MECHANISTIC STUDY OF MELATONIN: A SYSTEMATIC REVIEW

Abstract

Background: Melatonin, a neurohormone synthesized primarily in the pineal gland, plays a central role in regulating circadian rhythms and sleep-wake cycles.

Purpose: Beyond its chronobiotic functions, melatonin exhibits potent antioxidant, anti-inflammatory, immunomodulatory, and oncostatic properties. This review explores the multifaceted molecular and cellular mechanisms of melatonin across physiological and pathological conditions.

Methods: A systematic review following PRISMA guidelines was conducted using databases including PubMed, Scopus, Web of Science, and Google Scholar. Studies from 1990 to 2024 focusing on mechanistic insights were included.

Results: Melatonin influences key intracellular signaling pathways, modulates mitochondrial function, scavenges free radicals, and regulates gene expression. Its protective roles span neurological, cardiovascular, metabolic, reproductive, and oncological contexts.

Conclusion: Understanding these mechanisms provides insights into melatonin's therapeutic potential and its application in clinical medicine.

Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine predominantly produced by the pineal gland during the dark phase of the circadian cycle. It orchestrates the synchronization of circadian rhythms with environmental light-dark cycles, thereby regulating sleep-wake patterns. Beyond its role in circadian regulation, melatonin is implicated in a broad spectrum of physiological processes, including antioxidant defense, immune modulation, and cellular homeostasis [1,2].

Materials and Methods

This systematic review adhered to PRISMA guidelines. A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar for studies published between 1990 and 2024. Search terms included "melatonin," "circadian rhythm," "oxidative stress," "immunomodulation," "anticancer," "reproductive physiology," and "neuroprotection."

Inclusion criteria: Peer-reviewed studies focusing on molecular, cellular, physiological, and clinical aspects of melatonin.

Exclusion criteria: Non-English publications, conference abstracts, and studies lacking mechanistic insights.

Two independent reviewers screened titles and abstracts. Disagreements were resolved through discussion or consultation with a third reviewer. Data were extracted into standardized forms capturing molecular pathways, physiological roles, therapeutic potential, and experimental outcomes.

Data Analysis

Extracted data were qualitatively synthesized. Findings were categorized based on mechanistic pathways (receptor-mediated vs. receptor-independent), physiological systems (neurological, immunological, reproductive), and therapeutic applications. Emphasis was placed on molecular signaling cascades, oxidative stress response, and clinical relevance.

Results and Discussion

Melatonin exerts its biological effects through a complex network of molecular mechanisms that are both receptor-dependent and receptor-independent. The activation of its high-affinity G-protein-coupled receptors, MT1 and MT2, initiates several intracellular signaling pathways such as the cAMP/PKA/CREB, MAPK/ERK, and PI3K/Akt cascades. These pathways mediate a wide array of physiological responses including neuroprotection, regulation of gene expression, and modulation of cell proliferation and apoptosis [3]. In addition to receptor-mediated actions, melatonin interacts with intracellular molecules like calmodulin and nuclear receptors such as ROR/RZR, further extending its influence on cellular function [4].

A significant feature of melatonin is its potent antioxidant capacity. It not only directly scavenges free radicals like ROS and RNS but also enhances the activity of endogenous antioxidant enzymes such as SOD, GPx, and CAT. The formation of antioxidant metabolites like AFMK and AMK amplifies its radical-scavenging cascade. Simultaneously, melatonin suppresses the activity of pro-oxidant enzymes, reducing overall oxidative damage in cells and tissues [1,5].

Melatonin also demonstrates dual immunoregulatory roles. Under normal physiological conditions, it acts as an immune enhancer by promoting Th1 cytokine responses, while under pathological or inflammatory conditions, it exerts anti-inflammatory actions. It achieves this by downregulating key pro-inflammatory mediators such as TNF-α, IL-6, and IL-1β and by inhibiting critical inflammatory signaling hubs like NF-κB and the NLRP3 inflammasome [3,6,8]. Recent studies indicate that melatonin influences autophagy, a cellular housekeeping process, with implications in neurodegenerative disease modulation [8].

In oncology, melatonin emerges as a promising anticancer agent. It suppresses tumor proliferation, promotes apoptosis, inhibits angiogenesis, and modulates oncogenic signaling pathways. Its interaction with hormone receptors such as estrogen receptors in hormone-dependent cancers adds another layer of therapeutic relevance. Furthermore, melatonin enhances the efficacy of chemotherapeutic agents and helps mitigate their adverse effects. Recent findings show that melatonin also modulates the tumor immune microenvironment by regulating macrophage activity, fibroblast transformation, and tumor-derived exosome function, suggesting its potential in immuno-oncology [7,9,10].

As a principal circadian regulator, melatonin synchronizes the internal biological clock with environmental light-dark cycles. Its effects on the suprachiasmatic nucleus and peripheral clocks help regulate sleep, metabolism, and endocrine rhythms. Therapeutically, exogenous melatonin is used to manage disorders like jet lag, shift work disorder, and delayed sleep phase syndrome [2,6].

Melatonin plays a pivotal role in reproductive physiology, where it modulates the secretion of GnRH, sex steroid synthesis, and gametogenesis. During pregnancy, maternal melatonin not only crosses the placenta to establish fetal circadian rhythms but also provides antioxidant protection. These functions contribute to gestational success and the prevention of pregnancy complications like preeclampsia and fetal growth restriction [4].

Clinically, melatonin's applications span various domains. It is commonly used in treating circadian rhythm-related sleep disorders. In neurodegenerative diseases, it offers neuroprotection by combating oxidative stress and inflammation. In oncology, its role as a chemotherapy adjuvant is well-documented. Additionally, emerging evidence supports its benefits in metabolic disorders such as obesity and diabetes due to its anti-inflammatory and antioxidative properties [5,6,11].

Collectively, the diverse physiological roles and molecular mechanisms of melatonin underline its potential as a therapeutic agent in multiple disease contexts. Its safety profile, affordability, and multifactorial benefits make it a valuable molecule in integrative and personalized medicine.

Conclusion and Future Perspectives

Melatonin is a pleiotropic molecule with effects extending beyond sleep. It contributes to cellular protection, immune homeostasis, cancer therapy, and reproductive health. Future studies should explore receptor-independent mechanisms and optimal therapeutic strategies. Its integration into personalized medicine may enhance treatment outcomes across a spectrum of diseases.

Declarations

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- **Ethical Approval:** Not applicable.
- **Author Contributions:** B. Aliyu conceptualized and supervised the study. N.S. Kangiwa conducted the literature review and drafted the manuscript. U.Z. Umar contributed to data analysis and editing. All authors approved the final manuscript.
- **Data Availability:** All data are included in the article.

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