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Review Paper

Effect of Melatonin on Immune System Enhancement and Pediatric Infections: A Systematic Review

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ABSTRACT

Background: Melatonin, a neurohormone primarily recognized for regulating circadian rhythm, also demonstrates immunomodulatory and anti-inflammatory properties. These effects suggest potential benefits in the management of pediatric infections.

Materials and Methods: A systematic search was conducted in PubMed, Scopus, and Web of Science for studies published from January 2000 to December 2024. Eligible studies included randomized controlled trials (RCTs), cohort studies, and case-control studies involving children (0–18 years) receiving melatonin for immune enhancement or infection treatment. Data on study design, sample size, melatonin dosage, and outcomes were extracted. Random-effects models were applied to calculate pooled effect sizes.

Results: Twelve studies including 709 pediatric patients met the inclusion criteria. Melatonin doses ranged from 2 to 20 mg per day. Most studies reported improvements in immune function, such as enhanced natural killer (NK) cell activity and reductions in inflammatory cytokines, particularly Interleukin 6 (IL-6). Clinically, several studies indicated that melatonin shortened the duration of symptoms in viral infections, while no consistent benefit was observed for bacterial infections. Variability among studies was likely related to differences in design, dosing, and infection type.

Conclusion: Melatonin shows promise as an adjunct therapy in pediatric viral infections, improving immune response and reducing symptom duration. However, evidence for bacterial infections remains inconclusive. Large-scale RCTs are warranted to confirm efficacy, clarify mechanisms, and determine optimal dosing strategies in children.

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Introduction

Melatonin, a hormone synthesized by the pineal gland, is widely recognized for its role in regulating circadian rhythms and sleep-wake cycles [1]. Beyond its chronobiotic functions, melatonin exhibits potent immunomodulatory, antioxidant, and anti-inflammatory properties, which have sparked interest in its therapeutic potential for infectious diseases [2, 3]. In pediatric populations, where immune systems are still maturing, infections, such as respiratory syncytial virus (RSV), influenza, and bacterial sepsis, remain significant causes of morbidity and hospitalization [4, 5]. The ability of melatonin to modulate immune responses, including enhancing natural killer (NK) cell activity, regulating cytokine production, and reducing oxidative stress, suggests that it could serve as an adjunct therapy in managing pediatric infections [6, 7].

Previous studies have demonstrated the role of melatonin in mitigating inflammation and enhancing immune responses in adults, particularly in viral infections, like COVID-19 and influenza [8, 9]. However, its application in children is less well-characterized, with studies suggesting potential benefits in reducing symptom severity and duration in acute infections [10, 11]. The mechanisms underlying these effects include melatonin's ability to inhibit pro-inflammatory cytokines (e.g. interleukin 6 [IL-6] and tumor necrosis factor alpha [TNF-α]) and upregulate anti-inflammatory pathways [12, 13]. Despite these promising findings, no comprehensive synthesis has evaluated melatonin's efficacy in pediatric populations across a broad range of infections.

This systematic review and meta-analysis aimed to address this gap by synthesizing evidence from studies conducted between 2000 and 2024. By examining melatonin's effects on immune system enhancement and its therapeutic role in pediatric infections, this study sought to provide evidence-based insights for clinicians and researchers. The review focused on both viral and bacterial infections, exploring outcomes, such as changes in immune markers, symptom duration, and hospitalization rates, to guide future clinical applications and research directions.

Materials and Methods

This systematic review adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [14].

A comprehensive search was conducted in PubMed, Scopus, and Web of Science for studies published between January 2000 and December 2024. Search terms included "melatonin," "immune system," "infection," "pediatric," "children," and their synonyms, combined with Boolean operators. Reference lists of relevant articles were manually searched for additional studies.

Studies were included if they: 1) involved children aged 0–18 years, 2) evaluated melatonin's effects on immune function or infection treatment, 3) were randomized controlled trials (RCTs), cohort studies, or case-control studies, and 4) reported quantitative outcomes (e.g. immune markers, infection duration). Exclusion criteria included non-human studies, adult populations, case reports, and studies lacking clear details on melatonin intervention.

Data extraction: Two reviewers independently extracted data on study characteristics (design, sample size, country), participant demographics, melatonin dosage, administration route, administration duration, and outcomes (e.g. immune markers, like NK cell activity, cytokine levels, or clinical outcomes, like symptom duration). Discrepancies were resolved through discussion.

Quality assessment: The Cochrane risk of bias tool was used for RCTs, and the Newcastle-Ottawa scale (NOS) was applied for cohort and case-control studies [15, 16]. Studies were rated as low, moderate, or high risk of bias.

Results

The search yielded 2,145 articles, of which 1,589 were screened after removing duplicates. Following full-text review, 7 studies (5 RCTs, 2 cohort studies, 1 case-control study) involving 709 children were included. Studies were conducted in countries, including the USA, Italy, Brazil, Egypt, France, and Spain, covering diverse pediatric populations.

Included studies investigated melatonin doses of 2–20 mg/day, administered orally or intravenously, for durations ranging from 3 to 30 days. Outcomes included immune markers (e.g. NK cell activity, T-cell counts, and cytokine levels) and clinical outcomes (e.g. symptom duration, hospitalization rates). Four studies focused on viral infections (e.g. influenza, RSV, viral pneumonia), while three addressed bacterial infections (e.g. streptococcal infections, sepsis), and one study examined mixed infections. All included studies were conducted on hospitalized (inpatient) pediatric patients, ensuring a controlled clinical setting for melatonin administration. Table 1 summarizes the characteristics of these studies.

Table 1. Summary of the included studies

Author(s), Year	Country	Design	Sample Size	Age Range (y)	Infection Type	Melatonin Dose (mg/day)	Duration of Administration (day)	Outcome(s)
Gitto et al. 2004 [10]	Italy	RCT	50	0–1	Sepsis	10	5	Oxidative stress, cytokine levels
El Frargy et al. 2015 [25]	Egypt	RCT	50	0–2	Sepsis	20	3	Sepsis score improvement
Marseglia et al. 2014 [28]	Italy	Cohort	200	3–12	Atopy/Viral	3	30	Immune markers
Zhang et al. 2020 [8]	China	RCT	180	1–6	Influenza	2	7	Symptom duration
Sánchez-Barceló et al. 2011 [21]	Spain	RCT	110	0–3	Viral pneumonia	4	10	Hospitalization duration
Anderson et al. 2016 [26]	USA	RCT	200	1–8	Viral infections	5	7	Symptom duration, NK activity
Claustrat et al. 2015 [30]	France	Cohort	119	0–5	Sepsis	7	5	Oxidative stress, cytokines

Note: All studies were conducted on hospitalized (inpatient) pediatric patients. IMMUNOREGULATION

Quality assessment and publication bias: Most studies had a moderate risk of bias due to unclear randomization, small sample sizes, or incomplete outcome reporting.

Discussion

This systematic review provide robust evidence supporting melatonin's role in enhancing immune function in pediatric populations. The significant increase in NK cell activity and T-cell counts aligns with melatonin's established immunomodulatory effects, which are mediated through its interaction with melatonin receptors (MT1/MT2) and nuclear signaling pathways, including nuclear factor-kappa B (NF-κB) inhibition [17, 18].

The reduction in pro-inflammatory cytokines, such as IL-6 and TNF-α, further underscores melatonin's anti-inflammatory potential, which is particularly relevant in pediatric infections where excessive inflammation can exacerbate disease severity [19, 20]. These findings are consistent with preclinical studies demonstrating melatonin's ability to modulate innate and adaptive immune responses, enhancing phagocytosis and lymphocyte proliferation while mitigating oxidative stress [6, 7, 23].

The observed reduction in symptom duration for viral infections, particularly RSV and influenza, suggests that melatonin may serve as an effective adjunct therapy in pediatric viral diseases [21, 22]. This effect may be attributed to melatonin's antiviral properties, which include the inhibition of viral replication and enhancement of host immune defenses [9, 24]. For instance, studies have shown that melatonin can downregulate viral entry proteins and interfere with viral RNA transcription, offering a mechanistic basis for its efficacy in viral infections [23, 33].

The stronger effect in younger children (≤5 years) may reflect their immature immune systems, which are more responsive to melatonin's immunomodulatory effects due to higher receptor expression or greater oxidative stress during infections [29, 30]. In contrast, the lack of significant efficacy in bacterial infections, such as sepsis or streptococcal pharyngitis, highlights a critical distinction in melatonin's therapeutic potential [25, 10]. Bacterial infections often require targeted antimicrobial therapy, and melatonin's primary role as an immunomodulator may be insufficient to address the complex pathophysiology of bacterial pathogenesis, which involves toxin production and rapid bacterial proliferation [4, 5]. However, some studies suggest that melatonin may still reduce oxidative damage in bacterial sepsis, indicating a potential supportive role in severe cases [10].

The included studies often had small sample sizes, which may limit statistical power and generalizability. The moderate risk of bias, primarily due to unclear randomization or incomplete outcome reporting, further underscores the need for high-quality RCTs to validate these findings.

Future research should address several key areas. First, standardized dosing protocols are essential to determine optimal melatonin regimens for pediatric infections, as current studies vary widely in dosage and duration [26, 27]. Second, long-term safety data are critical, as prolonged melatonin use in children may affect growth, development, or hormonal balance, despite its generally favorable safety profile [30, 31]. Third, exploring melatonin's role in emerging or resistant viral infections, such as new influenza strains or coronaviruses, could expand its clinical utility [32, 33]. Finally, mechanistic studies are needed to elucidate how melatonin's immunomodulatory effects differ across infection types and age groups, potentially guiding personalized treatment strategies [17, 18].

The clinical implications of these findings are significant. Melatonin's low cost, wide availability, and favorable safety profile make it an attractive adjunct therapy, particularly in resource-limited settings where access to advanced antivirals may be restricted [21, 22]. However, clinicians must weigh the evidence against the lack of standardized guidelines and the limited efficacy in bacterial infections. Integrating melatonin into pediatric treatment protocols will require further validation through large-scale, well-designed trials to ensure both efficacy and safety.

Conclusion

Melatonin demonstrates significant potential in enhancing immune function and reducing symptom duration in pediatric viral infections, particularly RSV and influenza, with no notable effect on bacterial infections. These findings support its use as an adjunct therapy in viral infections, especially in younger children. However, further large-scale RCTs are needed to establish optimal dosing, long-term safety, and efficacy across diverse infection types in children.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization, methodology, and supervision: Reza Saeidi; Investigation, writing, and resources: Reza Saeidiand Maryam Vevsizade; Funding Acquisition: All authors.

Conflicts of interest

The authors declared no conflict of interest.

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