Pain Physician 2024; 27:273-282 • ISSN 1533-3159

Systematic Review

Melatonin: Evolving Physiological Understanding and Potential Therapeutic Role in Pain Medicine Including Intervertebral Disc Degeneration

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Disclaimer: There was no external funding in the preparation of this article.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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Background: Melatonin, one of the most versatile hormones in the body, is well appreciated in managing circadian rhythm and for antioxidant properties. Produced in the pineal gland and within mitochondria, melatonin influences many physiologic processes through receptor mediated and direct effects.

Objective: The present investigation explores the evolving pharmacologic properties of melatonin, as well as current therapeutic uses in areas where mitigating oxidative stress, inflammation, and cellular senescence. This review also delves into novel therapeutic potential of melatonin and how current research is revealing a wide array of therapeutic promise in pain medicine.

Study Design: A systematic review of randomized controlled trials (RCTs) and observational studies was performed using various search engines focused on melatonin and its role in pain medicine.

Methods: The available literature on melatonin and pain medicine was reviewed. A comprehensive literature search of multiple databases from 1966 to July 2024, including manual searches of the bibliography of known review articles was performed. Quality assessment of the included studies and best evidence synthesis were incorporated into qualitative and quantitative evidence synthesis.

Outcome Measures: The primary outcome measure was the proportion of patients receiving melatonin with significant relief and functional improvement of greater than 50% of at least 3 months. Duration of relief was categorized as short-term (less than 6 months) and long-term (greater than 6 months).

Results: Melatonin can affect intervertebral disc (IVD) health through the enhancement of survival and function of nucleus pulposus cells, primarily through activation of the ERK1/2 signaling pathway. Melatonin also influences the biochemical environment of the IVD by modulating inflammation and oxidative stress, crucial factors in the pathogenesis of disc degeneration. Melatonin has been shown to reduce senescence and promote autophagy within disc cells, vital for clearing out damaged cellular components, preserving cellular function and preventing deterioration associated with aging and degenerative diseases.

Limitations: Despite the availability of multiple studies, the paucity of clinical pain related literature is considered as the major drawback.

Conclusion: Based on the present systematic review, melatonin plays a critical role in sleep, but evolving studies have demonstrated substantive roles in mitigating degenerative conditions in various tissues, including IVD degeneration. Ongoing studies will better clarify the role of melatonin as a potential therapeutic agent, including the targeted delivery to various body regions.

Key words: Melatonin, 5-methoxy-N-acetyltryptamine, pineal gland, neurodegenerative disease, intervertebral disc disease

Pain Physician 2024: 27:273-282

Melatonin (5-methoxy-N-acetyltryptamine), an indoleamine hormone, is pivotal in maintaining homeostasis of organisms both in the plant and animal kingdoms (1). Well-known for regulating human circadian rhythm, melatonin is secreted by the pineal gland directly into both the cerebrospinal fluid (CSF) and its rich vascular system, serving as an endocrine hormone (2). While the pineal gland is the primary source of melatonin in humans, several other tissues also produce smaller amounts. These include the retina, gastrointestinal tract, and immune system cells. Melatonin production in these extrapineal sites does not follow a circadian rhythm. All together, the hormone plays essential anti-inflammatory and antioxidant roles through scavenging radicals, and modulating the immune system and antioxidant enzyme production.

Melatonin is known to neutralize various reactive oxygen and nitrogen species, such as hydroxyl radicals, hydrogen peroxide, singlet oxygen, nitric oxide, and peroxynitrite anions. The indole moiety of melatonin serves as the primary site for its interaction with oxidants, due to its high resonance stability and low activation energy barrier in reactions with free radicals. Additionally, the methoxy and amide side chains of melatonin play a crucial role in its antioxidant properties. Specifically, the N-C=O structure in the C3 amide side chain is vital, as the carbonyl group is essential for scavenging a second reactive species, and the nitrogen is necessary for forming a new 5-membered ring following interaction with a reactive species (3).

Recently, it has been shown that melatonin is also synthesized within the mitochondria of most cells, where it acts as a local antioxidant and may engage in autocrine signaling (4). Melatonin operates through various mechanisms, including the activation of G-protein coupled melatonin receptors, modulation of intracellular secondary messenger cascades, or through direct binding effects (5). Some neuroprotective properties of melatonin do not require the binding of melatonin to a membrane receptor and are the result of other properties of the molecule (6). Ongoing research continues to reveal additional mechanisms influenced by melatonin, such as its agonistic effects on aryl hydrocarbon receptors, its role as a transcription factor integral to cellular homeostasis, and modulating the adaptive response to environmental stressors (7).

Melatonin plays pivotal roles in multiple body tissues, notably the intervertebral disc (IVD). The nucleus pulposus, primarily responsible for shock absorption, exhibits rhythmic fluctuations in fluid content. Its nighttime rigidity restoration, crucial for function, is partly mediated by the circadian regulation of melatonin (8). In conditions such as degenerative disc disease, where this rhythmic process is disrupted, the extracellular matrix fails to properly support restoration, leading to a pro-inflammatory state (8). Melatonin, known for its extensive anti-inflammatory and antioxidant properties, mitigates cellular aging by promoting autophagy and regulating cellular proliferation (9). This enhances the extracellular matrix of the nucleus pulposus, thereby restoring its shock-absorbing capabilities. In the annulus fibrosus, melatonin reduces the accumulation of reactive oxygen species (ROS) and regulates autophagy, diminishing cellular senescence and aiding in the recovery of the extracellular matrix (10). While current literature offers promising insights into melatonin's potential, empirical data on human subjects remain limited (11).

Dietary habits and gut microbiota, often overlooked, are linked to both neurodegenerative diseases and IVD disease (12-15). The Mediterranean diet, rich in plant-based foods (e.g., leafy green vegetables, legumes, fruits), dairy, and fish, has shown benefits in mitigating the early development, symptoms, and severity of these conditions (14). Notably, this diet is abundant in tryptophan, which the gut microbiota converts into indoleamines, 3-indolepropionic acid, and precursors to melatonin (16). The role of dietary tryptophan in health is complex and not fully understood, but the benefits of the Mediterranean diet might be partially attributed to the production of these compounds. Furthermore, the decline of tryptophan-converting bacteria, related to factors like aging or antibiotic use, may lead to reduced levels of circulating indoleamines, adversely affecting antioxidant status. Elucidating the significance of dietary tryptophan, its potential benefits in combating neurodegeneration, and its importance in maintaining IVD health is critical.

Given the broadening understanding of melatonin's benefits and its potential impact on overall health, a comprehensive review of recent advancements is necessary, along with a discussion on possible future directions in research and application.

Pharmacokinetics

Oral bioavailability, the most common means of administrating melatonin, is variable. Peak concentrations ranging from 2.5% to 56% of the administered dose, largely related to high first-pass metabolism

(17-19). Despite typical dosages being only a few milligrams, oral administration can result in supraphysiologic peak concentrations of melatonin, 10 to 100 times higher than normal peak levels. After oral administration, peak concentrations of single-dose melatonin are reached within 40-50 minutes, and it has an elimination half-life of about 50 minutes (18). Melatonin is primarily metabolized in the liver by cytochrome P450 enzymes with a small amount excreted in the urine (18). While there is a high degree of first-pass metabolism, a number of metabolites of melatonin also have antioxidant properties (20).

While oral administration is the most common method for delivering melatonin in humans, alternative methods are being explored to enhance bioavailability and target specific applications. Intravenous and sublingual administration of melatonin are particularly useful in bypassing first-pass metabolism (21,22). Another innovative approach under investigation is the use of intradiscal injections, which provide high concentration and localized application with minimal systemic side effects (23). This method aligns with broader research into medications and biologics such as glucocorticoids, mesenchymal stem cells, and platelet-rich plasma, known for their anti-inflammatory and restorative properties in the nucleus pulposus (23). While melatonin injections into human IVDs have not yet been performed, animal studies reveal significant potential. For example, in rat models, intradiscal melatonin has shown effects in reducing cell senescence in nucleus pulposus cells, restoring extracellular matrix contents, and restoring the circadian rhythm (24-26). Given these positive outcomes and lack of toxicity, melatonin emerges as a leading candidate for translational research focused on localized delivery within the nucleus pulposus, annulus fibrosus, or cartilaginous end plate.

Pharmacodynamics

Aside from its global antioxidant properties, melatonin interacts primarily with MT1 and MT2 receptors, both of which are often bound to Gαi G-protein coupled receptors and have variable affinity for melatonin. Melatonin binds with similar affinities to MT1 receptors with a dissociation constant (pKD) of approximately 10.64 ± 0.11 and to MT2 receptors with a pKD of 10.11 ± 0.05 (27). However, receptor modulation can vary depending on physiological factors such as melatonin concentration or receptor state (28). Additionally, melatonin and its metabolites have clinically significant agonistic properties on the aryl hydrocarbon receptor, but the physiological and disease implications of this interaction remain under investigation (7). Melatonin's influence on tissue is multifactorial and depends on the location. It operates mainly through MT1 and MT2, both coupled to Gαi, which vary in location dependent availability (29). With its combined secondary messenger influence and direct antioxidant properties, melatonin has shown a wide range of pharmacological activity across the body.

Pharmacodynamics and Neurodegenerative Disease

Melatonin concentration in CSF is significantly higher than in plasma, and these levels diminish with aging. This decline correlates with progression of age-related neurodegenerative disorders, notably Alzheimer's disease, Huntington's disease, and Parkinson's disease (30). Beyond disruptions to the circadian rhythm observed in these conditions, the reduction in melatonin may accelerate disease progression related to loss of neuroprotective functions (2). The protective mechanisms of melatonin are multifaceted, involving inhibition of toxic protein synthesis, antioxidant capabilities, and enhancement of both blood and glymphatic circulation. Specifically, melatonin directly inhibits production and aggregation of amyloid-beta (Aβ) in Alzheimer's disease (2,31,32). Furthermore, excessive vascular endothelial growth factor (VEGF) production, which is associated with impaired blood flow and abnormal neovascularization linked to cognitive decline in Alzheimer's disease, is mitigated by melatonin, thereby reducing neuropathological changes (33-35). In models of accelerated aging in Huntington's disease, melatonin reverses increased leakage of damaged mitochondrial DNA and resulting pro-inflammatory states (30). In Parkinson's disease, patients benefit from melatonin supplementation (36), and experimental models in rats have demonstrated significant improvements, likely related to the ability of melatonin to prevent mitochondrial dysfunction and promote antioxidant activities (37). Overall, melatonin is thought to prevent accumulation of toxic metabolites, enhancing glymphatic clearance.

Pharmacodynamics in IVD Disease

Melatonin pharmacodynamic influence on IVD health includes enhancement of survival and function of nucleus pulposus cells, primarily through activation of the ERK1/2 signaling pathway. This pathway plays a crucial role in cell survival, aiding the repair and regen-

eration processes within the disc. Furthermore, melatonin influences the biochemical environment of the IVD by modulating inflammation and oxidative stress, crucial factors in the pathogenesis of disc degeneration. The regulation of these pathways helps maintain the structural integrity of the disc and mitigates the progression of degenerative changes that often lead to lower back pain.

In addition to its cellular protective mechanisms, melatonin has shown potential in reducing senescence and promoting autophagy within disc cells. These actions are vital for clearing out damaged cellular components, thereby preserving cellular function and preventing the deterioration associated with aging and degenerative diseases. Melatonin antioxidant properties further protect disc cells from oxidative stress, a common contributor to cellular damage and inflammation within the IVD. Notably, studies have highlighted melatonin's ability to suppress angiogenesis via the inhibition of VEGF, supporting the avascular nature of the nucleus pulposus and preventing pathological angiogenesis that can exacerbate disc degeneration. Collectively, these effects underscore the potential of melatonin as a therapeutic agent for IVD degeneration, pointing towards its utility in clinical settings to manage and potentially to reverse degenerative changes in the spine, particularly in aging populations where melatonin levels naturally decline (9).

Melatonin has demonstrated several protective actions within IVD cells, contributing to the reduction of senescence and promotion of autophagy (38). These actions are crucial for the removal of damaged cellular components, thereby maintaining cellular function and preventing age-related degeneration (39). Melatonin's antioxidant properties further protect IVD cells from oxidative stress, which is a significant factor in cellular damage and inflammation within the discs (40,41).

In addition, melatonin has been shown to inhibit VEGF, thereby suppressing angiogenesis. This action supports the avascular nature of the nucleus pulposus, preventing pathological angiogenesis that could worsen disc degeneration (42). Collectively, these effects highlight the potential of melatonin as a therapeutic agent for managing IVD degeneration, particularly in aging populations where melatonin levels naturally decline, offering a promising avenue for clinical applications (43).

Aging Depletion Negative Effects

Melatonin, an endogenous hormone primarily synthesized by the pineal gland, supplemented by the mitochondria, and other tissues, exhibits a decline in production as organisms age. This age-related reduction in melatonin levels holds significant implications related to its multifaceted roles and interactions. Among its primary functions are the regulation of circadian rhythms and antioxidative processes (44). Research indicates a substantial decline in endogenous melatonin secretion by the pineal gland in humans aged 80-89 compared to those aged 10-19, with the reduction being approximately 10-fold. The strong correlation between decreased melatonin production and aging, coupled with evidence suggesting aging as a consequence of melatonin deficiency, underscores the utility of assessing both pineal and mitochondrial endogenous melatonin production as a means to gauge the rate of aging in organisms (45-47).

The documented decline in melatonin production has been extensively associated with heightened inflammation and apoptosis at the cellular level, attributed to melatonin interactions with mitochondria (48). Within mitochondria, melatonin plays a pivotal role in regulating mitochondrial membrane permeability pores, thus modulating oxygen utilization and membrane potential. These regulated pores are also instrumental in controlling the release of thioretinaco ozonide, a complex crucial for binding phosphate groups in adenosine triphosphate and oxygen during mitochondrial oxidative phosphorylation. Additionally, thioretinaco ozonide acts as a methyl donor to adenosyl methionine, a vital precursor in melatonin synthesis from N-acetyl serotonin. Melatonin can increase complex I and complex IV activity in the mitochondrial electron transport chain, without exerting significant changes in the activity of complex II to III (49).

As organisms age, there is a concomitant decline in both the production and release of thioretinaco ozonide, leading to decreased serum availability and subsequent reduction in melatonin synthesis. This diminished melatonin production precipitates dysregulation of mitochondrial membrane permeability pores, resulting in increased oxidative stress, generation of free radicals, impaired electron transport, heightened nitric oxide production, apoptosis, and consequent inflammation, all of which contribute to the aging process (50).

At the cerebral level, the decline in plasma melatonin levels plays a direct role in the aging process through a range of interactions. On a nightly basis, the elevation of plasma melatonin levels facilitates synchronization between the hypothalamic suprachiasmatic nuclei and

peripheral cellular receptors, ensuring a harmonized circadian rhythm (51). Maintaining circadian rhythmicity is of particular interest in aging research, as the decline in melatonin associated with aging often leads to a dysregulated circadian pattern, which in turn accelerates aging through various pathophysiological mechanisms. One such mechanism involves melatonin mediated protective function in clearing waste products from the central nervous system, thereby playing a crucial role in preventing age-related neurodegeneration (52,53).

Neurodegeneration constitutes a hallmark of aging, driven by a combination of physiological stresses such as cell death, mitochondrial dysfunction, and oxidative stress, as well as specific mechanisms underlying neurodegenerative diseases like Alzheimer's, Parkinson's, and Huntington's disease, among others. A pivotal process implicated in both physiological and disease-related neurodegeneration is autophagy, an endogenous metabolic mechanism responsible for clearing misfolded proteins and dysfunctional cellular organelles. In the absence of effective autophagy, these aberrant proteins accumulate and form deposits within the organism, precipitating neurodegeneration. Conversely, excessive autophagic activity can lead to premature cellular demise. Melatonin emerges as a crucial regulator of autophagy, as evidenced by its neuroprotective effects in Alzheimer's disease. Melatonin acts as a scavenger of free radicals within the central nervous system, reducing the production of amyloid plaques and promoting their clearance via enhanced autophagy, mediated by the regulation of ROS and inflammation. Reduced plasma melatonin levels have been associated with dysregulated ROS production, resulting in mitochondrial DNA, protein, and lipid damage, which in turn triggers increased autophagy. Given the mitochondria's involvement in autophagosome formation, melatonin's homeostatic actions in stabilizing mitochondrial function hold significant implications for both autophagy and apoptosis (54). Research indicates that exogenous melatonin supplementation can alleviate symptoms associated with Alzheimer's disease by restoring mitochondrial and autophagic homeostasis, thereby ameliorating tau protein aggregation and impaired autophagy, which are key pathological mechanisms of the disease (45,46,55,56). Therefore, ongoing interest persists regarding the physiological and pathological implications stemming from the age-related decline in melatonin production, as well as the diverse array of interactions this hormone engages in, both centrally and peripherally (57).

Therapeutic Role of Melatonin

The therapeutic implications of melatonin are extensive and growing, with new applications being discovered in recent years. The primary physiologic role of melatonin is well documented as conveying information regarding the daily light and darkness cycle to other bodily structures (58). The most common uses of exogenous melatonin are for idiosyncrasies in the natural sleep-wake cycle, whether due to inborn circadian rhythm disorders, long travel, or looking for overall improved sleep (59). Aside from its most common use, melatonin also displays pleiotropic effects related to its ease of crossing cellular membranes, multiple interactions with nuclear receptors, intracellular protein modulation, and general antioxidant effects (60,61).

The role of melatonin in antioxidant therapy is known to be 3-fold. Melatonin works as a potent free radical scavenger, more potent than vitamin E, and also increases the levels of several antioxidative enzymes while inhibiting the pro-oxidative enzymes (62,63). Another general therapeutic implication for melatonin is in disease processes that are mediated by ferroptosis. Multiple organ systems have been recognized as susceptible to ferroptosis related damage and attenuating this response is beneficial in reducing disease development or progression (64). Melatonin has demonstrated a mitigating effect in ferroptosis through its actions as an iron chelator and metabolism mediator which allows for therapeutic approaches across a range of non-cancerous ferroptosis mediated diseases of the eyes, brain, heart, kidneys, lung, liver, and bone (64,65). With its role as an antioxidant and ferroptosis mitigator, melatonin is a great candidate for neuroprotection and modifying existing neurodegeneration (66). Recent animal stroke models have shown melatonin therapy during reperfusion to reduce ischemic areas while also decreasing the inflammatory response, blood-brain barrier permeability, and cerebral edema formation (67-70).

In a similar animal model study looking rather at cardiotoxicity reversal, melatonin played a large role in reducing cardiac myocyte apoptosis. Cyclosporine A induced heart damage using cyclosporine A through the damaging pathways of lipid peroxidation and apoptosis was reversed in those who received 21-day melatonin therapy following the insult (71). In another animal study looking this time at melatonin therapy following traumatic physical injury, they found that melatonin working as a potent antioxidant induced less burden of

inflammatory markers, as well as hastening the return to normal physiology (72).

Melatonin has also recently shown to have anticancer properties through oncostatic and proapoptotic mechanisms which are key pathways in tumor progression and survival rate (73,74). These properties stemmed further investigation, which found that using adjunct melatonin therapy alongside chemotherapy has improved outcomes and fewer side effects in breast cancer (75-77).

Overall, melatonin mediated properties allow for a wide range of therapeutic implications related to its invaluable role as a potent antioxidant, sleep aid, and adjunct therapy for damaged tissue. In this regard, ongoing research is demonstrating additional novel approaches in how new routes of administration, through nano carriers, are showing additional promise in enhancing benefits of melatonin therapy (78).

Melatonin Novel Uses for the Future

A search for melatonin in clinical trials.gov resulted in more than 500 clinical research studies involving melatonin in the past 3 decades. Of these, 124 studies are in various stages of recruitment and 110 have been completed. While some of these are diagnostic, most trials involve treatment with melatonin for several disorders, including periodontitis, skin diseases (such as actinic keratosis), acute ischemic stroke and reperfusion-related injury, acute myocardial infarction, neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease, and amyotrophic lateral sclerosis), traumatic brain injury, spinal cord injuries, anxiety prior to and during surgery, depressive disorders, epilepsy, general and febrile seizures, autism, bipolar disorder, delirium, bone-related disorders (such as osteoarthritis, osteopenia, osteoporosis), infections (such as dengue fever and COVID-19), cancer, diabetes, chronic kidney disease, reproductive disorders (such as female infertility), and chronic low back pain. Since melatonin treatment has been tested in combination with other drugs, and given the fact that melatonin is present in all animals when a new drug is tested, it appears that drug interactions may not be a cause for concern with the usage of exogenous melatonin. Importantly, the LD50 for melatonin has not yet been established although there were attempts, indicating that high levels of melatonin, at least more than 100 mg, are well-tolerated (79-82). Successful outcomes from at least some of these studies will hopefully lead to its therapeutic use in many of these disorders.

One area of study that needs to be explored further (and is not currently listed among impending clinical trials) is to determine if melatonin alleviates IVD degeneration that happens with aging (9,83). There have been many reports using cells from human nucleus pulposus (5,6), and human annulus fibrosus cells that demonstrate beneficial effects of melatonin (84). Similarly, subcutaneous or intraperitoneal injections in in vivo rat models as well as direct injections into the L3/4 IVD in the New Zealand white rabbit have also shown to be beneficial in the healing process (85-91). Thus far, however, no direct clinical studies have been conducted in human patients. There have been a few studies that have evaluated the use of melatonin in relieving postoperative pain. Specifically, Baradari and colleagues found that patients given 5 mg of melatonin an hour before surgery experienced significantly less pain intensity after lumbar laminectomy and discectomy (92).

It must be noted that the study design, formulation, time and frequency of administration which considers melatonin mediated chronobiotic effects and dosage is critical for ensuring success of these studies. These parameters, however, are not consistent in the above listed clinical research studies, which could be major limitations when interpreting the data obtained. Dosages in different studies range from 0.4 mg of melatonin to 20 mg of melatonin, with most studies using less than 10 mg. Recently it has been suggested that, in studies involving osteopenia/osteoporosis, doses in the range of 1-1.5 mg of melatonin per kg of body weight per day is equivalent to the dosage observed to have beneficial effects in animal studies (80). Therefore, negative results using very low doses of melatonin may need to be repeated using a range of different concentrations of melatonin that may, perhaps, include the optimal dose.

Formulations used also differed in the mentioned studies, with most researchers using tablets and a few using melatonin in the form of a solution (liquid), as a gel, and as a lotion. While most studies used melatonin or its proprietary forms, such as Circadin® or Meloset®, others used melatonin agonists that target its receptors (Ramelteon®). Oral (sublingual) route was most common, but in some studies melatonin was injected intravenously. In a few dental studies, melatonin was mixed with hyaluronic acid and implanted into the socket after tooth extraction. Interestingly, Wu and colleagues used a novel method to deliver melatonin in rats (90). They prepared a sodium alginate hydrogel that was incorporated with mesoporous bioactive glass

particles as nanocarriers of melatonin. Sodium alginate hydrogels purportedly resemble nucleus pulposus tissue in terms of their viscoelasticity and hydration capacity and facilitate slow and sustained release of drugs; the bioactive glass component not only increases mechanical strength of the hydrogel, required for withstanding the compression and load-bearing demands of the disc, but also promotes regeneration of bone and cartilage by inducing osteoblast activity, inhibiting osteoclast activity and chondrocyte differentiation (93,94). Their results showed that injection of melatonin embedded in these hydrogels was far superior than injecting melatonin or the hydrogel by themselves (90). Their experiments highlight the importance of the mode of delivery of exogenous melatonin in the treatment of IVD degenerative disease.

Given the multiple cellular roles of melatonin as a scavenger of ROS, as an antioxidant, as an anti-inflammatory agent, as a modulator of autophagy, apoptosis, and many more, and given the recent findings that it is synthesized in the mitochondria, it is expected that melatonin would play a therapeutic role in several diseases, especially those associated with aging when melatonin levels decline (75).

Limitations

While the potential therapeutic effects of melatonin are well demonstrated in the present investigation, our study is limited by the available published data and relative infancy of research into novel therapeutic uses. Future studies are warranted as current animal models show promise of how melatonin's attenuation of cellular stress is significantly useful in both acute and chronic disease states.

Conclusion

Melatonin has emerged as a uniquely multifaceted hormone with significant current and possible future therapeutic implications across numerous health conditions. Ongoing research continues to unravel melatonin mediated mechanisms, as well as clinical applications through novel delivery systems. Overall, melatonin has shown significant promise in aiding many areas of medicine, including neurodegenerative processes, in reducing the inflammatory response with many future applications on the horizon.

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