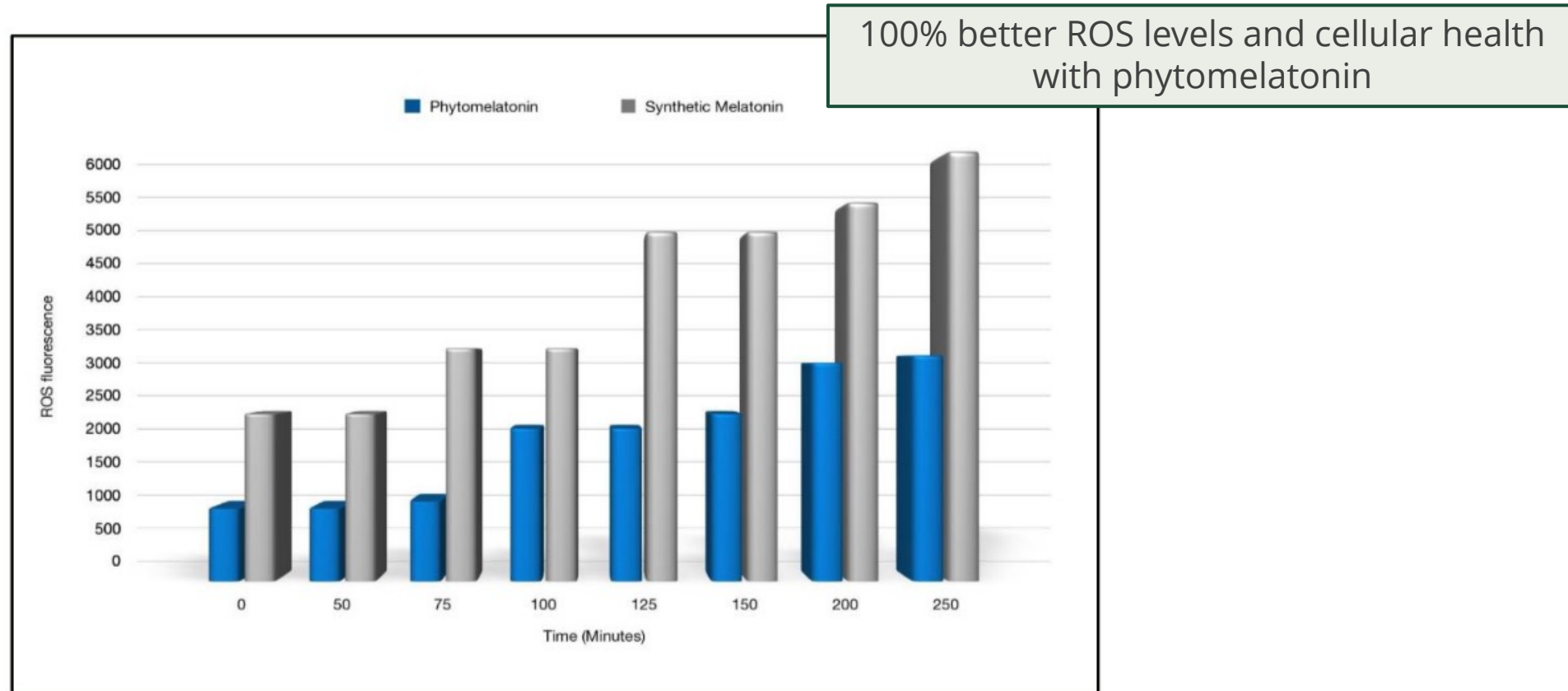
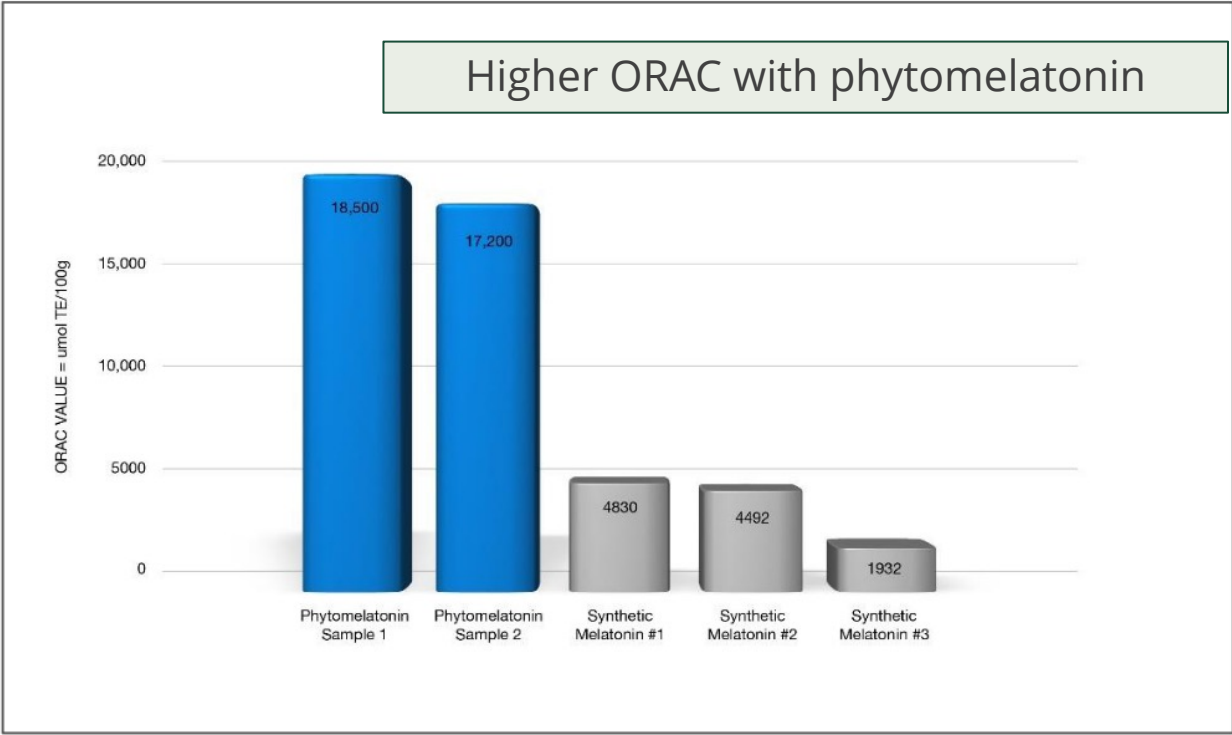


Figure 6. ROS fluorescence in human skin cell line by phytomelatonin (blue bars) and synthetic melatonin (gray bars). Data are expressed as ROS fluorescence using 50 mcg/mL for both phytomelatonin and synthetic melatonin. Values are derived from the original data presented in [34].

Higher ORAC value for phytomelatonin compared with synthetic melatonin



Source	ORAC
Phytomelatonin	17,200-18,500
Prunes	5770
Synthetic melatonin	1,932-4,830
Blueberries	2400
Kale	1770
Red bell pepper	710
Cherries	670

McBride J. High-ORAC Foods May Slow Aging. [Internet]. USDA Agricultural Research Service. 2022 [cited 2022 Oct 4]. Available from: <https://www.ars.usda.gov/news-events/news/research-news/1999/high-orac-foods-may-slow-aging/>

Figure 9. Oxygen radical absorbance capacity (ORAC) of two samples of phytomelatonin (blue bars) and three types of synthetic melatonin (gray bars) [271,272].

Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*. 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.

Overall summary of phytomelatonin vs. synthetic melatonin

- Phytomelatonin uses customized cultivation techniques to select the ideal location, soil, climate and optimal method/time to harvest based on plant cycles to naturally optimize melatonin levels
- Phytomelatonin contains other plant actives and no excipients, fillers, or binding agents.
- No toxic agents in phytomelatonin; possible risk for contaminants with synthetic melatonin
- The manufacture of synthetic melatonin generates significant pollution.
- Phytomelatonin outperforms synthetic melatonin in cell-based assays for inflammation and oxidative stress.

Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*. 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.

What about laboratory testing?

Parameter	Saliva	Urine	Blood
Measurement of	Melatonin circulating at the time of collection	Morning 6-sulfatoxymelatonin (aMT6s) measures peak nocturnal melatonin levels	Melatonin circulating at time of collection
Immediately suppressed by light	Yes	No	Yes
Easily collected	Yes	Yes	No
Collected at home	Yes	Yes	No
Storage	Placed in freezer for delivery to the labs	Can be stored at room temperature for up to 5 days or 20 degrees C for 2 years	Proper handling and storage of the sample is required by the lab
Collection considerations	Do not brush teeth or consume liquids 30 minutes prior to testing. Avoid lipstick or other lip products. Use of cotton swabs or paraffin chewing to collect saliva.	First pass urine collection. For frequent sampling, a catheter may be used.	Often requires catheter for frequent sampling and therefore not recommended for routine clinical use.
Requires low light (<30 lux) prior to collection	Yes	No	Yes
Number of samples	Every 30-60 minutes, generally for 6 hours	Once, in the morning or every 2-8 hours for 24-48 hours for increased accuracy	Variable
Used to determine	DLMO	Total nocturnal melatonin release	DLMO Cases of low melatonin (as this may not be captured in urine or saliva)



Organic Acid Tests (OATs)

Ordering Provider:
Rupa Health

Last Menstrual Period:

2022-12-02
Collection Times:
2023-02-27 05:22AM
2023-02-27 07:22AM
2023-02-27 05:13PM
2023-02-27 09:30PM

Category	Test	Result	Units	Normal Range
Nutritional Organic Acids				
Vitamin B12 Marker (may be deficient if high) - (Urine)				
	Methylmalonate (MMA)	Within range	0.8 ug/mg	0 - 2.5
Vitamin B6 Markers (may be deficient if high) - (Urine)				
	Xanthurenate	Within range	0.23 ug/mg	0.12 - 1.2
	Kynurenate	Within range	1.32 ug/mg	0.8 - 4.5
Glutathione Marker (may be deficient if low or high) - (Urine)				
	Pyroglutamate	Low end of range	32.2 ug/mg	28 - 58
Biotin Marker (may be deficient if high) - (Urine)				
	b-Hydroxyisovalerate	Within range	2.5 ug/mg	0 - 12.5
Gut Marker (potential gut putrefaction or dysbiosis if high) - (Urine)				
	Indican	Within range	52.4 ug/mg	0 - 100
Neuro-related Markers				
Dopamine Metabolite - (Urine)				
	Homovanillate (HVA)	Above range	12.8 ug/mg	3 - 11
Norepinephrine/Epinephrine Metabolite - (Urine)				
	Vanilmandelate (VMA)	Within range	3.7 ug/mg	2.2 - 5.5
Neuroinflammation Marker - (Urine)				
	Quinolinatate	Within range	3.1 ug/mg	0 - 9.6
Additional Markers				
Melatonin (*measured as 6-OH-Melatonin-Sulfate) - (Urine)				
	Melatonin* (Waking)	Within range	34.1 ng/mg	10 - 85
Oxidative Stress / DNA Damage, measured as 8-Hydroxy-2-deoxyguanosine (8-OHdG) - (Urine)				
	8-OHdG (Waking)	Within range	1.75 ng/mg	0 - 5.2



Indicators that melatonin may be imbalanced or insufficient

General Health Status

- Abnormal fatigue (mitochondrial dysfunction)
- Accelerated aging (e.g., hair graying, excessive skin fragility)
- Advanced age (40+ years old)
- Blindness or impaired sight
- Blood sugar imbalance
- Changes in the menstrual cycle
- Chronic inflammatory states (e.g., pain, redness, swelling)
- Chronic stress levels
- Difficulty with making seasonal transitions
- Gut dysbiosis
- Known gene variants or deletions in glutathione
- Low bone mineral density
- Mood changes/shifts
- Perimenopause or other fluxes in hormones
- Recurring immune-related issues, like colds, flus, COVID, cancer, etc.
- States of heightened oxidative stress (e.g., bouts of extensive exercise)

Indicators that melatonin may be imbalanced or insufficient

Food/Diet

- Increased intake of toxins such as heavy metals and endocrine disruptors
- Intake of caffeinated beverages close to bedtime

Work/Activities

- Exercise in a well-lit gym at night
- Travel at night in a well-lit airplane, train, or bus for extended periods
- Work at night or doing shift work
- Work in a daytime job that requires darkness (e.g., miners, X-ray technicians)

Indicators that melatonin may be imbalanced or insufficient

Home Environment

- Excessive exposure to artificial lighting (e.g., lamps, light fixtures) in surroundings between dusk and bedtime
- Exposure to computer, iPad, or other electronic devices in the evening hours when it is dark
- Exposure to one or more appliances at home that cast light at night
- Lack of exposure to morning light
- Television-watching on a TV screen at night

Sleep

- Book-reading (non-electronic books) before going to sleep
- Issues with acclimatization to different time zones with travel
- LED alarm clock next to the bed while sleeping
- Less than 5 hours of sleep per night
- Lights on during sleeping, even a night light
- Living in a well-lit neighborhood where the light from outside (e.g., from streetlamps, etc.) comes into the home at night
- Problems falling asleep or insomnia
- Use of a smartphone while in bed before going to sleep
- Warm body temperature at night

Melatonin supplements:

Contraindications

As with all supplements, interactions with medications should always be cross-referenced.

Due to isolated incidents and theoretical risks, general healthcare guidance is advised around the concomitant use of the following medications: ^{1,2}

- Anticoagulant/antiplatelets
- Anticonvulsants
- Antidiabetic drugs
- Antihypertensive drugs
- Caffeine
- CNS depressants
- Contraceptives
- Cytochrome P450 Substrates

1. Melatonin-Monograph [Internet]. Natural Medicines. 2023 [cited 2023 Jan 31]. Available from: <https://naturalmedicines-therapeuticresearch-com.scnmlib.idm.oclc.org/databases/food,-herbs-supplements/professional.aspx?productid=940> 2. Tuft C, Matar E, Menczel Schrire Z, Grunstein RR, Yee BJ, Hoyos CM. Current Insights into the Risks of Using Melatonin as a Treatment for Sleep Disorders in Older Adults. Clin Interv Aging. 2023 Jan;Volume 18:49-59.

Summary of Clinical Considerations for Assessing Personalized Melatonin Status

Clinical Aspect	Considerations
Genes, early life	Gene variants related to receptor activity, early life exposure to melatonin through breast milk, gene variants related to metabolic detoxification
Acute/Chronic triggers	Stressful events, bouts of poor-quality sleep, extensive travel across time zones, jet lag, inflammatory conditions, oxidative stress, shift work, dysregulated appetite, dysbiosis, artificial light at night, insufficient darkness, ultraprocessed diet
Bone health	May help with the balance of osteoblasts/osteoclasts
Brain & mood	Can influence cognition and mood; associated with neurotransmitters like serotonin through metabolic pathways; high kynurenine in depressed states
Cardiovascular	Produced in many tissues, transported widely, crosses lipid/water membranes
Detoxification	May be helpful with elimination of toxins in the brain through the glymphatic fluid (preliminary research); Personalized detoxification pathways may change the metabolism of melatonin, particularly CYP1A2 and sulfation enzymes.
Endocrine system	Communicates with other hormones through the circadian rhythm
Gastrointestinal tract	Produced by enterochromaffin cells; postprandial regulation; possible interaction with the gut microbiome
Immunity	May have effects on risk for certain cancers
Metabolism	Contained in high concentrations in the mitochondria

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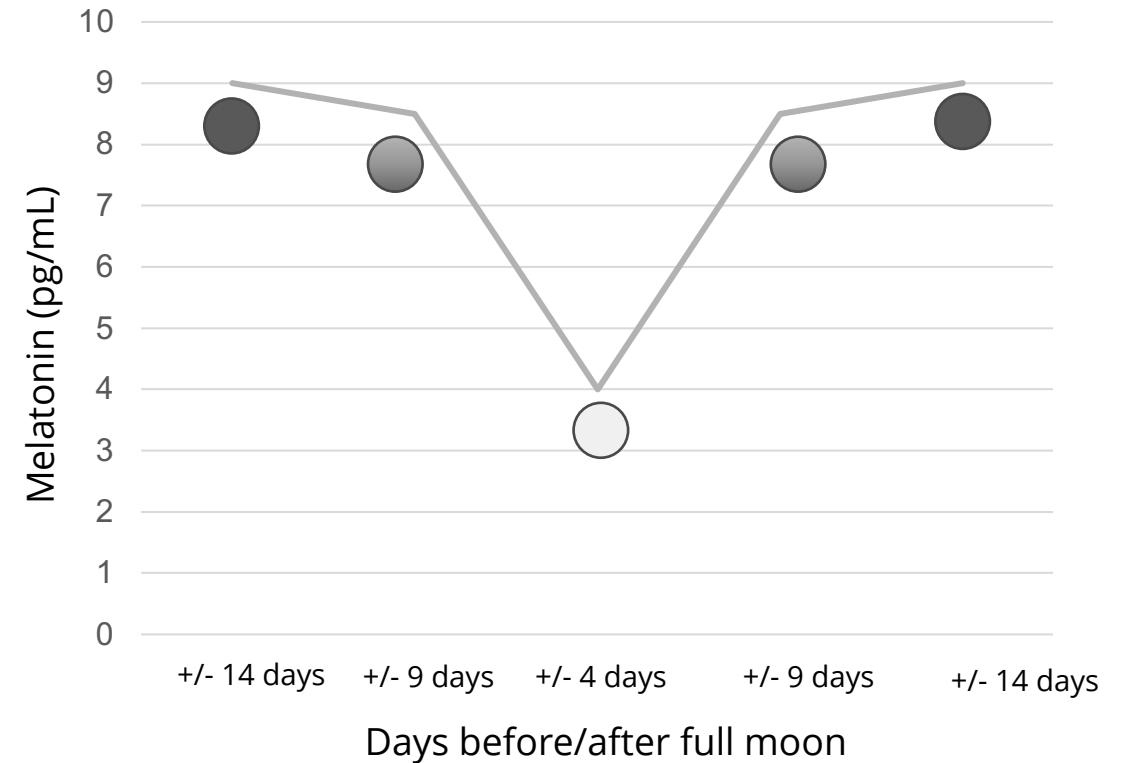
Lifestyle Factors Related to Melatonin Status

Clinical Aspect	Considerations
Sleep & relaxation	Aligning day-night rhythms will help to ensure healthy melatonin levels; ensuring sleep hygiene; wearing blue-light blocking glasses
Physical activity	May help increase serotonin and melatonin and result in less metabolic shunting through the kynurenine pathway
Nutrition	Found in both animal and plant sources; consider tryptophan-containing foods
Stress regulation & resilience	Related inversely to cortisol; upregulation of kynurenine pathway with stress; thus, the use of meditation, calming activities, bodywork, and creative arts, may help improve resilience

Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*. 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.

Full Moons Can Change Melatonin Levels

- Moon cycles (circalunar) can influence sleep and melatonin levels, irrespective of the increase in light.
- At full moon time, these were the findings:
 - Deep sleep decreased by 30% (measured by EEG delta activity during NREM sleep)
 - Time to fall asleep increased by 5 min
 - Total sleep duration was reduced by 20 min (measured by EEG)
 - Participants had less sleep quality and reduced endogenous melatonin levels.



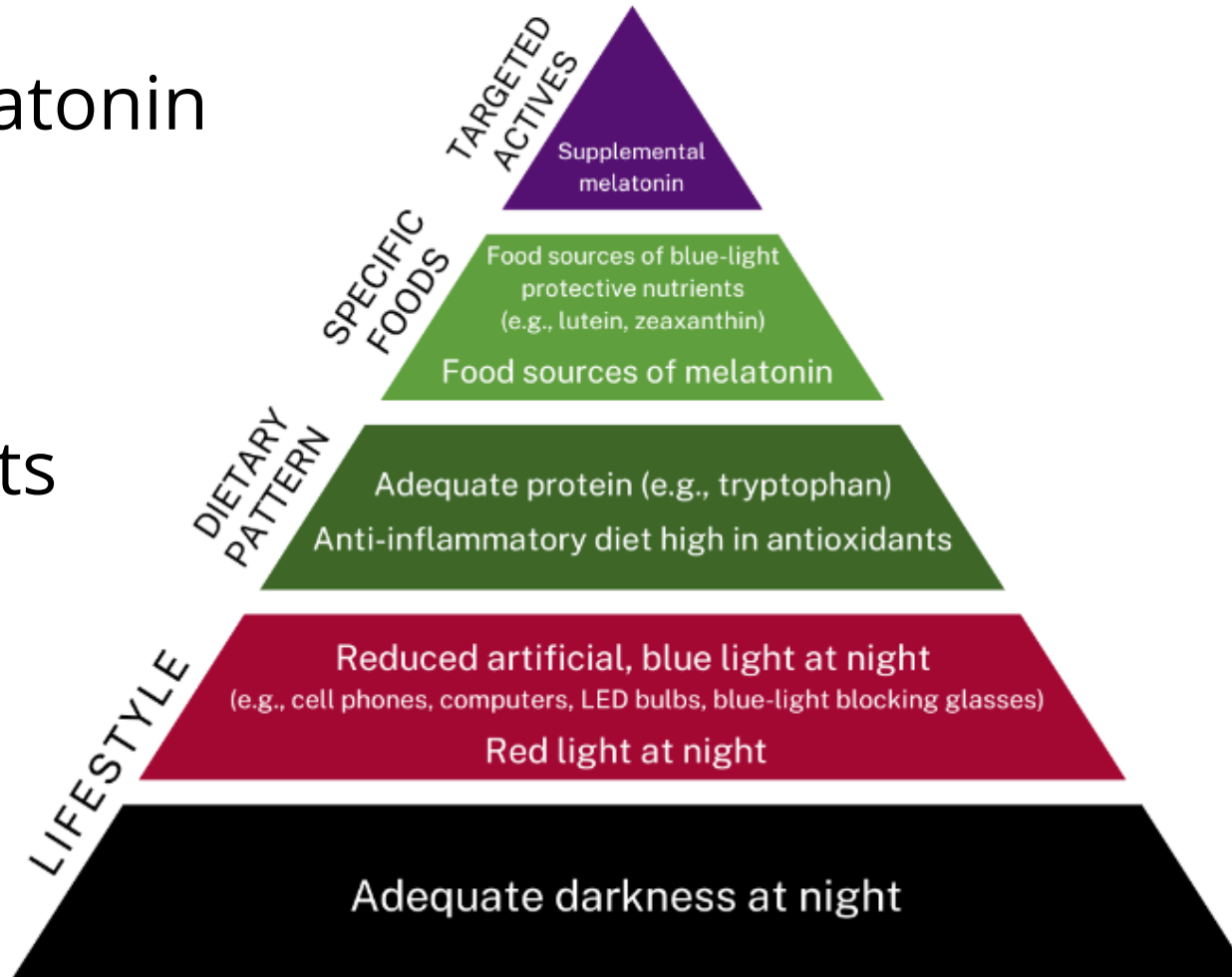
References: Cajochen C, Altanay-Ekici S, Münch M, Frey S, Knoblauch V, Wirz-Justice A. Evidence that the lunar cycle influences human sleep. *Curr Biol*. 2013 Aug 5;23(15):1485-8. doi: 10.1016/j.cub.2013.06.029. Epub 2013 Jul 25. PMID: 23891110.

Lifestyle Factors Related to Melatonin Status

Plant Melatonin

Protein + Plants

“Get light right”



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The Spirituality of Melatonin

Pineal gland referred to as
“the seat of the soul” by Rene Descartes

Tryptophan and serotonin posited as compounds
of “consciousness”. PMID: **26227538**

- Serum levels of melatonin and serotonin were higher in meditators compared with non-meditating controls. PMID: 37061347

- “The communication between systems is orchestrated by chemical messengers that transmit information, and in these, melatonin plays an important role.”

Bitzer-Quintero OK, Ortiz GG, Jaramillo-Bueno S, Ramos-González EJ, Márquez-Rosales MG, Delgado-Lara DLC, Torres-Sánchez ED, Tejeda-Martínez AR, Ramirez-Jirano J. Psycho-Neuro-Endocrine-Immunology: A Role for Melatonin in This New Paradigm. *Molecules*. 2022 Jul 30;27(15):4888. doi: 10.3390/molecules27154888. PMID: 35956837; PMCID: PMC9370109.



Review

Psycho-Neuro-Endocrine-Immunology: A Role for Melatonin in This New Paradigm

Oscar K. Bitzer-Quintero ¹, Genaro G. Ortiz ², Socorro Jaramillo-Bueno ³, Elsy J. Ramos-González ⁴, María G. Márquez-Rosales ¹, Daniela L. C. Delgado-Lara ^{2,5}, Erandis D. Torres-Sánchez ⁶, Aldo R. Tejeda-Martínez ¹ and Javier Ramirez-Jirano ^{1,*}

¹ Centro de Investigación Biomédica de Occidente, Instituto Mexicano del Seguro Social, Guadalajara 44340, Mexico; neuronim26@yahoo.com (O.K.B.-Q.); qfb_lupita@hotmail.com (M.G.M.-R.); atejeda7@hotmail.com (A.R.T.-M.)

² Departamento de Diciplinas Metodológicas y Filosóficas, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara 44340, Mexico; genarogabriel@yahoo.com (G.G.O.); daniela.delgadolar@gmail.com (D.L.C.D.-L.)

³ Hospital General Regional No 45, Instituto Mexicano del Seguro Social, Guadalajara 44100, Mexico; jsocorro@hotmail.com

⁴ Unidad de Investigacion Biomedica de Zacatecas, Instituto Mexicano del Seguro Social, Zacatecas 98000, Mexico; elsyjrg@gmail.com

⁵ Departamento Académico Formación Universitaria Ciencias de la Salud, Universidad Autónoma de Guadalajara, Guadalajara 44100, Mexico

⁶ Departamento de Ciencias Medicas y de la Vida, Centro Universitario de la Cienega, Universidad de Guadalajara, Guadalajara 47820, Mexico; erandisdheni@hotmail.com

* Correspondence: ramirez_jirano@hotmail.com



Citation: Bitzer-Quintero, O.K.; Ortiz, G.G.; Jaramillo-Bueno, S.; Ramos-González, E.J.; Márquez-Rosales, M.G.; Delgado-Lara, D.L.C.; Torres-Sánchez, E.D.; Tejeda-Martínez, A.R.; Ramirez-Jirano, J. Psycho-Neuro-Endocrine-Immunology: A Role for Melatonin in This New Paradigm. *Molecules* **2022**, *27*, 4888. <https://doi.org/10.3390/molecules27154888>

Abstract: Psychoneuroendocrinoimmunology is the area of study of the intimate relationship between immune, physical, emotional, and psychological aspects. This new way of studying the human body and its diseases was initiated in the last century’s first decades. However, the molecules that participate in the communication between the immune, endocrine, and neurological systems are still being discovered. This paper aims to describe the development of psychoneuroendocrinoimmunology, its scopes, limitations in actual medicine, and the extent of melatonin within it.

Keywords: immunology; endocrinology; neurology; psychology; melatonin

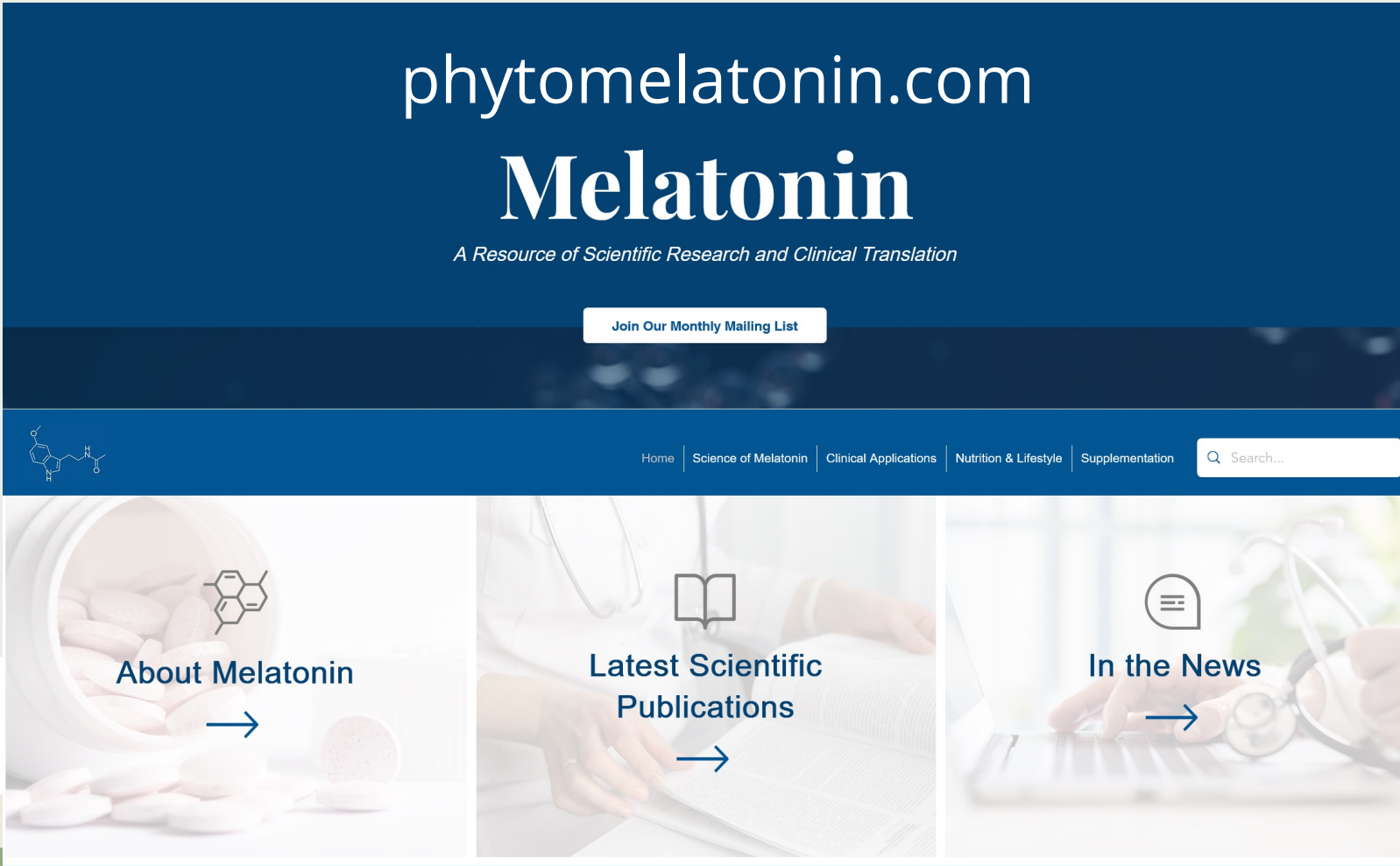
Summary

- Melatonin is a unique molecule which functions as an antioxidant, anti-inflammatory, chronobiotic, and mitochondrial regulator.
- It has become popularized over the years, especially for sleep, giving rise to increasing misinformation.
- There are distinct similarities between melatonin and vitamin D in the depth and breadth of their impact on health.
- Vitamin D deficiency can be perceived as a “sunlight deficiency” and reduced melatonin secretion as a result of “darkness deficiency” from overexposure to artificial blue light.
- First line of approach to healthy melatonin levels is to “get light right” before supplementation.
- Understanding the issues regarding supplementation, including the different formats available (animal, synthetic, and phytomelatonin), dosing, timing, contraindications, and nutrient combinations can be helpful in optimizing patient outcomes.

Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*. 2022 Sep 22;14(19):3934. doi: 10.3390/nu14193934. PMID: 36235587; PMCID: PMC9571539.

Ongoing resources

Check out this non-commercial, research website for the latest news, publications, and clinical summaries:



Thank you!

Deanna Minich, MS, PhD, CNS, IFMCP
deanna.minich@symphonynaturalhealth.com

Review

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

Deanna M. Minich ^{1,*}, Melanie Henning ², Catherine Darley ³, Mona Fahoum ⁴, Corey B. Schuler ^{5,6} and James Frame ^{7,8}

¹ Department of Human Nutrition and Functional Medicine, University of Western States, Portland, OR 97213, USA

² Department of Sports and Performance Psychology, University of the Rockies, Denver, CO 80202, USA

³ College of Naturopathic Medicine, National University of Natural Medicine, Portland, OR 97201, USA

⁴ School of Naturopathic Medicine, Bastyr University, Kenmore, WA 98028, USA

⁵ School of Nutrition, Sonoran University of Health Sciences, Tempe, AZ 85282, USA

⁶ Department of Online Education, Northeast College of Health Sciences, Seneca Falls, NY 13148, USA

⁷ Natural Health International Pty., Ltd., Sydney, NSW 2000, Australia

⁸ Symphony Natural Health, Inc., West Valley City, UT 84119, USA

* Correspondence: deannaminich@hotmail.com

Abstract: Melatonin has become a popular dietary supplement, most known as a chronobiotic, and for establishing healthy sleep. Research over the last decade into cancer, Alzheimer’s disease, multiple sclerosis, fertility, PCOS, and many other conditions, combined with the COVID-19 pandemic, has led to greater awareness of melatonin because of its ability to act as a potent antioxidant, immune-active agent, and mitochondrial regulator. There are distinct similarities between melatonin and vitamin D in the depth and breadth of their impact on health. Both act as hormones, affect multiple systems through their immune-modulating, anti-inflammatory functions, are found in the skin, and are responsive to sunlight and darkness. In fact, there may be similarities between the widespread concern about vitamin D deficiency as a “sunlight deficiency” and reduced melatonin secretion as a result of “darkness deficiency” from overexposure to artificial blue light. The trend toward greater use of melatonin supplements has resulted in concern about its safety, especially higher doses, long-term use, and application in certain populations (e.g., children). This review aims to evaluate the recent data on melatonin’s mechanisms, its clinical uses beyond sleep, safety concerns, and a thorough summary of therapeutic considerations concerning dietary supplementation, including the different formats available (animal, synthetic, and phytemelatonin), dosing, timing, contraindications, and nutrient combinations.

Keywords: melatonin; phytemelatonin; vitamin D; sleep; circadian rhythm; antioxidant; blue light; chronobiotic; chrononutrition; darkness deficiency



Citation: Minich, D.M.; Henning, M.; Darley, C.; Fahoum, M.; Schuler, C.B.; Frame, J. Is Melatonin the “Next Vitamin D”? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients* **2022**, *14*, 3934. <https://doi.org/10.3390/nu14193934>

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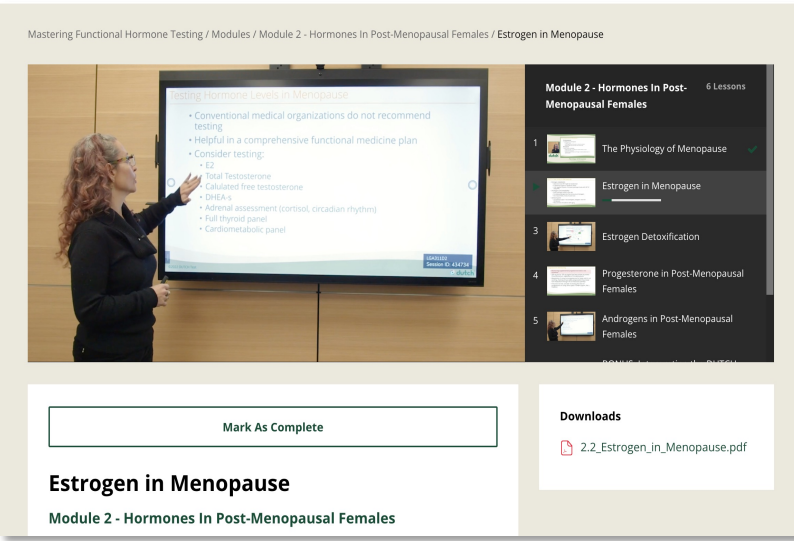
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