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REVIEW ARTICLE

Melatonin as an Antioxidant Supplement in Athletes: A Literature Review of Current Evidence

Taewan Kim MS, Jinkyung Cho PhD
College of Sport Science, Sungkyunkwan University, Suwon, Korea

PURPOSE: Melatonin (MT; N-acetyl-5-methoxytryptamine) is synthesized and released during the night in specialized pineal gland cells. Among its variety of physiological properties, recent research indicates that MT has both antioxidant and anti-inflammatory actions. The aim of this literature review was to summarize recent evidence that describes the effects of MT on the muscle function and preventive role of MT on exercise-induced muscle damage.

METHODS: This review included previous research using the PubMed, Science Direct, and Google Scholar databases.

RESULTS: We discussed the molecular structure and biological function of MT and the potential role of this hormone in antioxidant and anti-inflammatory processes. These activities have been studied in relation to the protection of muscle function against oxidative damage. In addition, MT is reported to have positive effects on muscle damage, lipid metabolism, and inflammatory responses in well-trained athletes following exercise training. Moreover, the potential beneficial effects of melatonin and mechanisms related to performance were revealed through improved sleep quality, muscle damage, and antioxidant levels in trained athletes.

CONCLUSIONS: Finally, this review suggested that possibilities of MT as a supplementation for athletes; however, further research is required to investigate the specific mechanisms involved, the dose and duration of use, and the beneficial and detrimental effects of MT on athletic performance.

Key words: Melatonin, Antioxidant, Performance, Recovery, Athlete

INTRODUCTION

Vigorous exercise training and submaximal muscle contraction elevates the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), inducing oxidative stress in skeletal muscle [1]. Increased ROS-induced oxidative stress negatively affects cellular components, including proteins and DNA, which can result in muscle damage and fatigue [2]. On the other hand, recent evidence emphasizes the significance of redox signaling on reactions of skeletal muscle following the exercise training, including the increase of mitochondrial biogenesis and endogenous antioxidants enzymes as well as other health benefits such as glucose metabolism, growth factor signaling and immune system [3,4]. In this respect, continuous repetitive training enhances antioxidant capacity and reduces oxidative damage [5].

Growing evidence shows that elite athletes can be susceptible to oxidative stress during frequent high-intensity training sessions, which results in greater oxygen consumption and increased ROS production [6]. In addition, insufficient rest and lack of proper recovery between training sessions preclude adequate repair and adaptation after exercise-induced muscle damage, which can lead to cumulative oxidative stress. Increased ROS production can induce the activation of cellular transcription factors such as NF-κB which control systemic inflammatory response [7]. Thus, maintaining a balanced ROS level is particularly important for minimizing muscle damage for athletes [8].

Antioxidants play a role in protection against the harmful effects of ROS by exercise training. Recently, melatonin (MT; *N*-acetyl-5-methoxytryptamine), which is a hormone produced in the pineal gland of the brain, has identified physiological properties that produce anti-inflammatory and antioxidant effects. Although pineal gland is the primary source of MT production and release into the bloodstream, the receptors

Corresponding author: Jinkyung Cho **Tel** +82-31-299-6900 **Fax** +82-31-299-6929 **E-mail** lovebuffalo@gmail.com
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and enzymes responsible for the synthesis of MT are located in various tissues [9,10]. In addition, previous studies have identified MT as a direct free radical scavenger that neutralizes reactive oxygen species (ROS) and reactive nitrogen species (RNS). Moreover, MT has been shown to improve mitochondrial function by enhancing the activity of antioxidant enzymes, thereby preventing oxidative damage [11-13].

MT has recently been shown to provide several potential benefits including those of improved sleep quality and antioxidant regulation. These positive aspects support the potential of MT to supplement the recovery process of athletes [14]. This review summarized the recent evidence regarding the molecular structure and biological functions of MT and the potential role of this hormone in antioxidant and anti-inflammatory processes.

METHODS

This study involved an extensive review of previous research using the PubMed, Science Direct, and Google Scholar databases. The keywords chosen for the searches were: "melatonin" AND ("antioxidant" OR "anti-inflammatory" OR "sleep") AND ("exercise" OR "exercise training" OR "high-intensity exercise" OR "athletes" OR "performance" OR "intensive exercise") AND ("muscle" OR "muscle strength" OR "muscle power" OR "muscle fatigue" OR "oxidative stress" OR "muscle damage" OR "inflammation").

Inclusion criteria followed was: 1) accessed to full-text articles, 2) published in English, 3) designed by randomized control study (RCT). Exclusion criteria followed was: 1) accessed by conference abstract and book, 2) published in other language than English.

RESULTS

1. Molecular structure and biological functions of melatonin

MT is a versatile and potent natural antioxidant that is produced by plants and mammals but can also be acquired through the consumption of fruits and vegetables [15]. The MT molecule is synthesized in specialized cells of the pineal gland called pinealocytes primarily during the dark phase of the day when there is a significant increase in the activity of the serotonin-*N*-acetyltransferase (arylalkylamine *N*-acetyltransferase; AA-NAT) enzyme. This enzyme converts 5-hydroxytryptamine (5HT; commonly known as serotonin) into *N*-acetylserotonin, which is further converted into MT through the action of the acetylserotonin *O*-methyltransferase enzyme (Fig. 1) [16].

MT is distinguished by its electron-rich aromatic indole heterocycle, which enables it to function as an electron donor and effectively reduce cell concentrations of electrophilic species. Furthermore, the side chains of MT present both hydrophilic and lipophilic properties, which allow for easy access across cell membranes, where the MT molecules can offer protection against oxidative damage [17,18]. In addition, the methoxy and amide groups present in MT enhance the free radical scavenging capability and complement the ability of the electron-rich indole to neutralize these harmful species. Furthermore, the electronic structure of the indole ring provides MT with high resonance stability, making it particularly effective against ROS. This combination of structural elements reinforces the effectiveness of MT as both an antioxidant and ROS scavenger [19,20]. The carbon atoms (C-atoms) within the indole ring structure attract hydroxyl radicals (HO) and nitric oxide radicals (NO) due to their low energetic barrier, which facilitates adduct formation [14,21]. These properties allow MT to efficiently scavenge a wide range of reactive species, including peroxyl radicals (ROO), singlet oxygen, and peroxynitrite ($ONOO^-$).

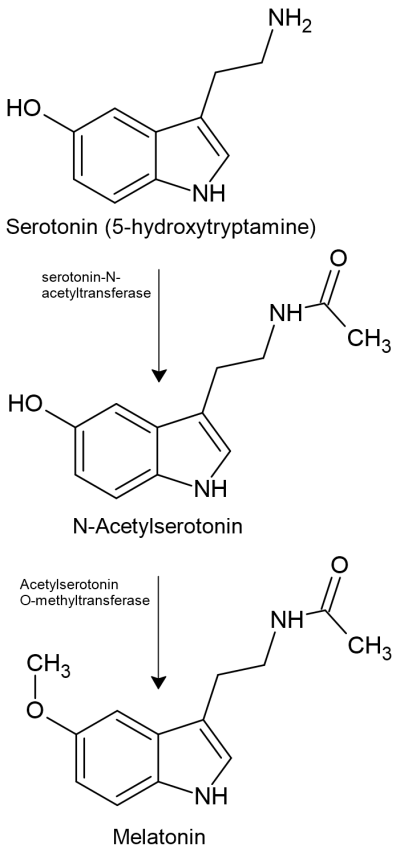

Fig. 1. Molecular structure of melatonin.

In addition, MT inhibits nitric oxide synthase and hypochlorous acid (HClO) activities [22] and has the ability to transform into several metabolites using oxidative and enzymatic pathways. The resultant metabolites, including 3-OHMT, 6-OHMT, AMK, and AFMK, are potent free radical scavengers [14] and significantly contribute to the comprehensive antioxidant effects of MT. MT can be distinguished from commonly used antioxidants by its capacity to effectively neutralize up to ten categories of ROS/RNS. This characteristic establishes MT as a more potent antioxidant than conventionally used compounds [23].

2. Secretion of melatonin

The majority of organisms, including humans, display a physiological and behavioral pattern that follows a 24-hour cycle in harmony with their environment, which is referred to as a circadian rhythm. Circadian rhythms collectively form a circadian system that ensures the synchronization of internal cellular clocks with daily environmental changes, especially the light-dark cycle [24]. The circadian system is hierarchically structured with a central pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN serves as a master clock that regulates neuroendocrine functions, autonomic responses, and sleep-wake cycles [11]. At night, the SCN generates a neural output signal that triggers MT production in the pineal gland. Thus, exposure to light and engagement in physical activity regulate the SCN and suppress the production of MT (Fig. 2) [25,26].

MT is produced through a series of biochemical steps. First, tryptophan is taken up from the bloodstream and converted into serotonin. Serotonin is then transformed into MT in a two-step process involving the sequential action of two enzymes: serotonin-*N*-acetyltransferase (NAT) and hydroxyindole-*O*-methyltransferase (HIOMT). Norepinephrine then binds to adrenergic β1 receptors, which initiates the synthesis of MT. This binding activates pineal adenylate cyclase, which results in an increase in cyclic AMP (cAMP) levels and de novo synthesis of NAT or its activator. The inducible cAMP early repressor is a form of the cAMP-responsive element modulator that is activated in conjunction with NAT and limits the night-time production of MT, contributing to the regulation of MT levels in the body [27,28].

MT is highly soluble in both lipids and water, which allows it to easily cross cell membranes, after which it is promptly released into the bloodstream rather than being stored within the pineal gland. Once established in the bloodstream, MT accesses various body fluids, tissues, and cellular compartments [29]. MT is primarily secreted during nighttime hours, with its highest levels in the bloodstream typically occurring at approximately 03:00-04:00; however, the timing can vary based on the chronotype of the individual. During the daytime, MT levels are either undetectable or relatively low, especially in well-rested individuals [27,30].

3. Role of melatonin: ant–inflammatory, antioxidant

MT is an immune modulator with pro- and anti-inflammatory properties, both in the context of diseases and in relation to mitochondrial function. It shows diverse effects on the immune system and mitochondria that suggest its therapeutic potential for a wide range of conditions. MT is a potent compound that improves mitochondrial function by act-

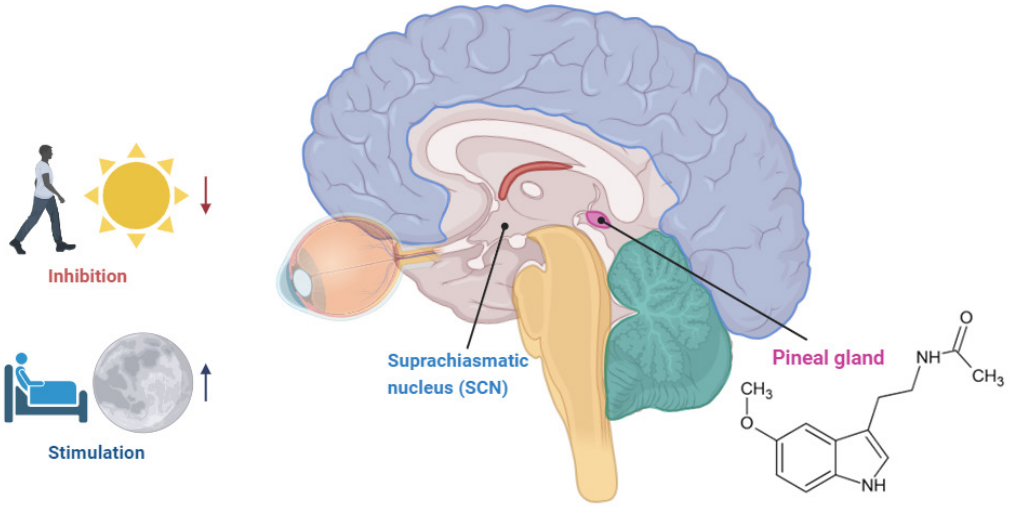

Fig. 2. Secretion of melatonin.

ing as a robust antioxidant that scavenges ROS and RNS [31-33].

The reduction of ROS by MT occurs through two main mechanisms: direct free radical scavenging and antioxidant enzyme stimulation, particularly those of glutathione reductase, glutathione peroxidase, superoxide dismutase, and catalase. Specifically, MT stimulates the synthesis of intrinsic antioxidants that collaborate synergistically with other free radical scavengers. In addition, MT inhibits the activity of pro-oxidant enzymes such as myeloperoxidase, eosinophil peroxidase, nitric oxide synthase, and cyclooxygenase-2 (COX-2), thereby indirectly affecting oxidative stress levels [34,35].

Mitochondrial dysfunction and inflammation are frequently associated with elevated nitric oxide (NO) levels due to effects induced by NO metabolites such as nitrosating derivatives (NO^+, HNO, N_2O_3, S-nitroso glutathione), peroxynitrite ($ONOO^-$), and free radicals that arise from peroxynitrite [the hydroxyl radical (•OH), the carbonate radical ($CO3^{\bullet-}$), and nitrogen dioxide (•NO2)]. These RNS and oxidizing radicals can partially disrupt the electron transport chain (ETC) by binding to iron and iron-sulfur clusters, nitrosating and nitrating components, and oxidizing ETC elements [36,37]. Antioxidative protection and mitochondrial function maintenance mitigate the effects of inflammation by promoting antioxidative processes and reducing the formation of free radicals and excessive levels of NO. NO production is regulated through the suppression of inducible nitric oxide synthase (iNOS) and nitric oxide synthase (nNOS) activities, contributing to the control of inflammation [38,39].

MT has been reported to inhibit high-mobility group box-1 (HMGB1) signaling and toll-like receptor-4 (TLR-4) activation, which prevents the activation of the inflammasome NLRP3, inhibits the activation of nuclear factor kappa B (NF-κB) and upregulates the expression of nuclear factor erythroid 2-related factor 2 (Nrf2). In addition, the downregulation of proinflammatory cytokines and upregulation of anti-inflammatory cytokines aids in the control of inflammatory responses and the protection of cells from damage [40,41].

4. Effects of melatonin on exercise performance

Several factors influence athlete performance, including physical fitness, skill proficiency, nutrition, overall conditioning, and recovery. MT could enhance exercise performance by improving sleep quality, reducing oxidative stress, and supporting post-exercise recovery. Research investigating the influence of MT supplementation on physical performance is ongoing. Tables 1, 2, and 3 summarize 21 representative studies that have examined the effects of MT supplementation on exercise performance, focusing on sleep quality, antioxidant effects, and recovery processes.

1) Sleep

Athletes must prioritize adequate and restorative sleep because the essential process of recovery occurs during this state. MT is closely associated with the quality of sleep and physical performance because when MT levels are elevated, tiredness and sympathetic nervous system suppression occurs, which ultimately contributes to high-quality sleep [42,43]. Table 1 shows representative studies that investigated the effects of MT on sleep quality, such as that of O'Donnell et al. [44], who showed that a decrease in salivary MT levels was linked to total sleep duration following night training in elite

Table 1. Representative experimental findings on the role of melatonin in regulating sleep quality

Reference	Test group	Methods	Main findings
O'Donnell et al. [44]	Elite female netball athletes (n = 10, age 23 ± 6 years)	- Salivary MT levels (before training, after night-time training, during a rest day) - Sleep monitoring using actigraphy	- Salivary MT levels before and after training↓ - Total sleep time↓
Cheikh et al. [45]	Male adolescent athletes (n = 10, age 15.4 ± 0.3 years)	- Con: placebo - MT group: 10 mg dose of MT following exhaustive late-evening exercise	- Total sleep time↑, sleep efficiency↑, stage-3 sleep↑, rapid-eye-movement (REM) sleep↑ - Sleep-onset latency↓, total duration of nocturnal awakenings after sleep-onset↓, duration of stage-1 and stage-2 sleep↓, fatigue↓, muscle soreness↓
Leonardo-Mendonça et al. [46]	Male resistance-trained athletes (placebo-treated n = 12, MT-treated n = 12)	- Con: placebo - MT group: 100 mg MT/d, taken 30 min before bedtime, for 4 wk - Salivary MT levels were monitored daily before and after MT administration	- MT modulated the circadian components of the sleep-wake cycle (duration of body temperature waveforms and nocturnal state) - Sleep efficiency↑
Rostamdokht et al. [47]	Martial art athletes (MT n = 15, placebo n = 15)	- MT, growth hormone, cortisol, and growth hormone-cortisol ratio were analyzed (before, in the middle, and after the fasting period)	- MT↑, growth hormone↑, the growth hormone-cortisol ratio↑, sleep quality↑ - Cortisol levels↓, body fat percentage↓

female netball athletes. Cheikh et al. [45] provided evidence that the administration of 10 mg of exogenous MT after high-intensity evening training resulted in improved sleep quality, increased total sleep duration, and reduced sleep latency. In addition, Leonardo-Mendonça et al. [46] demonstrated the beneficial effects of MT in extending the duration of body temperature waveforms and maintaining a steady nocturnal state, which resulted in improved sleep efficiency in male resistance-trained athletes. Furthermore, Rostamdokht et al. [47] showed that MT supplementation effectively increased total sleep duration, decreased sleep initiation delays, and improved sleep overall quality in martial arts athletes who experienced disruptions in their wake-sleep cycle and metabolic imbalances due to Ramadan fasting. These findings suggest that MT is strongly associated with sleep quality and has the potential to enhance the recovery of athletes.

2) Antioxidants

Exercise provides sustained high-oxygen delivery to working muscles, including those involved in respiration. In elite athletes, this is largely achieved through an increase in cardiac output, adaptations of trained muscles, and amelioration of the deleterious effects of exercise-related oxidative stress. When exercise intensity reaches or exceeds 50% of the maximum rate of oxygen consumption (VO_{2max}), ROS/RNS levels are increased [14,24], and MT has a superior ability to efficiently neutralize ROS/RNS levels when compared to other antioxidant compounds [23]. Table 2 presents an overview of representative studies that have explored the effects of MT on antioxidant activity. Farjallah et al. [48] demonstrated that MT intake resulted in a reduction of post-exercise indicators of liver injury (aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyltransferase) and an enhancement of post-exercise markers of kidney function such as creatinine. Oral MT supplementation has been shown to

Table 2. Representative experimental findings on the role of melatonin in antioxidation

Reference	Test group	Methods	Main finding
Farjallah et al. [48]	Professional soccer players (n = 12, age 17.54 ± 0.78 years)	- MT or placebo ingestion - Blood sample collection (at rest and after the test)	- Post-exercise liver damage↓, aspartate aminotransferase↓, alanine aminotransferase↓, gamma-glutamyltransferase↓ - Post-exercise renal function marker, creatinine↑
Farjallah et al. [49]	Professional soccer players (n = 20)	- Daily MT or placebo ingestion - Repeated sprint ability test before and after an intensive six-day training camp - Blood sample collection (at rest and after the test)	- Oxidative stress marker, malondialdehyde↓, muscle damage↓, muscle pain↓ - Activity of superoxide dismutase↑, performance↑
Leonardo-Mendonça et al. [50]	Male resistance trained athletes (MT-treated n = 12, placebo-treated n = 12)	- Con: placebo - MT group: 100 mg MT, taken 30 min before bedtime for 4 wk	- Oxygen radical absorption capacity↑, - Lipid peroxidation and nitrite plus nitrate levels↓, oxidation protein products↓
Czuczejko et al. [51]	Football players (n = 47), rowers (n = 19), adults non-training males (control, n = 15)	- Con: placebo - MT group: 5 mg MT daily before sleep for 30 d - Blood sample collection	- Glutathione and malondialdehyde↓ - MT concentration↑, activities of superoxide dismutase-1 and glutathione peroxidase↑
Ortiz-Franco et al. [52]	Male high-intensity interval training athletes (n = 14, age 20-37 years)	- 20 mg MT daily for 2 wk - Blood collection (before and after treatment)	After 2 wk intervention - Plasma MT levels↑, total antioxidant capacity and glutathione peroxidase activity↑ - DNA damage in isolated lymphocytes assessed by a comet assay↓
Maldonado et al. [53]	Male football players (MT group n = 8, control group n = 8, age 18 to 20 years)	- Con: placebo - MT group: 6 mg MT 30 min prior to exercise	- Total antioxidant activity↑, IgA levels↑ - Triglyceride levels following high-intensity exercise↓
Cheikh et al. [54]	Volleyball players (n = 14, age 14.5 ± 0.52 years)	- Running-based anaerobic sprint test at 20:00 - Subsequent consumption of either a 10 mg MT tablet or a placebo at 22:00 - Repeated test the next morning 07:30 - Blood sample collection (before and after exercise)	- Peak power↑, mean power↑ - Total time↓, fatigue index↓, white blood cells↓, neutrophils↓, lymphocytes↓, ultra-sensitive C-reactive protein↓, creatine kinase↓, lactate dehydrogenase↓, aspartate aminotransferase↓, malondialdehyde↓, homocysteine↓
Farjallah et al. [55]	Professional soccer players (n = 20, age: 18.8 ± 1.3 years)	- Intensive training program for 6 d - 5 mg oral dose of MT daily or a placebo - Blood sample collection	- Oxidation protein products↓ - Enhanced activity of antioxidant enzyme↓, creatinine↓, creatine kinase↓, gamma-glutamyltransferase↓

Table 3. Representative experimental findings on the role of melatonin in muscle damage

Reference	Test group	Methods	Main finding
Su et al. [59]	Mice (control group n=10; skeletal muscle injury group n=10; skeletal muscle injury group with MT n=10)	- Glycerol-induced muscle injury - Examination of muscle degradation and regeneration after treating growth medium or differentiated medium with MT - Rotarod test - Micro-computed tomography scans - Immunohistochemistry analyses	Pax7 expression↑, skeletal muscle differentiation↑, enhanced muscle fiber morphology↑
Lee et al. [60]	Postmenopausal women (n=78)	- Evaluation of metabolic risk factors - Dual-energy X-ray absorptiometry - Determination of sarcopenia - Urine 6-sulfatoxymelatonin (aMT6s) levels	- Sarcopenia prevalence↑ with higher aMT6s quartiles - Association between the fourth quartile of aMT6s and sarcopenia
Obayashi et al. [61]	Older adults (n=760)	- Overnight urinary 6-sulfatoxymelatonin excretion (UME) - Assessments of grip and quadricep strength	- Strong association between higher quartiles and increased grip and quadricep strength - Grip and quadricep strength↑ in Q4
Rondanelli et al. [62]	Older sarcopenic patients: isocaloric placebo (n=44), MT (1 mg/day, n=42), essential amino acids (4 g/day, n=40), eAA+MT (4 g eAA and 1 mg melatonin/day, n=30).	- Dual X-ray absorptiometry - Handgrip test - Biochemical parameters, albumin and CRP (before and after 4 wk MT intervention)	- Total fat-free mass↑ with essential amino acids - Albumin levels↓, gynoid and android fat %↓
Ben Dhia et al. [67]	Obese people (n=23, age: 33.26±9.81 years, BMI: 37.75±8.87 kg.m^{-2})	- Two experimental sessions: 1) high-intensity interval exercise (HIIE) combined with a placebo, 2) HIIE combined with MT at a dosage of 3 mg - HIIE consisted of 8 intervals performed at 90% of the maximal aerobic power (MAP)+2 min of recovery at 45% of the MAP - Blood sample collection 5 min before and after each session	- C-reactive protein↓, white blood cells↓, neutrophils↓, creatine kinase↓, aspartate aminotransferase↓, alanine aminotransferase↓, lipid and protein peroxidation↓, malondialdehyde↓, uric acid↓, total bilirubin↓ - Thiol↑, catalase↑
Ochoa et al. [68]	Amateur runners MT group (MG, n=10) control group (CG, n=10)	- Con: placebo - MG group: 3 mg MT capsules - Mountain run and ultra-endurance	- Exercise-induced TNF-α, IL-6, and IL-1ra levels↓ - MT inhibited the effects of pro-inflammatory cytokines
Mehanna et al. [58]	Rats (MT treated group n=40; untreated group n=40)	- MT group: soleus muscle injury with MT injection (10 mg/kg/day) - Untreated group: soleus muscle injury with ethanol injection (4.5%) - Observed on Days 1, 4, 7, and 14 after the injury	- Twitch force of the injured muscle↑, MT1a receptor mRNA expression↑ on Days 1, 4, 7, and 14 - Bax↓ in the injured muscle
Ma et al. [65]	Lambs (n=120)	- MT implants - Monitored for 60 days - Muscle and adipose tissue collection - Transcriptome sequencing analysis	- Growth rate of body weight↑, body skew length↑, cross-sectional area of muscle fibers↑ - Apoptotic signaling↓
Abdulwahab et al. [66]	Rats (n=20)	- Daily dose of 10 mg/kg MT via gavage for 15 days - Examination of diabetic cardiomyopathy and pancreatic injury	- Oxidative stress↓, proinflammatory cytokines↓, Bax↓, caspase-3↓, P53↓ - Glutathione levels↑, glutathione peroxidase activity↑, IL-10↑, Bcl-2↑

reduce oxidative stress (malondialdehyde) and muscle damage (creatine kinase and lactate dehydrogenase), enhance the activity of the primary antioxidant enzyme (superoxide dismutase), and alleviate muscle pain, thereby mitigating the performance declines that were observed in soccer players after training [49]. Leonardo-Mendonça et al. [50] demonstrated that supplementation with MT resulted in an increase in oxygen radical absorption capacity, a decrease in lipid peroxidation, and a reduction in nitrite and nitrate levels in resistance-training athletes. Czuczejko et al. [51] showed that MT supplementation caused a significant reduction in oxidative stress markers, specifically glutathione and malondialdehyde, in professional athletes who used intense training methods. These reductions were complemented by a significant increase in the MT concentration and the activities of superoxide dismutase-1 and glutathione peroxidase, which safeguarded tissues against the detrimental effects of reactive oxygen and reactive nitrogen species and inflammatory processes. Ortiz-Franco et al. [52] used a comet assay to reveal that the oral administration of MT re-

sulted in increased plasma MT levels, which resulted in an improvement in total antioxidant capacity and a reduction in DNA damage in isolated lymphocytes. Maldonado et al. [53] showed that MT treatment in football players reversed oxidative stress and improved IgA levels and lipid metabolism. Moreover, Cheikh et al. [54] and Farjallah et al. [55] stated that MT intake reduced liver damage in both volleyball and soccer players. This reduction in liver damage was associated with increased antioxidant enzyme activity and decreased oxidative stress. These results suggest a strong connection between MT and antioxidant activity, indicating the potential of this hormone to enhance athletic performance.

3) Muscle damage

In addition to enhancing sleep quality, reducing oxidative stress, and improving post-exercise recovery, MT affects the rhythmic regulation of several physiological processes either directly or indirectly, which can enhance the physical performance of athletes. The ability of MT to readily cross the blood-brain barrier and enter subcellular compartments within cells contributes to its wide-ranging effects, including muscle recovery and anti-apoptotic and anti-inflammatory responses [56]. Table 3 summarizes the representative studies that examined the effects of MT on muscle damage.

Damaged muscle tissues undergo a muscle regeneration process that involves myolysis to remove excessive debris and break down non-functional muscle components. Muscle progenitor cells then activate, proliferate, differentiate, and merge with existing myofibers to create newly restored functional myofibers [57,58]. MT promotes muscle recovery and hypertrophy by enhancing gene expression and increasing the number of satellite cells. Since these satellite cells are vital for muscle growth and regeneration, MT is a key factor for optimizing muscle health and performance. Su et al. [59] demonstrated a rapid increase in Pax7 expression that effectively restored skeletal muscle differentiation and improved muscle fiber morphology in mice with glycerol-induced muscle injury. MT is associated with muscle recovery and hypertrophy; therefore, MT levels are closely aligned with muscle strength and mass. Lee et al. [60] demonstrated a relationship between urinary MT levels and sarcopenia in postmenopausal women, and Obayashi et al. [61] found a correlation between urinary MT levels and muscle strength in patients with sarcopenia. Furthermore, Rondanelli et al. [62] revealed that administering MT in conjunction with essential amino acids increased total fat-free mass. These findings emphasize the impact of MT on muscle health and performance.

As previously mentioned, MT exerts neuroprotective effects by decreasing oxidative stress and inflammation and diminishing neural apoptosis through the activation of the Wnt/β-catenin signaling pathway [63,64]. A recent study by Mehanna et al. [58] demonstrated significantly increased twitch force and MT1a receptor mRNA levels in the injured soleus muscles of rats. In addition, those authors noted a decrease in the Bax level of the injured muscles, indicating the anti-apoptotic and anti-inflammatory actions of MT. Ma et al. [65] provided evidence that MT treatment significantly increased the cross-sectional area of muscle fibers in lambs. This effect was attributed to the ability of MT to elevate the growth hormone and testosterone levels, which mediated the apoptosis signaling pathways. Abdulwahab et al. [66] reported that the administration of MT led to significant normalization of serum glucose levels and improved insulin levels in diabetic rats. Moreover, MT effectively prevented oxidative stress and inhibited increases in proinflammatory cytokines and the expression of Bax, caspase-3, and P53, while enhancing anti-inflammatory cytokine IL-10 and anti-apoptotic protein Bcl-2. Although there is lack of supportive information for protective effects of MT on exercise-induced muscle damage to recommend to athletes, anti-inflammatory properties of MT could have beneficial performance-related outcomes such as muscle recovery after intense workouts. A study conducted by Dhia et al. [67] demonstrated that MT intake mitigated the increase in inflammatory markers, including C-reactive protein and white blood cells, as well as oxidative stress and muscle damage in obese individuals after high-intensity interval exercise. Similarly, Ochoa et al. [68] indicated that MT prevented the overexpression of pro-inflammatory mediators induced by strenuous exercise in amateur athletes.

Consequently, MT has shown potential to enhance athletic performance through its anti-apoptotic and anti-inflammatory properties; therefore, it is a promising candidate for aiding in athlete recovery after intense physical activity. However, more research needs to be clarified the use of MT as a supplement for athletes.

CONCLUSIONS

MT has recently been recognized for its therapeutic effects and potential as a dietary supplement to support an exercise routine. This review focuses on the beneficial effects of MT, particularly those of improving sleep quality and mitigating exercise-induced oxidative stress and muscle damage. However, research on the use of MT as a supplement for athlete performance or recovery remains limited, and its effects based on factors such as timing and dosage have not been clearly established. Moreover,

unpleasant side effects of melatonin have occasionally been reported. As melatonin's therapeutic significance is related to sleep, its diurnal ingestion could result in symptoms like sleepiness, alertness deficiency, poor coordination and loss of balance. Additionally, there have been observations of a slight increase in blood pressure linked to nitric oxide synthase downregulation [69]. Therefore, further research is required to investigate the specific mechanisms of MT and their positive and negative effects on performance in athletes.

CONFLICT OF INTEREST

The authors declare that they do not have conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: J Cho; Formal analysis: J Cho; Methodology: J Cho; Project administration: J Cho; Writing - original draft: J Cho, T Kim; Writing - review & editing: J Cho, T Kim.

ORCID

Taewan Kim https://orcid.org/0000-0001-9072-5838
Jinkyung Cho https://orcid.org/0000-0002-4500-3622

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