

Other Compounds Found in Plant-Based Melatonin and Synthetic Melatonin: The Good, The Bad and The Ugly

By Gene Bruno, MS, MHS, RH(AHG)
Chief Scientific Officer, Nutraland USA, Inc.

Previously, I wrote an article providing an overview of the scientific difference between synthetic melatonin and plant-based melatonin. In the current article I will expand on this, with a focus on the other compounds found in these two forms of melatonin, and the potential impact those compounds may have on our health. Let's start with Somnatural® phytomelatonin.

SOMNATURAL®PHYTOMELATONIN

Somnatural® phytomelatonin is natural, plant-based, Vegan Certified, Non-GMO Project Verified, kosher, and halal, which has broad appeal. In addition, laboratory analysis of Somnatural® reveals that it also contains 2-hydroxymelatonin and N-acetylserotonin. These two naturally occurring compounds may be present at a collective level of 2% in Somnatural® phytomelatonin addition to its natural phytomelatonin.

The significance of this is that these two compounds may offer potential health benefits.

2-hydroxymelatonin

Laboratory research¹ found that there is a synergistic stimulating effect of 2-hydroxymelatonin and a specific bone protein (bone morphogenetic protein (BMP)-4). Together, they were found beneficial for anabolic effects on bone.

Other research has shown that 2-hydroxymelatonin could contribute to plant stress resistance², promoting resistance to physical stresses³. In fact, research has shown that 2-hydroxymelatonin alleviated the effects of simultaneous physical stressors (e.g., a combination of cold and drought) in plants⁴.

In laboratory research, the anti-cancer activity of 2-hydroxymelatonin was found to be more potent than that of melatonin for immune health⁵.

N-Acetylserotonin

Laboratory research found that N-acetylserotonin inhibited hydrogen peroxide from causing oxidative damage to cells^{6 7}.

Laboratory research has shown that N-acetylserotonin has neuroprotective properties, and can exert neuroprotective effects by inhibiting oxidative stress, anti-apoptosis, regulating autophagy dysfunction, and anti-inflammatory⁸.

Brain-derived neurotrophic factor (BDNF) is a key molecule in the body that plays an important role in nerve survival and growth, serves as a neurotransmitter modulator, and participates in neuronal plasticity (i.e., adaptability to changes in environment), which is essential for learning and memory⁹. BDNF itself is important for long-term memory¹⁰. In multiple studies, N-acetylserotonin has been shown to promote the production of BDNF^{11 12 13}.

Research suggests that N-acetylserotonin may play an important role in mood regulation and may have antidepressant activity, which may be due to its ability to promote BDNF¹⁴.

Likewise, research¹⁵ has shown that N-acetylserotonin may play an important role in mood regulation, as well as stimulate proliferation of neuroprogenitor cells (i.e., cells that give rise to many different nerve cells) and prevent some of the negative effects of sleep deprivation. It may also turn out to play a role in mitigating common, age-related cognitive decline¹⁶.

SYNTHETIC MELATONIN

By comparison, synthetic melatonin may also contain other compounds that are *not* necessarily desirable. Consider that there are four different production methods for producing synthetic melatonin. During the production process, a large number of side products or residual compounds of the melatonin preparation processes also appear. Here is a list of some of the most common of these which are present in the commercially available synthetic melatonin preparations. Most occur at concentrations below 0.5%¹⁷:

- 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-hydroxytryptamine derivatives
- 5-methoxytryptamine derivatives
- N-acetyl- and diacetyl-indole derivatives
- 1,3-diphthalimidopropane
- hydroxy-bromo-propylphthalimide
- chloropropylphthalimide

Below are descriptions of some of these contaminants:

1,2,3,4-tetrahydro- β -carboline-3-carboxylic acid

1,2,3,4-Tetrahydro- β -carboline is a serotonin reuptake inhibitor and metabolite of tryptamine.¹⁸ *In vivo*, 1,2,3,4-tetrahydro- β -carboline reduces serotonin levels in rat forebrain. It induces serotonin-mediated hyperactivity syndrome (HHS) in rats.¹⁹ It is not known if this compound will have similar side effects to those of other serotonin reuptake inhibitors, including feeling agitated, shaky or anxious, feeling or being sick, indigestion, diarrhea or constipation, loss of appetite and weight loss, dizziness, blurred vision, dry mouth, excessive sweating, sleeping problems or drowsiness, headaches, loss of libido (reduced sex drive), difficulty achieving orgasm during sex or masturbation in men, difficulty obtaining or maintaining an erection (erectile dysfunction).²⁰

1,1'-ethylidenebis-(tryptophan) (so-called peak E)

The eosinophilia-myalgia syndrome (EMS) is an inflammatory disease that occurred in epidemic proportions in the United States during 1989. Cases of EMS were also reported in Europe and elsewhere. Clinically, EMS resembles the Spanish toxic oil syndrome. EMS has been associated with ingestion of

manufactured L-tryptophan that contained the trace contaminant 1,1'-ethylidenebis(tryptophan), aka, "peak E"²¹.

3-(phenylamino)alanine & 2-(3-indolylmethyl)-tryptophan

In addition to 1,1'-ethylidenebis(tryptophan), another trace contaminant, 3-(phenylamino)alanine, has been reported as having been ingested in significantly greater amounts of both 3-(phenylamino)alanine in EMS patients. 3-(phenylamino)alanine is chemically similar to 3-phenylamino-1,2-propanediol, an aniline derivative isolated from samples of oil that were consumed by persons in whom the toxic oil syndrome developed. The discovery of an aniline-derived contaminant raises the possibility that EMS and toxic oil syndrome may have a common etiologic trigger.²² Likewise, 2-(3-indolylmethyl)-tryptophan is another one of the contaminants identified in the pathogenesis of eosinophilia-myalgia syndrome.²³

Formaldehyde-melatonin/Formaldehyde-melatonin condensation products/ hydroxymelatonin isomers

Three different commercially available melatonin preparations were analyzed by on-line HPLC-electrospray ionization-tandem mass spectrometry. All three samples contained the same impurities at the approximately 0.1-0.5% level of parent melatonin. One compound was determined to be a C-2 oxidation product of hydroxymelatonin and a group of four regioisomers were identified as melatonin-formaldehyde condensation products (*Note*: This is not the same as 2-hydroxymelatonin which, as previously noted, is a beneficial compound). These latter contaminants are structural analogues of the case-associated peak "E" found in L-tryptophan implicated in onset of eosinophilia-myalgia syndrome.²⁴

5-hydroxytryptamine derivatives

Some 5-hydroxytryptamine derivatives may be distinguished from tryptamine in exerting high intrinsic activity at receptors in vascular and neuronal models relevant to migraine.²⁵

CONCLUSION

It should be noted that in a scientific journal article, "Phytomelatonin versus synthetic melatonin in cancer treatments"²⁶, the researchers propose that phytomelatonin is a desirable alternative to synthetic melatonin. Their rationale for this is as follows:

"The interest of this proposal arose from the need to avoid the unwanted by-products present in synthetic melatonin preparations. The substitution of synthetic melatonin by phytomelatonin in medical treatments could also lead to substantial improvements in the results."

Nutraland USA offers clean, plant-based and sustainable branded ingredients supported by science. Our nutraceuticals are good for you, and good for the planet. For more information about how you can use Somnatural® phytomelatonin in your dietary supplements, contact gene.bruno@nutrallandusa.com; 949-988-7615.

REFERENCES

¹ Lee SH, Hwang JW, Han Y, Lee KY. Synergistic stimulating effect of 2-hydroxymelatonin and BMP-4 on osteogenic differentiation in vitro. *Biochem Biophys Res Commun*. 2020 Jul 5;527(4):941-946.

² Yu Y, Lv Y, Shi Y, Li T, Chen Y, Zhao D, Zhao Z. The Role of Phyto-Melatonin and Related Metabolites in Response to Stress. *Molecules*. 2018 Jul 28;23(8):1887.

-
- ³ Hy-Jung L, Kyoungwhan B. 2-Hydroxymelatonin promotes the resistance of rice plant to multiple simultaneous abiotic stresses (combined cold and drought). *J Pineal Res.* 2016; 61(3):303-16.
- ⁴ Lee HJ, Back K. 2-Hydroxymelatonin promotes the resistance of rice plant to multiple simultaneous abiotic stresses (combined cold and drought). *J Pineal Res.* 2016 Oct;61(3):303-16.
- ⁵ Yang Y, Zhou R, Park SY, Back K, Bae WK, Kim KK, Kim H. 2-Hydroxymelatonin, a Predominant Hydroxylated Melatonin Metabolite in Plants, Shows Antitumor Activity against Human Colorectal Cancer Cells. *Molecules.* 2017 Mar 14;22(3):453.
- ⁶ Yidian W, Jihe K, Xudong G, Daxue Z, Mingqiang L, Xuwen K. N-Acetylserotonin Protects Rat Nucleus Pulposus Cells Against Oxidative Stress Injury by Activating the PI3K/AKT Signaling Pathway. *World Neurosurg.* 2023 May 9:S1878-8750(23)00621-6.
- ⁷ Kang J, Wang Y, Guo X, He X, Liu W, Chen H, Wang Z, Lin A, Kang X. N-acetylserotonin protects PC12 cells from hydrogen peroxide induced damage through ROS mediated PI3K / AKT pathway. *Cell Cycle.* 2022 Nov;21(21):2268-2282. doi: 10.1080/15384101.2022.2092817.
- ⁸ Kang JH, Guo XD, Wang YD, Kang XW. Neuroprotective Effects of N-acetylserotonin and Its Derivative. *Neuroscience.* 2023 May 1;517:18-25.
- ⁹ Bathina S, Das UN. Brain-derived neurotrophic factor and its clinical implications. *Arch Med Sci.* 2015 Dec 10;11(6):1164-78.
- ¹⁰ Bekinschtein P, Cammarota M, Kathe C, Slipczuk L, Rossato JI, Goldin A, Izquierdo I, Medina JH. BDNF is essential to promote persistence of long-term memory storage. *Proc Natl Acad Sci U S A.* 2008 Feb 19;105(7):2711-6.
- ¹¹ Yoo JM, Lee BD, Sok DE, Ma JY, Kim MR. Neuroprotective action of N-acetyl serotonin in oxidative stress-induced apoptosis through the activation of both TrkB/CREB/BDNF pathway and Akt/Nrf2/Antioxidant enzyme in neuronal cells. *Redox Biol.* 2017 Apr;11:592-599.
- ¹² Iuvone PM, Boatright JH, Tosini G, Ye K. N-acetylserotonin: circadian activation of the BDNF receptor and neuroprotection in the retina and brain. *Adv Exp Med Biol.* 2014;801:765-71.
- ¹³ Yoo DY, Nam SM, Kim W, Lee CH, Won MH, Hwang IK, Yoon YS. N-acetylserotonin increases cell proliferation and differentiating neuroblasts with tertiary dendrites through upregulation of brain-derived neurotrophic factor in the mouse dentate gyrus. *J Vet Med Sci.* 2011 Nov;73(11):1411-6.
- ¹⁴ Tosini G, Ye K, Iuvone PM. N-acetylserotonin: neuroprotection, neurogenesis, and the sleepy brain. *Neuroscientist.* 2012 Dec;18(6):645-53.
- ¹⁵ Tosini G, Ye K, Iuvone PM. N-acetylserotonin: neuroprotection, neurogenesis, and the sleepy brain. *Neuroscientist.* 2012 Dec;18(6):645-53..
- ¹⁶ Oxenkrug G, Ratner R. N-acetylserotonin and aging-associated cognitive impairment and depression. *Aging and Disease.* 2012; 3(4):330-8.
- ¹⁷ Arnao MB, Hernández-Ruiz J. The Potential of Phytomelatonin as a Nutraceutical. *Molecules.* 2018 Jan 22;23(1):238.
- ¹⁸ Rommelspacher H, Bade P, Coper H, et al. Inhibition of the reuptake of serotonin by tryptoline. *Naunyn Schmiedebergs Arch. Pharmacol.* 1976; 292(1): 93-95.
- ¹⁹ Pannier L, Rommelspacher H. Actions of tetrahydronorharmane (tetrahydro- β -carboline) on 5-hydroxytryptamine and dopamine mediated mechanisms. *Neuropharmacology.* 1987; 20(1):1-8 .
- ²⁰ Side effects - Selective serotonin reuptake inhibitors (SSRIs). NHS. Page last reviewed: 8 December 2021. Retrieved June 22, 2023 from <https://www.nhs.uk/mental-health/talking-therapies-medicine-treatments/medicines-and-psychiatry/ssri-antidepressants/side-effects/>
- ²¹ Yamaoka KA, Miyasaka N, Inuo G, Saito I, Kolb JP, Fujita K, Kashiwazaki S. 1,1'-Ethylidenebis(tryptophan) (Peak E) induces functional activation of human eosinophils and interleukin 5 production from T lymphocytes: association of eosinophilia-myalgia syndrome with a L-tryptophan contaminant. *J Clin Immunol.* 1994 Jan;14(1):50-60.
- ²² Mayeno AN, Belongia EA, Lin F, Lundy SK, Gleich GJ. 3-(Phenylamino)alanine, a novel aniline-derived amino acid associated with the eosinophilia-myalgia syndrome: a link to the toxic oil syndrome? *Mayo Clin Proc.* 1992 Dec;67(12):1134-9.
- ²³ Williamson BL, Johnson KL, Tomlinson AJ, Gleich GJ, Naylor S. On-line HPLC-tandem mass spectrometry structural characterization of case-associated contaminants of L-tryptophan implicated with the onset of eosinophilia myalgia syndrome. *Toxicol Lett.* 1998 Oct 15;99(2):139-50.

²⁴ Naylor S, Johnson KL, Williamson BL, Klarskov K, Gleich GJ. Structural characterization of contaminants in commercial preparations of melatonin by on-line HPLC-electrospray ionization-tandem mass spectrometry. *Adv Exp Med Biol.* 1999;467:769-77.

²⁵ John GW, Pauwels PJ, Perez M, Halazy S, Le Grand B, Verscheure Y, Valentin JP, Palmier C, Wurch T, Chopin P, Marien M, Kleven MS, Koek W, Assie MB, Carilla-Durand E, Tarayre JP, Colpaert FC. F 11356, a novel 5-hydroxytryptamine (5-HT) derivative with potent, selective, and unique high intrinsic activity at 5-HT_{1B/1D} receptors in models relevant to migraine. *J Pharmacol Exp Ther.* 1999 Jul;290(1):83-95.

²⁶ Arnao MB, Hernández-Ruiz J. Phytomelatonin versus synthetic melatonin in cancer treatments. *Biomed Res Clin Prac.* 2018; 3(3):1-6.