

## APPLICATIONS

- Sleep Support
- Immune Support
- Antioxidant Support



## INTRODUCTION

Endogenous melatonin has many important functions in the body. Its biological roles can be receptor-dependent, such as sleep maintenance and circadian rhythm support, or receptor-independent, such as antioxidant support.<sup>1</sup> While melatonin is best known as a product of the pineal gland, it can be produced by other areas in the body as well, including the retina and gastrointestinal tract.<sup>2</sup>

Melatonin can be found in animal foods such as eggs and fish, as well as in plant foods such as nuts, germinated seeds and legumes, mushrooms, and fruits.<sup>3,4,5,6</sup> Studies have shown that melatonin is well-absorbed from dietary sources.<sup>7</sup> Supplemental melatonin may assist the body's natural processes that support healthy sleep, maintain healthy immunity, and support normal antioxidant function.\*

Melatonin is made at our U.S. manufacturing facility using a specialized proprietary process in which we solvate synthetic melatonin powder into a water/ethanol blend. While melatonin supplements are available from both animal and synthetic sources, we use synthetic melatonin to avoid the potential risk of zoonotic infection. Because Melatonin is made in our own facility, we control all aspects of quality, including stringent ID testing, microbial testing, and heavy metal testing. NutraMedix rigorously follows current good manufacturing practices (cGMP), as do our suppliers.

## SLEEP SUPPORT

Endogenous melatonin is a neuroendocrine hormone produced by the pineal gland that helps to regulate the 24-hour circadian rhythm.\* In the body, tryptophan is converted to 5-hydroxytryptophan, then to serotonin, then to N-acetylserotonin, and finally to melatonin.<sup>3</sup> Melatonin secretion is controlled by retinal ganglion cells that receive light and dark cues from the environment and convey this information

to the suprachiasmatic nucleus (SCN) in the hypothalamus. The SCN, in turn, triggers melatonin release from the pineal gland which regulates the sleep-wake cycle.<sup>1</sup>

While melatonin is continually produced, blood levels are higher in the evening to help prepare for sleep.<sup>8</sup> Daytime light helps to suppress melatonin secretion, promoting alertness. Soon after sunset, melatonin levels begin to rise in preparation for sleep. It should be noted that normal melatonin secretion may be delayed by external cues such as blue light from screens too close to bedtime.<sup>8</sup> Melatonin levels also decrease with age, particularly after the age of 60.<sup>9</sup>

Exogenous melatonin may be helpful to support and maintain a normal circadian rhythm.\* It may also help to support normal, healthy sleep as appropriate for shift work or a given time zone.\*<sup>10</sup> A meta-analysis of 17 studies involving 284 participants concluded that supplemental melatonin may help to support healthy sleep latency, maintain normal sleep efficiency, and support healthy sleep duration.\*<sup>11</sup> In addition, it may help to maintain a normal percentage of REM sleep and maintain melatonin levels already within the normal range.\*<sup>12,13</sup>

## IMMUNE SUPPORT

Melatonin may help to support normal cytokine production.\* In vitro studies have shown that melatonin may help to support Th1 cells and cytokines such as IL-2 and interferon-gamma already within the normal range.\* It may also help to support healthy monocyte function and normal IL-6 production, already within the normal range.\*<sup>14</sup> In innate immunity, melatonin may help to maintain levels of natural killer (NK) cells already within the normal range.\*<sup>14</sup> In adaptive immunity, melatonin may help to maintain CD69 from CD4+ helper T cells already within the normal range.\*<sup>14</sup>

Leukocytes both produce and respond to melatonin.\*<sup>2,15,16</sup> Endogenous melatonin interacts with calmodulin in the cytosol; with nuclear binding receptors in monocytes and lymphocytes; and with MT1 and MT2 G-protein coupled receptors in cell membranes; all of which help to regulate a healthy immune response.\*<sup>17,18</sup> Supplemental melatonin may help to maintain normal immune homeostasis.\*<sup>15</sup> In addition, melatonin may help with healthy inflammatory response.\*<sup>15</sup>

As melatonin levels decrease with age, there are repercussions for both innate immunity and adaptive immunity, including humoral and cellular immunity.<sup>18</sup> This leads to a suboptimal immune response, particularly of NK cells, interferon-gamma, and associated cytokines and chemokines.<sup>18</sup> For these reasons, it may be prudent to consider supplemental melatonin for healthy immune support, particularly in older individuals.

## OTHER USES

### Antioxidant Support

Endogenous melatonin and its metabolites help to support antioxidant activity for both reactive oxygen species (ROS) and reactive nitrogen species (RNS).<sup>17,19</sup> Melatonin may help to support normal free radical scavenging, maintain levels of antioxidant and prooxidant enzymes already within the normal range, and support mitochondrial function.\*<sup>17</sup> Antioxidant support is attributed to various mechanisms, from interactions between melatonin and calmodulin to the support of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx).<sup>17,20</sup>

Melatonin also supports normal non-enzymatic antioxidant activity.\*<sup>20</sup> In the mitochondria, melatonin helps to stabilize the inner membrane and supports normal functioning of the electron transport chain, which helps to maintain normal ATP production.\*<sup>17</sup> It also helps to maintain intracellular glutathione levels already within the normal range.\*<sup>18</sup> Melatonin supports antioxidant activity in both lipophilic and lipophobic environments and is widely distributed to tissues and cells, including cell membranes, cytosol, and cellular organelles.\*<sup>20</sup> Some researchers have found melatonin's antioxidant support to be more robust than that of vitamin E.\*<sup>21</sup>

## SAFETY AND CAUTIONS

Melatonin is generally well tolerated when used as recommended. The most common side effects are drowsiness, dizziness, nausea, and headache. Melatonin has been used in doses up to 10 mg daily for 2 months and in doses up to 8 mg

daily for 6 months.<sup>22</sup> Serious side effects are rare. One study in postmenopausal women taking 6 mg daily for 2 weeks found that melatonin may increase levels of VLDL and triglycerides.<sup>23</sup> At 3 mg per day, some study participants developed a rash, though at the same rate as placebo.<sup>22</sup> Melatonin may cause gastrointestinal effects such as nausea and abdominal cramps, though generally at the same rate as placebo and usually with prompt resolution.<sup>22,24,25</sup> In healthy adults between the ages of 60-71 years given a single dose of 3 mg melatonin, participants experienced increased postural swaying which could theoretically increase the risk of falls.<sup>26</sup> Cognitive function in older adults, however, is not affected.<sup>26</sup> Melatonin may cause a temporary dip in mood, and may worsen depression in those diagnosed.<sup>27,28</sup> Reports are mixed as to whether melatonin may decrease or increase the risk of seizures.<sup>22</sup>

Melatonin may have additive effects with anticoagulant, antiplatelet, hypoglycemic, and CNS depressant drugs.<sup>22,29</sup> It may decrease the effects of anticonvulsants,<sup>30</sup> immunosuppressants,<sup>31</sup> and extended-release nifedipine.<sup>32</sup> Theoretically, melatonin may have additive effects with antihypertensive drugs,<sup>33</sup> though it may also decrease the effects.<sup>32</sup> Oral contraceptive drugs may increase the adverse effects of melatonin due to the alteration of endogenous melatonin.<sup>34</sup> CYP1A2 and CYP2C19 substrates may increase levels of melatonin, and melatonin may increase levels of these substrates.<sup>22</sup> There is insufficient safety data available in pregnancy and lactation, thus melatonin should be avoided in these states. Those using melatonin should be advised to avoid driving for 4-5 hours after consumption, as it may cause daytime drowsiness.<sup>22</sup>

Safety not documented in breastfeeding or pregnant women, or in children under 3 years of age due to insufficient safety research.

**\* This statement has not been evaluated by the Food and Drug Administration. This product is not intended to treat, cure, or prevent any diseases.**

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