Magna Neurologica Vol. 4, No. 2, July 2026

https://journal.uns.ac.id/magna-neurologica
DOI: 10.20961/magnaneurologica.v4i2.3298
eISSN: 2985-3729 pISSN: 2963-6027

REVIEW ARTICLE **OPEN ACCESS**

MELATONIN SUPPLEMENTATION IN MULTIPLE SCLEROSIS: A SYSTEMATIC REVIEW

Muvida*, Yunandia Rahmawati, Helen Anince Heretringgi

***Correspondence**: muvidamd@gmail.com*
Department of Neurology, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia

Article History:
Received: February 12, 2026
Accepted: April 24, 2026
Published: July 15, 2026

Cite this as:
Muvida, Rahmawati Y, Heretringgi HA. Melatonin Supplementation in Multiple Sclerosis: A Systematic Review. Magna Neurologica 4(2) July 2026: 195-204. 10.20961/magnaneurologica.v4i2.3298

ABSTRACT

Background: Multiple sclerosis (MS) is a chronic neurodegenerative disease marked by progressive inflammation and demyelination, in which symptom management remains challenging. Melatonin has potential antioxidant and anti-inflammatory effects, but evidence of its efficacy in MS is limited.
Objective: This systematic review evaluated the effects of melatonin supplementation on inflammatory biomarkers and symptom-related outcomes in patients with MS using randomized controlled trials (RCTs).
Methods: This systematic review was conducted on November 10, 2025, using PubMed, Scopus, and ScienceDirect, including English-language RCTs published within the past ten years. Study quality was assessed using the Cochrane Risk of Bias 2 tool, and the review followed PRISMA guidelines with PROSPERO registration (CRD420251273486).
Results: A total of 12 RCTs involving 406 participants were included. Inflammatory biomarkers demonstrated heterogeneous responses, particularly for TNF-α and IFN-1β, with no significant changes observed in C-reactive protein (CRP), whereas oxidative stress biomarkers showed more consistent improvement. Regarding clinical outcomes, melatonin supplementation was associated with improvements in certain symptoms, including pain and fatigue, although findings varied across studies. Cognitive performance particularly executive function, information processing speed, and visuospatial memory showed relatively consistent improvement, while no significant changes were observed in global neurological disability or overall quality of life.
Conclusion: Melatonin supplementation in patients with MS demonstrates consistent benefits in reducing oxidative stress and provides limited improvement in symptoms such as pain, fatigue, and cognitive function; however, it does not confer significant benefits on global disability or overall quality of life.

Keywords: cognitive function, disability, inflammatory biomarkers, melatonin, multiple sclerosis

Introduction

Multiple Sclerosis (MS) is a chronic neurodegenerative disease affecting more than 2.5 million people worldwide.[1] It is characterized by immune-mediated damage to myelin and axons, primarily driven by lymphocytic infiltration within the central nervous system.[2] This infiltration results in demyelination, axonal damage, and neurodegeneration. Importantly, the role of immune cells like Th17, regulatory T cells (Tregs), and B cells has been identified as central in MS pathogenesis. The clinical manifestations of MS vary depending on the location of lesions within the central nervous system and can include sensory and visual disturbances, motor and coordination impairments, as well as spasticity, fatigue, pain, and cognitive deficits.[3]

Melatonin is a neurohormone primarily secreted by the pineal gland, with its production and release regulated by the suprachiasmatic nuclei of the hypothalamus in response to light and dark cycles. It plays a crucial role in regulating circadian rhythms, influencing sleep-wake cycles, and maintaining homeostasis in the central nervous system. Beyond its role in sleep regulation,

melatonin has shown promising effects due to its antioxidant and anti- inflammatory properties, making it a potential therapeutic agent for various neurodegenerative and inflammatory conditions, including MS.[4,5]

Several studies have suggested beneficial roles for melatonin supplementation in patients with MS, with reported improvements in various symptoms such as fatigue, pain, and cognitive function. However, the results across these studies have been heterogeneous, with some showing significant benefits while others report minimal or no effect.[6–8] Given this variability, there is a need for a comprehensive evaluation to better understand the potential therapeutic effects of melatonin in MS. Therefore, this systematic review was conducted to critically assess the available evidence and provide a clearer understanding of the efficacy and mechanisms of melatonin supplementation in MS management.

Methods

Study Design

This systematic review utilized qualitative methods to evaluate the effects of melatonin supplementation in MS. The reporting followed the guidelines set by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[9] The review was registered with PROSPERO (International Prospective Register for Systematic Reviews) on January 18, 2026, under registration number CRD420251273486.

Eligibility Criteria

A literature search was conducted to evaluate the effects of melatonin supplementation on inflammatory biomarkers and symptom-related outcomes in patients with MS. MS is a chronic inflammatory demyelinating disorder, characterized by immune-mediated damage to myelin and axons, primarily driven by lymphocytic infiltration within the central nervous system, and is diagnosed based on the McDonald criteria.

This systematic review included RCTs with at least one intervention involving oral melatonin supplementation in patients diagnosed with MS. The eligibility criteria for the studies included: (1) studies published in the last 10 years; (2) written in English; (3) involving adult patients (≥18 years) diagnosed with MS according to the McDonald criteria; (4) focusing on relapsing- remitting multiple sclerosis (RRMS) with mild to moderate disability; (5) utilizing oral melatonin supplementation with a clearly defined dosage; and (6) including a control group (placebo or standard care). Exclusion criteria included: (1) animal studies or non-human experimental models; (2) studies involving patients with progressive MS without separate analysis; (3) studies involving patients with severe disability; (4) observational studies, case reports, or case series; and (5) editorial articles, commentaries, narrative reviews, or conference abstracts without complete data.

Search Strategies and Screening Process

A comprehensive literature search was conducted on November 10, 2025, across PubMed, Scopus, and ScienceDirect to identify relevant studies on melatonin supplementation in patients with MS. The search terms included combinations of Medical Subject Headings (MeSH) and free-text keywords: “melatonin,” “multiple sclerosis,” “inflammatory biomarkers,” “symptom-related outcomes,” and “RCTs,” combined using Boolean operators AND and OR to refine and broaden the search results.

The screening of relevant articles was conducted through duplicate removal, title and abstract screening, followed by full-text assessment. Duplicates were removed using the Rayyan Manager application. Studies failing to meet the inclusion criteria were excluded. Two independent reviewers (M and HAH) screened the titles and abstracts based on the inclusion and exclusion criteria. The remaining articles were then assessed in full-text by two reviewers (M and YR). Any disagreements that could not be resolved by the reviewers were discussed with YR.

Risk of Bias Assessment

The risk of bias in the included studies was evaluated using the Cochrane Risk of Bias 2 (RoB2) tool for RCTs and the Cochrane RoB2 tool for crossover studies for studies with this design. These tools assess various domains, such as randomization, allocation concealment, blinding, incomplete outcome data, and selective reporting, to identify potential sources of bias. Based on responses to the signaling questions, an algorithm was used to suggest the likelihood of bias for each domain. All domains were then categorized as having a high, low, or some concerns regarding the risk of bias, in accordance with the criteria outlined in the Cochrane Handbook. The assessment was conducted independently by two reviewers (M and YR), with any disagreements resolved through discussion with a second reviewer (YR).

Data Extraction and Synthesis

Data extraction was performed by M, YR, and HAH, with validation by the second reviewer (YR). Key information extracted from each included study included: title, author(s) and year, country, sample size, study design, type of MS, inclusion and exclusion criteria, intervention, comparator, type of evaluation, time horizon, main outcome, and secondary outcome. This data was synthesized to identify patterns, assess the effects of melatonin supplementation on MS-related biomarkers, and evaluate symptom-related outcomes, including pain,

quality of life (QoL), depression, cognitive performance, disability, and fatigue. The results of the data synthesis were concluded in a descriptive narrative, focusing on the effectiveness of melatonin supplementation in improving these outcomes in MS patients.

Results

Summary of Selected Studies

A total of 1,422 records were identified from PubMed, ScienceDirect, and Scopus. After removing 66 duplicates, 1,356 records were screened, with 1,056 records excluded due to irrelevance (78%). 300 reports were retrieved, but 6 were not accessible. After assessing 294 reports for eligibility, 85 were excluded based on incorrect publication type (29%), 81 for wrong population (28%), 79 for wrong intervention (27%), and others for issues with outcomes, study design, or language. Finally, 12 studies were selected for inclusion in the final analysis, as summarized in Figure 1.

A total of 12 studies involving 406 patients with MS were evaluated to investigate the effects of melatonin supplementation. These studies were conducted in various countries, including Tunisia (5),[6,8,10–12] the United States (2),[7,13] Mexico (1),[14] the United Kingdom (1),[15] and Iran (3),[16–18] using a randomized controlled trial (RCT) design. Of these, 3 studies were crossover RCTs. Additionally, two articles by Jallouli et al.[11,12] were pilot studies for the later, more comprehensive study by Jallouli et al.[8]

The studies primarily focused on patients diagnosed with relapsing-remitting multiple sclerosis (RRMS), although some studies also included patients with secondary progressive (SPMS) and primary progressive multiple sclerosis (PPMS). Common inclusion criteria included adult patients aged 18 to 60 years, with an Expanded Disability Status Scale (EDSS) score ranging from 0 to 6, in stable clinical condition (i.e., no recent relapse), and those on stable disease-modifying therapy (DMT) for at least 6 months prior to enrollment. The dosage of melatonin varied across studies, ranging from 3 mg to 25 mg per day, administered at night, typically 30 minutes to 1 hour before bedtime. The duration of melatonin administration ranged from 2 weeks to 12 months, with most studies administering melatonin for 12 weeks. The control groups in most studies received placebo (identical tablets or capsules).

Various outcomes were measured across the studies, including cardiac autonomic function assessed by heart rate variability (HRV), oxidative stress markers, and biochemical evaluations. Other outcomes included dynamic postural stability, muscle strength, walking performance, and fall risk. Additionally, quality of life, sleep quality, and serum levels of pro-inflammatory cytokines and melatonin were also evaluated. The studies included in this review are presented in Table 1.

Risk of Bias in the included studies

The Cochrane RoB2 tool was used to assess the risk of bias in the included studies, with the RoB2 for RCTs and the Cochrane RoB tool for crossover RCTs applied where appropriate. Most studies showed low risk across most domains, while a few studies raised some concerns related to issues in randomization, carryover effects, and missing outcome data. The summary of the risk of bias assessment is presented in Figure 2 and Figure 3.

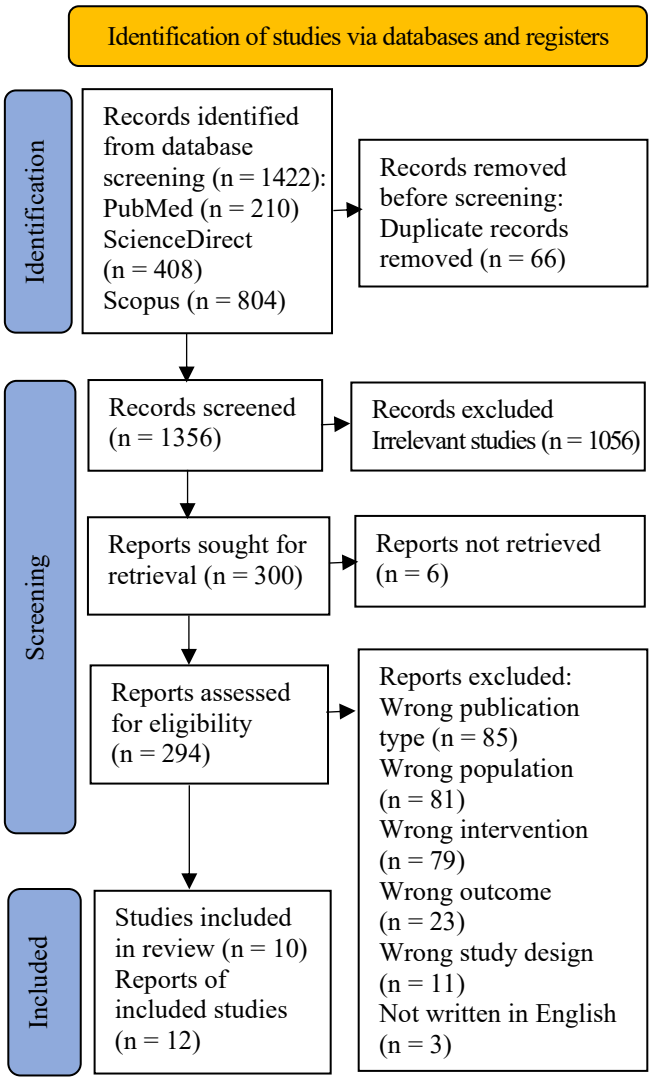

Figure 1. PRISMA Flow Diagram for Study Selection Process

Effects of Melatonin on Inflammatory Biomarkers

The analysis of inflammatory biomarkers revealed heterogeneous results across studies, particularly with TNF-α and IFN-1β, which showed variable effects, suggesting a context-dependent or inconsistent impact of melatonin.[14,16,18] However, biomarkers of oxidative stress, such as Malondialdehyde (MDA), Advanced Oxidation

Protein Products (AOPP), and Reduced Glutathione (GSH), exhibited consistent and significant changes, particularly in the study by Jallouli et al., indicating that melatonin has a notable antioxidant effect. These findings emphasize melatonin's neuroprotective potential by reducing oxidative stress. On the other hand, C-reactive protein (CRP), a non-specific marker of systemic inflammation, was not sensitive enough to detect inflammatory changes in MS during the short duration of the intervention.[6]

Melatonin and Pain

Melatonin supplementation at a dose of 6 mg at night led to a significant reduction in Visual Analog Scale (VAS) scores compared to placebo, with a relative reduction of 5.74%, indicating a notable decrease in overall pain levels. Additionally, Neuropathic Pain 4 Questions (DN4) scores significantly decreased after melatonin consumption compared to placebo, with a relative reduction of 27.30%, suggesting a meaningful reduction in neuropathic pain. Furthermore, chronic melatonin administration was associated with a significant reduction in pain scores compared to baseline and/or placebo, supporting its potential role in managing persistent pain conditions.[10,11]

Melatonin and Depression

Assessment of depressive symptoms using the Beck Depression Inventory (BDI) revealed heterogeneous results. In the study by Roostaei et al.[17], no significant differences were observed in the changes in BDI-II scores between the melatonin and placebo groups after the intervention ($p = 0.76$), indicating that melatonin had no significant effect on depression. In contrast, Sanchez-Lopez et al.[14] found that melatonin supplementation resulted in a statistically significant reduction in BDI scores compared to placebo, suggesting a meaningful improvement in depressive symptoms in patients with MS.

Melatonin and Cognitive Performance

Melatonin supplementation has been associated with significant improvements in global cognitive function in patients with MS, particularly in executive function and information processing speed, as measured by the Montreal Cognitive Assessment (MoCA). This finding is consistent with improvements observed on other cognitive assessment tools. The Trail Making Test (TMT-A and TMT-B) showed significant improvement in completion times, especially on TMT-B, reflecting enhancements in executive function and cognitive switching. Symbol Digit Modalities Test (SDMT) also demonstrated a significant increase in scores, indicating improved information processing speed.[8,12]

Additionally, the Brief Visual Memory Test (BVMT) showed significant improvements in visual-spatial memory, while the Rey Complex Figure Test (RCFT), both in copy and delayed recall, indicated significant improvements in visuoconstructive ability and non-verbal memory. However, no significant changes were found in the Simple Reaction Time (SRT) test, suggesting that simple attention was not influenced by melatonin supplementation.[8]

Melatonin and Disability

Most studies did not demonstrate significant improvements in global disability, as measured by scales such as EDSS or Patient Determined Disease Steps (PDDS), following melatonin supplementation.[7,17] However, improvements were observed in specific functional parameters, including strength, balance, and motor performance, with some studies reporting meaningful gains. These results suggest that melatonin supplementation has a more consistent effect on specific functional aspects rather than on overall disability progression in patients with MS.[11]

Melatonin and Fatigue

The effects of melatonin on fatigue in MS were heterogeneous across studies. Among the five studies that evaluated melatonin's impact on fatigue, two used the Modified Fatigue Impact Scale (MFIS), while others employed Fatigue Severity Scale (FSS), NeuroQoL–Fatigue, and Hooper Index–Fatigue subscale (HI-fatigue) as outcome measures.

In studies using the FSS, melatonin supplementation at a dose of 3 mg for 12 weeks led to a significant reduction in fatigue scores compared to placebo, with a relative reduction of approximately 32%, indicating a clinically meaningful improvement in fatigue. Similarly, HI- fatigue scores significantly decreased after acute melatonin supplementation (6 mg at night), with a reduction of about 40% compared to placebo, suggesting a short-term anti-fatigue effect.[10] However, studies using the MFIS did not show significant changes in total fatigue scores from baseline to 12 months, and no significant differences were found between the melatonin 3 mg and 5 mg doses.

Additionally, while NeuroQoL–Fatigue scores did not reveal significant differences between melatonin and placebo, there was a trend towards improvement in fatigue during the intervention period. Furthermore, although no significant improvement was seen in the total MFIS score, a trend was observed in the cognitive subscale, suggesting some benefit in specific aspects of fatigue related to cognitive function.[7,11,13,17]

Table 1. Summary of Studies on Melatonin Supplementation in Multiple Sclerosis

Author, Year (References)	Country	Sample Size	Study Design	Tipe MS	Dose	Time Horizon	Comparator	Main Outcome	Secondary Outcome
Jallouli 2024[6]	Tunisia	32	RCT	RRMS	3 mg/night	12 weeks	Placebo	Cardiac Autonomic Function	Oxidative stress and antioxidant status, sleep quality and quantity
Smoot 2024[7]	United States	30	RCT	RRMS	3 mg/night	12 months	Placebo	Change in 24-hour urinary 6-sulfatoxymelatonin (6-SMT) concentrations over time	Serum melatonin concentration; correlation between urine 6-SMT and serum melatonin; patient-reported outcomes (MFIS, MSIS-29, PSQI, PDDS-PS); safety and adverse events
Jallouli 2025[10]	Tunisia	27	RCT	RRMS	3 mg/night	12 weeks	Placebo	Dynamic postural stability measured by center of pressure mean velocity (CoPVm) during dynamic balance tasks	Walking performance (stride length, walking speed, cadence); fall risk (Four Square Step Test); sleep quality (PSQI); fatigue (FSS); neuropathic pain (DN4); quality of life (MuSiQoL)
Sanchez-Lopez 2018[14]	Mexico	36	RCT	RRMS	25 mg/night	6 months	Placebo, alongside standard IFN-β-1b therapy	Change in serum pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and oxidative stress markers (lipoperoxides, nitric oxide catabolites)	EDSS progression; relapse rate; depression level (Beck Depression Inventory); safety and tolerability
Drake 2018[15]	United Kingdom	34	RCT	RRMS, SPMS, PPMS	2 mg/night	6 weeks	Placebo	Change in mean number of nocturia episodes per night (bladder diary)	LUTS (ICIQ-MLUTS/FLUTS); nocturia QoL (ICIQ-NQoL); MS quality of life (MSQoL); sleep quality (PSQI); nocturnal urine volume; EDSS; adverse events
Yosefi-Fard 2020[16]	Iran	50	RCT	RRMS	3 mg/night	24 weeks	Placebo + routine interferon-β therapy	Change in serum interferon-1β (IFN-1β) level	Change in serum vitamin B12 level; anthropometric parameters

Table 1. Summary of Studies on Melatonin Supplementation in Multiple Sclerosis

Author, Year (References)	Country	Sample Size	Study Design	Tipe MS	Dose	Time Horizon	Comparator	Main Outcome	Secondary Outcome
Hsu 2021[13]	United States	30	Crossover RCT	RRMS, SPMS, PPMS	0.5 - 3 mg/night	4 weeks total (2 weeks melatonin + 2 weeks placebo)	Placebo	Mean total sleep time measured by actigraphy	Sleep quality and disturbance (PSQI, ISI); sleep efficiency; fatigue (NeuroQoL-Fatigue); daytime sleepiness (ESS); mood (HADS); walking ability (MSWS-12); step count by actigraphy
Jallouli 2025[8]	Tunisia	27	RCT	RRMS	3 mg/night	12 weeks	Placebo	Changes in knee muscle strength, manual dexterity (NHPT), and static postural balance	Mood status (HADS); cognitive performance (MoCA, SDMT, TMT, BVMT, RCFT); safety and adverse events
Roostaei 2015[7]	Iran	26	RCT	RRMS	3 mg/night	12 months	Placebo + interferon beta	Relapse rate; change in EDSS; number and volume of new T2 and gadolinium-enhancing MRI lesions	Change in MSFC; fatigue (MFIS); depression (BDI-II); safety and tolerability
Yosefifard 2019[18]	Iran	50	RCT	RRMS	3 mg/night	24 weeks	Placebo + routine interferon therapy	Change in serum interleukin-1 beta (IL-1β) level	Change in serum tumor necrosis factor-alpha (TNF-α) level; anthropometric parameters
Jallouli 2024[11]	Tunisia	14	Crossover RCT	RRMS	6 mg single dose	Acute, single-night intervention	Placebo	Improvement in dynamic postural balance and lower-extremity muscle strength	Fatigue, sleep quality, reduced nociceptive and neuropathic pain, adverse effects
Jallouli 2024[12]	Tunisia	50	Crossover RCT	RRMS	6 mg single dose	Acute, single-night intervention	Placebo	Improvement in postural balance parameters (reduced center-of-pressure sway and path length), functional mobility and fall risk	Improved cognitive performance (MoCA), sleep quality (SSQ), unipedal stance time

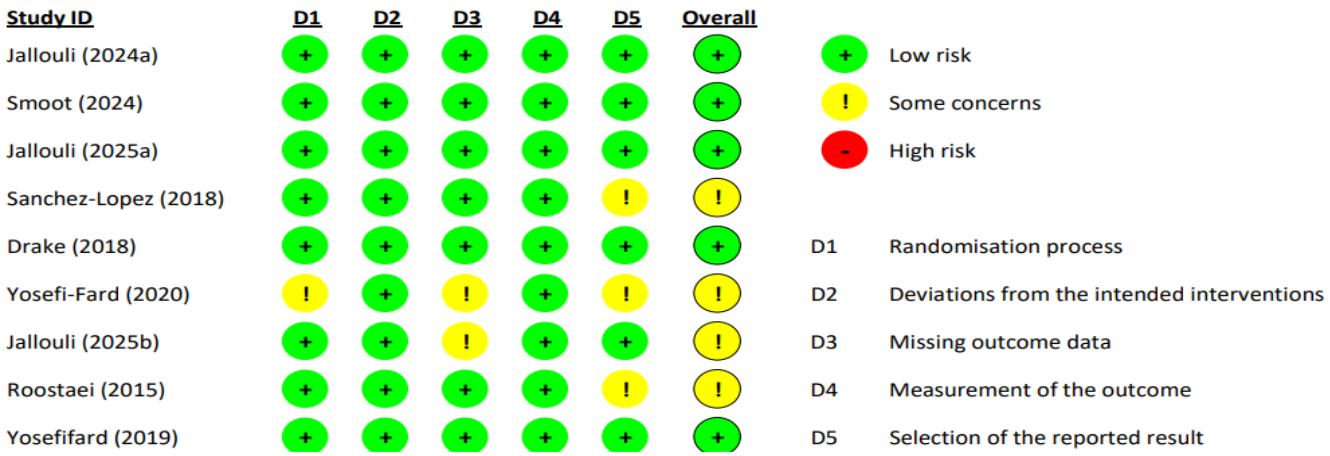

Figure 2. Risk of bias assessment for included randomized controlled trials using the Cochrane RoB 2 tool

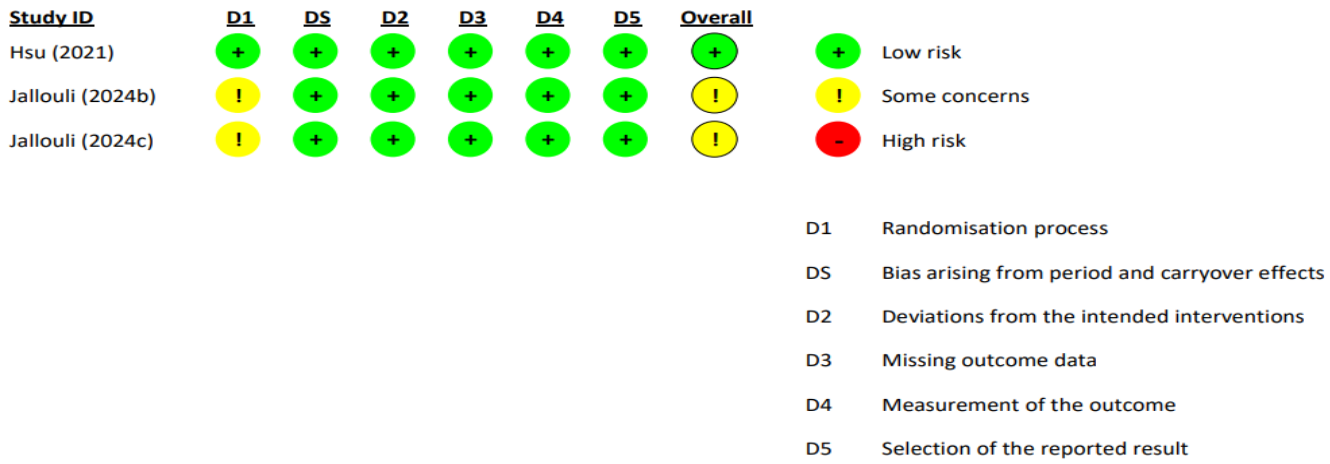

Figure 3. Risk of bias assessment for included crossover randomized controlled trials using the Cochrane RoB 2 tool for crossover trials

Melatonin and Quality of Life (QoL)

Three studies assessed the effects of melatonin on the quality of life (QoL) of patients with MS, using different tools and reporting varied results. In the study utilizing the Multiple Sclerosis International Quality of Life questionnaire (MuSiQoL), no significant difference was found in the QoL scores between the melatonin and placebo groups after 12 weeks of supplementation, indicating no significant effect of melatonin on global QoL. Similarly, in the Multiple Sclerosis Quality of Life scale (MSQoL), melatonin did not show significant improvements in global QoL scores compared to placebo. However, within the MSQoL subscale for physical and role limitations, a significant improvement was observed in specific physical domains, including overall physical health and role limitations due to physical problems, although the improvement was not consistent across other QoL domains.[10,15]

In the study using the ICIQ-NQoL, no significant difference in QoL related to nocturia was found between melatonin and placebo. Additionally, an MS-specific QoL questionnaire did not report significant improvements in global QoL following melatonin supplementation, although some improvement was noted in sleep and fatigue-related symptoms. Overall, most studies indicated that melatonin supplementation did not result in significant improvements in global QoL in patients with MS. However, some improvements were observed in specific QoL domains, particularly those related to physical function and role limitations.[7,15]

Discussion

Principal Findings

The principal findings of this systematic review suggest that melatonin supplementation offers significant benefits in managing specific symptoms of MS, particularly in reducing oxidative stress and improving pain, fatigue, and cognitive function. The analysis of twelve RCTs involving 406 participants revealed that melatonin supplementation consistently led to reductions in oxidative stress biomarkers, highlighting its potential antioxidant effect. From a pathophysiological perspective, melatonin can enhance the differentiation of type 1 regulatory T cells while inhibiting the differentiation of T helper 17 (Th17) cells. It also reduces the levels of TNF-α and IL-1β by

suppressing the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway and alleviates oxidative and inflammatory conditions by stimulating the expression of the nuclear factor erythroid 2-related factor 2 (Nrf-2) gene.[19] However, inflammatory biomarkers like TNF-α and IFN-1β showed varying results across different studies, indicating that the effect of melatonin on inflammation may depend on specific factors. This discrepancy can be attributed to the difference in melatonin dosage used in the two studies. The study by Sanchez-Lopez et al.[14] used a higher melatonin dosage of 25 mg once daily, which resulted in significant reductions in both TNF-α and IL-1β. In contrast, Yosefifard et al.[18] used a lower dose (3 mg/day), which led to a significant reduction only in IL-1β, suggesting that the higher dose may be more effective in reducing both cytokines.

No significant changes were observed in C-reactive protein (CRP), indicating that it may not be a sensitive marker for assessing the effects of melatonin on inflammation in MS patients during short interventions. The results for CRP in the study by Jallouli et al.[6] are similar to those reported by Wang et al.[20] in patients with COVID-19, where no significant change in CRP was observed following melatonin supplementation. This lack of significance in both studies could be due to several factors. CRP is a non- specific inflammatory marker, and its response may not always correlate with the specific inflammatory pathways that melatonin targets, particularly in conditions like MS, where the inflammation is complex and multifactorial. Additionally, the dose and duration of melatonin in both studies might not have been sufficient to affect CRP levels, and individual factors like disease stage and concurrent treatments may have influenced the results.[21]

The observed reduction in both overall and neuropathic pain following melatonin supplementation suggests a potential analgesic role of melatonin in patients with MS. The improvement in VAS scores indicates a meaningful decrease in global pain perception, while the substantial reduction in DN4 scores highlights a specific benefit in neuropathic pain, which is a common and challenging symptom in MS. These findings are biologically plausible given melatonin's known anti-inflammatory, antioxidant, and neuroprotective properties, as well as its modulatory effects on central pain pathways and nociceptive processing.[10] Furthermore, the benefit observed with chronic melatonin administration suggests that sustained exposure may be necessary to achieve stable pain control, possibly through cumulative effects on neuroinflammation and oxidative stress. Taken together, these results support the role of melatonin as a symptom-targeted adjunctive therapy for pain management in MS, particularly for neuropathic pain, although its effects appear to be symptomatic rather than disease-modifying.[11] These clinical findings are supported by mechanistic evidence. As reviewed by Kuthati et al.[22] the analgesic effects of melatonin are mediated through multiple neurobiological pathways relevant to neuropathic pain. Melatonin exerts antinociceptive and anti-allodynic effects primarily via activation of MT2 melatonin receptors, with additional modulation of opioid, GABAergic, NMDA, and nitric oxide–related pathways. Moreover, melatonin possesses potent antioxidant and anti-inflammatory properties, attenuating oxidative stress, microglial activation, and pro-inflammatory cytokine release mechanisms that play a central role in the pathogenesis of neuropathic pain. Together, these pathways provide a strong biological rationale for the pain-reducing effects of melatonin observed in patients with MS.[22]

Melatonin may influence depression through its ability to regulate circadian rhythms and modulate neuroinflammatory processes. It exerts anti-inflammatory and antioxidant effects by reducing pro-inflammatory cytokine activity, oxidative stress, and neurotoxicity, while supporting neuroplasticity in brain regions involved in mood regulation. Through these mechanisms, melatonin may contribute to the improvement of depressive symptoms beyond its role in sleep regulation.[23] The inconsistent findings regarding the effects of melatonin on depressive symptoms may be explained by differences in study design, melatonin dosage, baseline severity of depression, and patient characteristics. While Sánchez-Lopez et al.[14] demonstrated a significant improvement in depressive symptoms, Roostaei et al.[17] did not observe a meaningful effect. These discrepancies may also relate to variations in circadian rhythm disruption, sleep disturbances, and inflammatory burden among study populations. Given melatonin's role in circadian regulation and modulation of neuroinflammatory pathways, its impact on depression in MS may vary across patient groups.

The observed improvements in executive function, information processing speed, and visuospatial memory suggest that melatonin may have a beneficial effect on higher-order cognitive domains in patients with MS.[8,12] Melatonin may influence cognitive performance through its ability to regulate circadian rhythms, improve sleep quality, and provide neuroprotective effects. By stabilizing the sleep–wake cycle, melatonin supports memory consolidation, executive functioning, and information processing. In addition, its antioxidant and anti-inflammatory properties help reduce oxidative stress and neuroinflammation, preserve neuronal integrity, and promote synaptic plasticity. These effects may explain why melatonin preferentially improves higher-order cognitive domains rather than simple attention or reaction time.[24]

The absence of significant improvement in global disability measures such as EDSS and PDDS suggests

that melatonin supplementation may not substantially influence the overall progression of neurological disability in MS.[7,17] These scales primarily capture long-term structural and functional impairment, which may be less responsive to short- to medium-term interventions. In contrast, the observed improvements in specific functional parameters, including strength, balance, and motor performance, indicate that melatonin may exert beneficial effects at a symptomatic or functional level. This pattern suggests that melatonin's therapeutic potential in MS may lie in enhancing functional performance and daily activity rather than modifying long-term disability trajectories.

The heterogeneous effects of melatonin on fatigue observed across studies likely reflect differences in outcome measures, intervention duration, and fatigue domains assessed. Improvements were more consistently reported in studies using perception-based scales, such as the Fatigue Severity Scale and Hooper Index, suggesting that melatonin may be more effective in reducing the subjective experience of fatigue, particularly in short-term or acute settings.[10,11] In contrast, studies employing the Modified Fatigue Impact Scale, which captures broader physical, cognitive, and psychosocial dimensions of fatigue over longer periods, did not demonstrate significant overall improvements, although trends were observed in specific domains such as cognitive fatigue. These findings suggest that melatonin's effects on fatigue may be more pronounced in certain components of fatigue, particularly those related to sleep quality, circadian regulation, and cognitive effort, rather than in long-term functional fatigue. The lack of consistent improvement in global fatigue measures may also reflect the multifactorial nature of fatigue in MS, which involves neurological, psychological, and systemic contributors.[25]

Most studies did not demonstrate significant improvements in global quality of life with melatonin supplementation, likely because comprehensive QoL measures capture multiple domains that may not be substantially influenced by short-term or symptom-focused interventions. However, improvements in specific physical and role-related domains suggest that melatonin may positively affect aspects of daily functioning linked to symptom burden. The lack of effect on nocturia-related QoL further indicates that melatonin's benefits on quality of life are selective rather than global.[7,15]

Implication of Clinical Practice

The findings of this review indicate that melatonin supplementation may offer a beneficial adjunctive approach in the management of MS, particularly for alleviating symptoms such as pain, fatigue, and cognitive impairments, attributed to its antioxidant and anti-inflammatory effects. While the evidence suggests positive outcomes for symptom improvement, melatonin should not be regarded as a substitute for conventional therapies, but rather as a complementary treatment. Given its favorable safety profile, melatonin could be considered within a multidisciplinary treatment plan for MS. However, further research with extended follow-up periods and standardized outcome measures is necessary to fully determine its long-term efficacy and optimal clinical application.

Strengths and Limitations

Melatonin supplementation in patients with MS demonstrates consistent benefits in reducing oxidative stress and provides limited improvement in symptoms such as pain, fatigue, and cognitive function; however, it does not confer significant benefits on global disability or overall quality of life.

Conclusion

Melatonin supplementation may provide beneficial adjunctive effects in patients with MS, particularly in reducing oxidative stress and improving selected symptoms such as pain, fatigue, and cognitive performance. However, current evidence remains limited by small sample sizes and study heterogeneity, and no consistent benefit has been demonstrated for global disability or overall quality of life.

Research Ethics

This article relies on previously published studies that obtained ethical approval and informed consent; hence, institutional review board approval and written informed consent were not necessary.

Declaration of Interests

The authors declare no conflict of interest regarding the publication of this article.

References

1. Rodriguez Murua S, Farez MF, Quintana FJ. The Immune Response in Multiple Sclerosis. Annu Rev Pathol; 2022. 17:121–39. DOI: 10.1146/annurev-pathol-052920-040318
2. Olek MJ. Multiple Sclerosis. Annals of Internal Medicine; 2021. DOI: 10.7326/AITC202106150
3. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis: A Review. JAMA; 2021. 325(8):765–79. DOI: 10.1001/jama.2020.26858
4. Vasey C, McBride J, Penta K. Circadian Rhythm Dysregulation and Restoration: The Role of Melatonin. Nutrients; 2021. 13(10). DOI: 10.3390/nu13103480
5. Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J. Is Melatonin the "Next Vitamin D"?: A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. Nutrients; 2022. 14(19). DOI: 10.3390/nu14193934

6. Jallouli S, Jallouli D, Damak M, Sakka S, Ghroubi S, Mhiri C, et al. 12-week melatonin intake attenuates cardiac autonomic dysfunction and oxidative stress in multiple sclerosis patients: a randomized controlled trial. Metab Brain Dis; 2024. 40(1):52. DOI: 10.1007/s11011-024-01428-2
7. Smoot K, Gervasi-Follmar T, Marginean H, Chen C, Cohan S. Impact of oral melatonin supplementation on urine and serum melatonin concentrations and quality-of-life measures in persons with relapsing multiple sclerosis. Mult Scler Relat Disord; 2024. 90:105799. DOI: 10.1016/j.msard.2024.105799
8. Jallouli S, Ghroubi S, Bouattour N, Sakka S, Damak M, Mhiri C, et al. Effects of Melatonin Supplementation on Muscle Strength, Manual Dexterity, and Postural Balance in Patients Living with Multiple sclerosis - A Randomized Controlled Trial. J Diet Suppl; 2025. 22(2):236–61. DOI: 10.1080/19390211.2024.2449030
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Rev Esp Cardiol (Engl Ed); 2021. 74(9):790–9. DOI: 10.1016/j.rec.2021.07.010
10. Jallouli S, Ghroubi S, Damak M, Sakka S, Elleuch MH, Mhiri C, et al. 12-week melatonin supplementation improved dynamic postural stability and walking performance in persons living with multiple sclerosis: A randomized controlled trial. Behav Brain Res; 2025. 476:115191. DOI: 10.1016/j.bbr.2024.115191
11. Jallouli S, Ghroubi S, Sakka S, Ben Dhia I, Damak M, Yahia A, et al. Effects of a nighttime melatonin ingestion on dynamic postural balance and muscle strength the following morning in people living with multiple sclerosis: A preliminary study. Clin Neurol Neurosurg; 2024. 238:108165. DOI: 10.1016/j.clineuro.2024.108165
12. Jallouli S, Ghroubi S, Dhia IB, Yahia A, Elleuch MH, Sakka S, et al. Effect of melatonin intake on postural balance, functional mobility and fall risk in persons with multiple sclerosis: a pilot study. Int J Neurosci; 2024. 134(2):137–47. DOI: 10.1080/00207454.2022.2090353
13. Hsu WY, Anderson A, Rowles W, Peters KE, Li V, Stone KL, et al. Effects of melatonin on sleep disturbances in multiple sclerosis: A randomized, controlled pilot study. Mult Scler J Exp Transl Clin; 2021. 7(4):20552173211048756. DOI: 10.1177/20552173211048756
14. Sanchez-Lopez AL, Ortiz GG, Pacheco-Moises FP, Mireles-Ramírez MA, Bitzer-Quintero OK, Delgado-Lara DLC, et al. Efficacy of Melatonin on Serum Pro-inflammatory Cytokines and Oxidative Stress Markers in Relapsing Remitting Multiple Sclerosis. Arch Med Res; 2018. 49(6):391–8. DOI: 10.1016/j.arcmed.2018.12.004
15. Drake MJ, Canham L, Cotterill N, Delgado D, Homewood J, Inglis K, et al. Results of a randomized, double blind, placebo controlled, crossover trial of melatonin for treatment of Nocturia in adults with multiple sclerosis (MeNiMS). BMC Neurol; 2018. 18(1):107. DOI: 10.1186/s12883-018-1114-4
16. Yosefi-Fard M, Vaezi G, Maleki-Rad AA, Faraji F, Hojati V. Effect of Melatonin on Serum Levels of INF-1β and Vitamin B12 in Patients With Multiple Sclerosis: A Randomized Controlled Trial. Iran J Toxicol; 2020. 14(1):19–24. DOI: 10.32598/ijt.14.1.19
17. Roostaei T, Sahraian MA, Hajeaghaee S, Gholipour T, Togha M, Siroos B, et al. Impact of Melatonin on Motor, Cognitive and Neuroimaging Indices in Patients with Multiple Sclerosis. Iran J Allergy Asthma Immunol; 2015. 14(6):589–95.
18. Yosefifard M, Vaezi G, Malekirad AA, Faraji F, Hojati V. A Randomized Control Trial Study to Determine the Effect of Melatonin on Serum Levels of IL-1β and TNF-α in Patients with Multiple Sclerosis. Iran J Allergy Asthma Immunol; 2019. 18(6):649–54. DOI: 10.18502/ijaai.v18i6.2177
19. Lorenzut S, Negro ID, Pauletto G, Verriello L, Spadea L, Salati C, et al. Exploring the Pathophysiology, Diagnosis, and Treatment Options of Multiple Sclerosis. J Integr Neurosci; 2025. 24(1):25081. DOI: 10.31083/JIN25081
20. Wang XC, Wu GL, Cai YF, Zhang SJ. The safety and efficacy of melatonin in the treatment of COVID-19: A systematic review and meta-analysis. Medicine (Baltimore); 2022. 101(39):e30874. DOI: 10.1097/MD.0000000000030874
21. Zarezadeh M, Khorshidi M, Emami M, Janmohammadi P, Kord-Varkaneh H, Mousavi SM, et al. Melatonin supplementation and pro-inflammatory mediators: a systematic review and meta-analysis of clinical trials. Eur J Nutr; 2020. 59(5):1803–13. DOI: 10.1007/s00394-019-02123-0
22. Kuthati Y, Lin SH, Chen IJ, Wong CS. Melatonin and their analogs as a potential use in the management of Neuropathic pain. J Formos Med Assoc; 2019. 118(8):1177–86. DOI: 10.1016/j.jfma.2018.09.017
23. Won E, Na KS, Kim YK. Associations between Melatonin, Neuroinflammation, and Brain Alterations in Depression. Int J Mol Sci; 2022. 23(1). DOI: 10.3390/ijms23010305
24. Sumsuzzman D, Choi J, Jin Y, Hong Y. Neurocognitive effects of melatonin treatment in healthy adults and individuals with Alzheimer's disease and insomnia: A systematic review and meta-analysis of randomized controlled trials. Neurosci Biobehav Rev; 2021. 127:459–73. DOI: 10.1016/j.neubiorev.2021.04.034
25. Zisapel N. New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. Br J Pharmacol; 2018. 175(16):3190–9. DOI: 10.1111/bph.1411