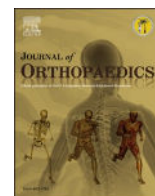


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## Therapeutic potential of melatonin in musculoskeletal medicine

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## ABSTRACT

Melatonin, traditionally recognised for regulating circadian rhythms, has gained increasing attention in pharmaceutical science due to its pleiotropic actions extending beyond sleep physiology. Evidence from PubMed-indexed studies demonstrates that melatonin exerts receptor-dependent and receptor-independent effects relevant to musculoskeletal health, including antioxidant, anti-inflammatory, mitochondrial, and epigenetic regulation. In bone, it promotes osteoblast differentiation, suppresses osteoclastogenesis, and preserves microarchitecture, with promising applications in the treatment of osteoporosis and fracture healing. In cartilage, melatonin protects chondrocytes from oxidative stress and apoptosis, modulates non-coding RNAs, and shows enhanced efficacy when delivered through intra-articular sustained-release systems, making it a potential adjunct in osteoarthritis therapy. In muscle and tendon, it limits exercise-induced damage, prevents sepsis-related myopathy, and promotes collagen synthesis and organised matrix remodelling. In spinal cord injury, melatonin reduces oxidative stress, preserves neuronal integrity, and enhances neuroregeneration. In intervertebral disc degeneration, it counteracts apoptosis, inflammation, and ferroptosis. Sports medicine applications include attenuation of oxidative stress and inflammatory markers in highly trained athletes, with indirect benefits on recovery and adaptation, although direct improvements in performance remain uncertain. Oncological studies have highlighted the anti-proliferative, pro-apoptotic, and anti-metastatic effects of osteosarcoma, with synergy observed when these effects are combined with chemotherapy. Novel pharmaceutical formulations such as nanoparticles and hydrogels further expand therapeutic potential, supported by a favourable safety profile. Despite robust preclinical evidence, translation into clinical practice requires large, well-designed trials. Melatonin should therefore be considered a promising adjunct in orthopaedics, rehabilitation, sports medicine, and trauma care, with future research aimed at optimising delivery and validating efficacy.

## 1. Introduction

Melatonin, also known as N-acetyl-5-methoxytryptamine, is a highly pleiotropic indoleamine that has long been recognised primarily for its role in circadian regulation and the synchronisation of biological rhythms.<sup>1,2</sup> However, in recent decades, it has attracted growing interest within biomedical sciences due to its diverse actions extending well beyond sleep physiology.<sup>3,4</sup> Initially isolated from the bovine pineal

gland in 1958, melatonin is now known to be produced not only in the pineal gland but also in multiple extrapineal sites, including the gastrointestinal tract, bone marrow, retina, and immune cells, which collectively contribute to its widespread systemic distribution.<sup>5,6</sup> Its synthesis is derived from tryptophan via serotonin, with activity tightly regulated by exposure to light and darkness through the suprachiasmatic nucleus.<sup>6</sup> The recognition that melatonin is present in virtually all organisms, from bacteria to humans, underlines its evolutionary

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conservation and suggests essential physiological functions.<sup>7</sup> At a mechanistic level, melatonin exerts its biological actions through both receptor-mediated and receptor-independent pathways. The two membrane receptors MT1 and MT2, belonging to the G protein-coupled receptor family, mediate circadian and neuroendocrine effects.<sup>8,9</sup> At the same time, intracellular actions include scavenging reactive oxygen and nitrogen species, modulation of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, regulation of mitochondrial function, and interaction with nuclear receptors, including ROR $\alpha$ .<sup>10,11</sup> These multifaceted mechanisms confer a unique combination of chronobiotic, antioxidant, anti-inflammatory, and immunomodulatory properties, which have been consistently documented in both experimental and clinical studies available on PubMed.<sup>12–15</sup> Importantly, melatonin is amphiphilic, allowing it to cross cell membranes, mitochondrial barriers and the blood–brain barrier, which enhances its therapeutic potential in musculoskeletal and neurological conditions.<sup>16</sup>

From a clinical perspective, the spectrum of melatonin's potential applications has broadened considerably. In orthopaedics and rehabilitation medicine, preclinical evidence suggests that melatonin promotes osteoblast differentiation, inhibits osteoclastogenesis, and protects chondrocytes from apoptosis, thereby supporting bone formation and preserving cartilage.<sup>17–19</sup> In sports medicine, supplementation has been shown to reduce exercise-induced oxidative stress and modulate inflammatory cytokines, thereby indirectly facilitating recovery and potentially reducing the risk of overtraining.<sup>20</sup> In trauma settings, melatonin has demonstrated neuroprotective effects in models of spinal cord injury by attenuating oxidative damage, stabilising the blood–spinal cord barrier, and promoting neuroregeneration.<sup>21,22</sup> These observations are consistent with melatonin's broader pharmacological profile, which has been linked to cardiovascular, metabolic, oncological, and neurodegenerative disorders, underscoring its systemic importance.<sup>23–25</sup> Furthermore, several studies have drawn analogies between melatonin and vitamin D, given their broad immunomodulatory roles, their responsiveness to environmental factors such as light and dark cycles, and their emerging status as molecules with profound impact on multiple organ systems.<sup>26,27</sup>

Another relevant aspect concerns the pharmacokinetics and safety profile of melatonin. Endogenous production ranges between 0.1 and 0.9 mg per day in adults, peaking during night hours, with secretion progressively declining after the third decade of life.<sup>28,29</sup> Age-related decline is accompanied by altered circadian rhythms, increased susceptibility to oxidative stress, and a higher prevalence of degenerative musculoskeletal conditions, thereby suggesting a possible contributory role of reduced melatonin availability in orthopaedic pathologies.<sup>30,31</sup> Exogenous administration, whether synthetic or phytomelatonin derived from plant sources, has been widely studied and appears to be safe, even at relatively high doses, with minimal side effects reported.<sup>32,33</sup> Nevertheless, issues related to bioavailability, half-life, and interindividual variability require further pharmacological optimisation, particularly for potential intra-articular or local delivery systems under investigation in musculoskeletal disorders.<sup>34,35</sup>

Despite the plentiful preclinical evidence, translating these findings into clinical practice remains limited. PubMed-indexed studies highlight melatonin's potential as an adjunct in bone healing, cartilage preservation, tendon repair, and muscle recovery, yet large-scale, high-quality randomised controlled trials in orthopaedics, rehabilitation, and sports medicine are still lacking. The potential of melatonin does not lie in being a universal cure, but in its possible integration into targeted therapeutic strategies, where its distinctive biochemical profile could complement established pharmacological or surgical treatments. In this context, a thorough review of existing evidence is crucial for defining realistic applications, pinpointing knowledge gaps, and setting priorities for future research in orthopaedics, sports medicine, rehabilitation, and trauma care.

## 2. Methods

All the clinical studies investigating the implications of melatonin in musculoskeletal medicine were accessed. Only studies published in peer-reviewed journals were considered. Given the author's language capabilities, articles in English, German, Italian, French, and Spanish were eligible. Studies with levels I to IV of evidence, as defined by the Oxford Centre for Evidence-Based Medicine,<sup>36</sup> were considered. In October 2025, the following databases were accessed: PubMed, Web of Science, and Scopus. The Medical Subject Headings (MeSH) used for the database search are reported in Table 1.

## 3. Mechanisms of action relevant to the musculoskeletal system

Melatonin influences musculoskeletal tissues through receptor-dependent and receptor-independent mechanisms.<sup>37</sup> The canonical receptors MT1 and MT2, widely expressed in bone, cartilage, muscle, and intervertebral discs, modulate intracellular signalling cascades that regulate proliferation, differentiation, and apoptosis.<sup>8,9</sup> In osteoblasts, activation of MT2 enhances matrix mineralisation and bone morphogenetic protein expression.<sup>17</sup> At the same time, in osteoclasts, it suppresses differentiation by disrupting RANKL–NF $\kappa$ B signalling, thereby promoting an overall pro-anabolic and anti-resorptive balance.<sup>17</sup>

Receptor-independent actions are equally critical. Melatonin is a potent free radical scavenger capable of neutralising hydroxyl radicals, superoxide anions, and peroxynitrite.<sup>38</sup> Its metabolites, such as N<sup>1</sup>-acetyl-N<sup>2</sup>-formyl-5-methoxykynuramine, prolong this antioxidant effect.<sup>39</sup> Moreover, melatonin indirectly enhances endogenous defences by activating nuclear factor erythroid 2-related factor 2, which increases the expression of superoxide dismutase, catalase, and glutathione peroxidase.<sup>40,41</sup> In musculoskeletal tissues, where oxidative stress drives osteoarthritis, osteoporosis, muscle atrophy, and disc degeneration, this redox regulation is of major therapeutic relevance.<sup>30,31</sup>

Mitochondrial protection represents another hallmark. Melatonin accumulates within mitochondria, stabilising the electron transport chain, reducing cytochrome c release, and preventing the opening of the permeability transition pore.<sup>42,43</sup> These actions limit apoptosis in skeletal muscle fibres, chondrocytes, and disc cells, preserving structural integrity.<sup>18,19,44</sup> Parallel anti-inflammatory effects arise from suppression of nuclear factor  $\kappa$ B activity, leading to reduced tumour necrosis factor- $\alpha$ , interleukin-1 $\beta$ , and interleukin-6, while favouring interleukin-10.<sup>13,14</sup>

Finally, melatonin modulates ferroptosis and autophagy, processes central to bone and cartilage homeostasis.<sup>45,46</sup> By attenuating lipid peroxidation and iron overload, it protects osteoblasts in diabetic osteoporosis and maintains matrix-producing cells in degenerative discs.<sup>47,48</sup> Collectively, these mechanisms underscore melatonin's capacity to integrate circadian biology, redox homeostasis, and

**Table 1**

Strings used for the search in each database (WoS: Web of Science).

|        |   |
|--------|---|
| PubMed | ("Melatonin" [Mesh] OR melatonin OR "N-acetyl-5-methoxytryptamine") AND (bone OR cartilage OR muscle OR tendon OR ligament OR joint OR spine OR "spinal cord" OR "disc degeneration" OR fracture OR regeneration OR rehabilitation OR sports OR exercise OR athletic OR performance OR recovery OR trauma OR osteoarthritis OR osteoporosis OR sarcoma OR cancer) |
| Scopus | TITLE-ABS-KEY (melatonin OR "N-acetyl-5-methoxytryptamine") AND TITLE-ABS-KEY (bone OR cartilage OR muscle OR tendon OR ligament OR joint OR spine OR "spinal cord" OR fracture OR regeneration OR rehabilitation OR sport OR exercise OR athletic OR performance OR trauma OR osteoarthritis OR osteoporosis OR sarcoma OR cancer)                               |
| WoS    | TS=(melatonin OR "N-acetyl-5-methoxytryptamine") AND TS=(bone OR cartilage OR muscle OR tendon OR ligament OR joint OR spine OR "spinal cord" OR fracture OR regeneration OR rehabilitation OR sport OR exercise OR athletic OR performance OR trauma OR osteoarthritis OR osteoporosis OR sarcoma OR cancer)   |

regenerative signalling in the musculoskeletal system.

#### 4. Bone health and regeneration

The role of melatonin in bone metabolism has become increasingly evident, with accumulating evidence from preclinical and clinical studies suggesting that it plays a key regulatory role in skeletal homeostasis.<sup>49,50</sup> Experimental data indicate that melatonin promotes osteoblast differentiation and enhances matrix mineralisation through the upregulation of bone morphogenetic proteins and osteocalcin, while simultaneously suppressing osteoclastogenesis by interfering with RANKL-mediated signalling.<sup>51–53</sup> This dual action contributes to an overall anabolic shift that favours bone formation over resorption, a mechanism of particular importance in osteoporosis and fracture healing.<sup>54,55</sup>

Animal studies have consistently demonstrated that melatonin supplementation enhances bone microarchitecture, increases bone mineral density, and accelerates fracture healing.<sup>56,57</sup> In ovariectomised models, used as a surrogate for postmenopausal osteoporosis, melatonin administration counteracts bone loss and restores trabecular integrity, primarily through antioxidant and anti-inflammatory pathways.<sup>58</sup> Clinical investigations, although still limited in scale, have reported positive associations between serum melatonin levels and bone density, with supplementation improving bone turnover markers in postmenopausal women.<sup>59,60</sup>

At a mechanistic level, the protective effects of melatonin extend beyond cellular differentiation, encompassing mitochondrial stability, suppression of oxidative stress, and modulation of ferroptosis, which is increasingly recognised as a driver of bone loss in metabolic conditions such as diabetes.<sup>61</sup> Furthermore, melatonin's ability to regulate circadian rhythms appears to influence bone remodelling, as disruption of light–dark cycles and reduced melatonin secretion are associated with increased fracture risk.<sup>50,62</sup>

#### 5. Cartilage and joint applications

Cartilage degeneration is a central feature of osteoarthritis, driven by an imbalance between catabolic and anabolic processes within chondrocytes.<sup>63</sup> Recent PubMed-indexed studies, have highlighted the ability of melatonin to protect cartilage by attenuating oxidative stress, suppressing inflammation, and modulating gene expression through non-coding RNAs.<sup>64,65</sup> Experimental models show that melatonin reduces the production of pro-inflammatory cytokines such as interleukin-1 $\beta$  and tumour necrosis factor- $\alpha$ , while promoting anti-inflammatory pathways, thereby limiting extracellular matrix degradation.<sup>66,67</sup> Its antioxidant properties further protect chondrocytes from reactive oxygen species-induced apoptosis, preserving cartilage integrity in conditions of mechanical overload and metabolic stress.<sup>31</sup> Beyond classical pathways, melatonin has been shown to regulate microRNAs, long non-coding RNAs and circular RNAs involved in chondrocyte survival, apoptosis, and matrix synthesis.<sup>19,68</sup> This epigenetic modulation represents a novel therapeutic angle, opening perspectives for personalised treatment of osteoarthritis.<sup>19</sup> Parallel research has focused on innovative delivery strategies to overcome the short half-life and poor bioavailability of melatonin. Intra-articular formulations utilising nanoparticles, hydrogels, and scaffolds have demonstrated sustained release, improved local bioavailability, and superior protective effects on cartilage compared to systemic administration.<sup>35,69,70</sup> These approaches may be particularly valuable in early osteoarthritis, where local modulation of the joint environment can delay structural progression.<sup>70,71</sup>

#### 6. Muscle, tendon and ligament healing

The regenerative capacity of skeletal muscle and connective tissues is strongly influenced by oxidative stress and inflammatory responses,

which often compromise recovery after trauma, surgery or intense physical activity.<sup>72,73</sup> Evidence from PubMed-indexed studies demonstrates that melatonin exerts protective and regenerative effects on these tissues through its antioxidant, anti-inflammatory, and mitochondrial-stabilising properties.<sup>24,74</sup> In critically ill patients, experimental work has shown that melatonin attenuates sepsis-induced myopathy by reducing muscle wasting, modulating mitochondrial function and limiting apoptosis, thereby preserving contractile performance.<sup>75</sup> These findings are consistent with animal and human studies, in which supplementation has been shown to reduce exercise-induced oxidative stress and biomarkers of muscle damage, leading to faster recovery and a decreased risk of overtraining.<sup>76–78</sup> In tendinous and ligamentous tissue, melatonin has been reported to enhance fibroblast proliferation, regulate collagen type I synthesis and suppress inflammatory infiltration at the site of injury.<sup>79,80</sup> Such effects contribute to more organised collagen deposition and improved biomechanical strength during the remodelling phase of healing.<sup>80</sup> Although direct clinical evidence remains scarce, preclinical models of tendon and ligament repair provide strong support for melatonin's role in accelerating tissue regeneration.<sup>79–82</sup> Moreover, its regulation of extracellular matrix remodelling appears relevant in conditions such as Achilles tendon injuries and anterior cruciate ligament reconstruction.<sup>83,84</sup>

Altogether, the available data suggest that melatonin has the potential to function as a valuable adjunct in rehabilitation protocols for muscle, tendon and ligament injuries, offering both cytoprotective effects and enhancement of intrinsic repair processes. Rigorous clinical trials are required to validate these promising experimental and translational findings.

#### 7. Spine and nervous system

Spinal pathologies represent a major field where melatonin has shown therapeutic promise, particularly in the context of traumatic spinal cord injury (SCI) and intervertebral disc degeneration (IDD).<sup>21,85,86</sup> Experimental evidence from PubMed-indexed studies demonstrates that melatonin administration following SCI reduces oxidative stress, stabilises the blood–spinal cord barrier, and attenuates apoptosis of neurons and glial cells.<sup>87,88</sup> These effects are achieved through modulation of mitochondrial function, inhibition of nuclear factor  $\kappa$ B activity, and enhancement of endogenous antioxidant defences.<sup>89–91</sup> Importantly, melatonin has also been shown to promote axonal regeneration and synaptic plasticity, which are critical for functional recovery in rehabilitation settings.<sup>92,93</sup> Combination approaches using biomaterials, exercise training, and pharmacological agents such as corticosteroids appear to enhance these neuroprotective and neuroregenerative outcomes, suggesting a potential role for melatonin as an adjunct rather than a stand-alone therapy.<sup>94–96</sup>

In degenerative spine conditions, particularly IDD, melatonin demonstrates protective effects on nucleus pulposus and annulus fibrosus cells.<sup>86,97</sup> Studies reveal that melatonin reduces extracellular matrix degradation, inhibits apoptosis, and suppresses pro-inflammatory cytokines, including interleukin-1 $\beta$  and tumour necrosis factor- $\alpha$ . Moreover, its regulation of ferroptosis, a form of iron-dependent programmed cell death, further protects disc cells against degeneration associated with oxidative stress and metabolic imbalance.<sup>48,98–100</sup> Given that IDD represents one of the leading causes of chronic low back pain<sup>101,102</sup>, the potential of melatonin to preserve disc integrity through redox regulation and anti-apoptotic actions is particularly relevant for clinical translation.<sup>97</sup>

#### 8. Sports medicine and rehabilitation

In the field of sports medicine, melatonin has been investigated as both a recovery aid and a modulator of physiological stress responses induced by high-intensity training.<sup>77,103</sup> A recent systematic review of randomised controlled trials in highly trained athletes concluded that

melatonin supplementation, typically in doses ranging from 5 to 100 mg, consistently improved antioxidant status and reduced markers of oxidative stress and inflammation, including tumour necrosis factor- $\alpha$  and interleukin-6, while enhancing anti-inflammatory cytokines such as interleukin-10.<sup>104</sup> These effects were accompanied by attenuation of exercise-induced muscle and liver damage, highlighting its role in protecting tissues exposed to repetitive strain and metabolic overload.<sup>104</sup>

While direct improvements in sports performance parameters such as strength, power, and speed remain inconclusive, the indirect benefits mediated through better redox balance, reduced systemic inflammation, and improved sleep quality may contribute significantly to recovery and long-term athletic adaptation.<sup>104</sup> Sleep, a fundamental determinant of recovery, is enhanced by melatonin's chronobiotic action, which re-aligns circadian rhythms often disrupted in elite athletes by travel, competition schedules, or overtraining.<sup>103,105,106</sup> This restoration of sleep architecture helps stabilise anabolic–catabolic hormonal balance, favouring protein synthesis and muscle repair.<sup>107</sup>

From a rehabilitation perspective, melatonin's capacity to reduce oxidative stress and modulate inflammatory pathways suggests potential in structured recovery programmes following musculoskeletal surgery or trauma.<sup>20,74</sup> Its safety profile and oral availability further strengthen its attractiveness as a supportive intervention in athletes and patients undergoing intensive rehabilitation.<sup>108,109</sup> Nevertheless, controlled clinical trials specifically designed for orthopaedic and sports rehabilitation contexts are still required to validate these promising translational findings.

## 9. Pharmaceutical perspectives and safety

Pharmaceutical interest in melatonin has expanded considerably, moving beyond its established role as an oral supplement for sleep regulation to the exploration of advanced formulations for targeted musculoskeletal applications.<sup>35</sup> A major limitation of conventional melatonin is its short half-life and variable oral bioavailability,<sup>110</sup> which have spurred the development of novel delivery systems such as nanoparticles, hydrogels and polymer-based scaffolds.<sup>111,112</sup> Preclinical studies demonstrate that intra-articular delivery using controlled-release platforms prolongs melatonin's local presence and enhances its chondroprotective and anti-inflammatory effects compared to systemic administration, offering promising perspectives for the treatment of osteoarthritis.<sup>68,71</sup> Similar approaches have been investigated for bone regeneration, where scaffold-mediated delivery facilitates osteoblast activation and mineralisation while reducing oxidative stress in the local microenvironment.<sup>113</sup>

In addition to delivery strategies, interest has grown in differentiating between synthetic melatonin and phytemelatonin, which is derived from plant sources.<sup>114,115</sup> Both forms share comparable biological activity, yet phytemelatonin may offer advantages in terms of metabolic compatibility and patient acceptance.<sup>116</sup> From a safety perspective, melatonin is generally well-tolerated, with studies showing minimal adverse effects, even at doses substantially higher than those used clinically.<sup>33,117</sup> Concerns about long-term use, particularly in children and specific populations, remain under investigation, but available data indicate a favourable safety profile, especially compared with other pharmacological agents.<sup>118,119</sup>

For orthopaedics, sports medicine and rehabilitation, the ability to combine safety with versatile delivery options positions melatonin as a unique candidate for adjunctive therapy. Nonetheless, rigorous clinical validation is still lacking, and further studies are required to optimise dosing, delivery mode, and timing to maximise its therapeutic potential.

Despite strong experimental evidence, the clinical use of melatonin in orthopaedics and rehabilitation remains limited. Future studies should prioritise randomised controlled trials assessing its role in fracture healing, osteoarthritis, tendon repair, and post-surgical recovery, with clearly defined outcomes and mechanistic endpoints. Innovative pharmaceutical strategies such as nanoparticle carriers, injectable

hydrogels, and scaffold-based systems require translational validation, as they could optimise local delivery and reduce systemic variability. Combination approaches with biologics, including platelet-rich plasma or stem cells, also deserve attention in regenerative orthopaedics. In oncology, melatonin's oncostatic properties may complement chemotherapy. In sports medicine, further work is needed to establish whether its antioxidant and anti-inflammatory actions yield measurable performance benefits. Collaborative multicentre research will be crucial to move from preclinical promise to clinical integration.

## 10. Conclusion

Melatonin has emerged as a pleiotropic molecule with significant implications for orthopaedics, sports medicine, rehabilitation, and trauma care. Acting through receptor-mediated and direct biochemical pathways, it regulates oxidative stress, inflammation, apoptosis, and circadian biology, thereby supporting bone formation, protecting cartilage, preserving muscle and tendon integrity, and offering neuro-protection in spinal injury and disc degeneration. Preclinical and translational studies further highlight its oncostatic potential in osteosarcoma and its role as an adjunct in rehabilitation and athletic recovery. Pharmaceutical advances, including novel delivery systems, strengthen its prospects, while its favourable safety profile distinguishes it from many conventional agents. Nonetheless, robust clinical trials are needed to validate efficacy and optimise therapeutic protocols. Melatonin should therefore be considered a promising adjunctive tool in musculoskeletal medicine, with future research required to define its precise clinical positioning.

### Consent to participate

Not applicable.

### Consent to publish

Not applicable.

### Credit author statement

FM: Conceptualization, methodology, supervision, writing – original draft, revision, and final approval; LS: Literature screening, data organization, manuscript editing, and revision; FS: Literature search, data interpretation, and writing; MKM: Validation, manuscript review, and editing; JE: Critical revision and final approval of the manuscript; RV: Supervision, conceptual input, and final approval of the submitted version.

All authors have agreed to the final version to be published and agree to be accountable for all aspects of the work.

### Ethical approval

This study complies with ethical standards.

### Registration and protocol

The present review was not registered.

### Availability of data and materials

The datasets generated during and/or analysed during the current study are available throughout the manuscript.

### Ethical statement

Not applicable. This article is a review of previously published studies and does not contain any new studies with human participants or

animals performed by any of the authors.

### Patient and/or guardian consent

Not applicable. This study did not involve human participants, identifiable data, or images requiring consent.

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### Conflict of interest statement

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