Advances in Pharmacology and Therapeutics Journa

SHAHID SADOUGHI UNIVERSITY OF MEDICAL SCIENCES

Review Article

Emerging Insights into Melatonergic Modulation of Epileptogenesis and Seizure Control: An Updated Review

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Received: 08 Jun 2026; Revised: 01 Aug 2026; Accepted: 09 Sep 2026

Abstract

Epilepsy affects approximately 50 million individuals globally, with nearly 30% exhibiting refractory symptoms despite advances in antiseizure medications. There is an urgent need for adjunctive therapies that target underlying pathophysiological mechanisms such as oxidative stress and neuronal hyperexcitability. This review evaluates melatonin's therapeutic potential in epilepsy management by synthesizing evidence from preclinical models, clinical trials, and mechanistic studies. Melatonin demonstrates pleiotropic anticonvulsant properties mediated through MT1/MT2 receptor-dependent and independent pathways. Key mechanisms include potent antioxidant activity via ROS scavenging, glutathione homeostasis, and Nrf2 pathway activation. It also exerts anti-inflammatory effects by suppressing NF-κB and modulating microglial polarization, while restoring excitatory-inhibitory balance through enhanced GABAergic transmission and inhibition of glutamatergic excitotoxicity. Additional molecular targets include CREB phosphorylation, BDNF expression, and ROR-mediated regulation of circadian genes. Melatonin further preserves mitochondrial integrity and synchronizes circadian rhythms frequently disrupted in epileptogenesis. Preclinical studies consistently report reduced seizure severity and frequency across models including PTZ and kainic acid-induced epilepsy. Human clinical trials, though heterogeneous, indicate that adjunctive melatonin significantly ameliorates seizure severity and sleep disturbances in adults, with a favorable safety profile. Effects on seizure frequency remain inconsistent, particularly in pediatric cohorts with infantile spasms; meta-analytic data support improvements in severity and sleep latency without increased adverse events. In conclusion, melatonin represents a promising, safe, and accessible adjunctive therapy for epilepsy, especially for mitigating seizure severity and comorbid sleep disorders. Future research should prioritize large-scale multicenter randomized controlled trials to establish standardized dosing protocols, optimize administration timing, and identify patient subgroups most likely to benefit.

Keywords: Anticonvulsants, Epilepsy, Melatonin, Neuroprotective Agents, Oxidative Stress, Seizures.

Citation: Mashhadi Akbar Boojar M. Emerging Insights into Melatonergic Modulation of Epileptogenesis and Seizure Control: An Updated Review. Adv Pharmacol Ther J. 2026;6(2): 99-118. DOI: https://doi.org/10.18502/aptj.v6i2.???

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Introduction

Epilepsy remains one of the most prevalent neurological disorders, affecting approximately 50 million people globally and posing significant challenges due to its refractory nature in about 30% of cases (1,2). Despite advances in antiseizure medications, many patients continue to experience uncontrolled seizures, highlighting the urgent need for adjunctive therapies that target underlying pathophysiological mechanisms such as oxidative stress and neuronal hyperexcitability (3-5). Recent studies have underscored the role of oxidative imbalance in epileptogenesis, where excessive reactive oxygen species (ROS) contribute to neuronal damage and seizure propagation, thereby exacerbating disease progression (6,7).

The melatonergic system, primarily mediated by the pineal gland hormone melatonin and its receptors MT1 and MT2, regulates circadian rhythms, sleep-wake cycles, and neuroprotection through antioxidant and anti-inflammatory pathways (8,9). Melatonin has pleiotropic effects, including modulating gamma-aminobutyric acid (GABA)-ergic transmission and inhibiting excitotoxic cascades, both pivotal in maintaining neuronal homeostasis (10). Dysregulation of this system has been implicated in various neuropsychiatric conditions, including epilepsy, where altered melatonin levels correlate with increased seizure susceptibility (11).

Emerging preclinical and clinical evidence over the past five years supports melatonin's anticonvulsant potential as an add-on therapy, showing reductions in seizure severity and frequency in animal models and human cohorts (12). For instance, melatonin add-on therapy has been shown to improve electroencephalogram (EEG) features and sleep quality in pediatric epilepsy patients, potentially via enhanced GABA-mediated inhibition and attenuated oxidative stress (11). However, discrepancies in dosing, administration timing, and patient populations necessitate an updated synthesis of these findings to guide future therapeutic strategies (10).

What specifically necessitates this updated review is the unprecedented surge in high-quality evidence over the past five years (2020–2025), which has fundamentally reshaped our understanding of melatonin's therapeutic landscape in epilepsy. Unlike previous reviews, this period has witnessed critical breakthroughs in elucidating the precise molecular cascades, such as the Nrf2-mediated antioxidant response, NLRP3 inflammasome suppression, and ROR-dependent circadian gene regulation, that bridge melatonin's pleiotropic effects with epileptogenesis (1,9). Furthermore, the accumulation of larger, well-designed randomized controlled trials and recent comprehensive meta-analyses has provided more robust clinical data, clarifying its efficacy in mitigating seizure severity and sleep comorbidities, while highlighting the nuances of chronotherapy and patient-specific responses. By synthesizing these recent mechanistic discoveries with the latest clinical outcomes, this review aims to provide a timely, evidence-based framework that not only updates the current knowledge but

also identifies critical gaps, thereby guiding the design of future precision-medicine trials and optimizing melatonin's integration into refractory epilepsy management.

Methods

To ensure a comprehensive and rigorous synthesis of the current evidence, the literature search and study selection for this updated review were conducted in accordance with the preferred reporting items outlined in the PRISMA 2020 guidelines. We systematically searched major electronic databases, including PubMed, Scopus, Web of Science, and Embase, for articles published between January 2000 and December 2025to capture advances in the literature. The search strategy utilized a combination of Medical Subject Headings (MeSH) and free-text keywords, such as ("melatonin" OR "melatoninergic system" OR "MT1/MT2 receptors") AND ("epilepsy" OR "seizures" OR "epileptogenesis" OR "anticonvulsant"). The inclusion criteria encompassed: (1) original preclinical (in vivo and in vitro) and clinical studies (including randomized controlled trials, cohort, and case-control studies) investigating the effects of melatonin on seizure control or epileptogenesis; (2) mechanistic studies elucidating the molecular pathways (e.g., oxidative stress, neuroinflammation, GABAergic modulation); and (3) articles published in peer-reviewed English-language journals. Conversely, the exclusion criteria were applied to filter out: (1) review articles, editorials, letters to the editor, and conference abstracts to avoid data duplication; (2) case reports with a sample size of fewer than five patients, unless they provided unique mechanistic insights; (3) studies focusing solely on melatonin's effects on sleep disorders without any seizure or epilepsy-related outcomes; and (4) animal studies lacking appropriate control groups or methodological rigor. We prioritized studies with robust methodological quality, adequate sample sizes, and validated outcome measures to ensure the reliability of the synthesized data. The titles and abstracts of the retrieved articles were independently screened, and full-text articles were assessed for eligibility based on the aforementioned criteria.

Therapeutic Effects of Melatonin in Various Diseases

Melatonin's multifaceted therapeutic profile stems from its potent antioxidant and anti-inflammatory properties, which mitigate oxidative stress and cytokine-mediated inflammation across diverse pathologies (12). In circadian rhythm sleep disorders, melatonin supplementation has restored sleep architecture and reduced fatigue, and novel synthetic analogs with enhanced receptor affinity have improved clinical outcomes (13). Furthermore, its immunomodulatory effects have been linked to enhanced immune surveillance and reduced chronic inflammation, positioning melatonin as a versatile nutraceutical in preventive medicine (14).

In neurological disorders, melatonin exhibits neuroprotective effects by modulating excitotoxicity and promoting neuronal survival,

particularly in neurodegenerative conditions such as Alzheimer's and Parkinson's disease (13). Clinical trials indicate that adjunctive melatonin therapy improves sleep quality and cognitive function in insomnia associated with these disorders, potentially delaying disease progression through GABAergic enhancement and amyloid-beta clearance (15). Additionally, in epilepsy models, melatonin's anticonvulsant actions via MT1/MT2 receptor activation underscore its broader neuroprotective potential in seizure-related neurodegeneration (12).

Beyond the central nervous system, melatonin has shown promise in metabolic and immune-related diseases, where it ameliorates insulin resistance and glycemic control in diabetes by suppressing oxidative damage to pancreatic beta cells (16,17). In immune dysregulation syndromes exacerbated by sleep deprivation, melatonin restores T-cell function and cytokine balance, offering a therapeutic bridge between circadian disruption and systemic inflammation (17). These pleiotropic benefits highlight melatonin's role as an adjunctive agent in managing multifaceted diseases and warrant further translational research (18).

Effect of Melatonin on Seizures: Animal Studies

Preclinical investigations over the past five years have consistently demonstrated melatonin's anticonvulsant potential in various rodent and non-rodent epilepsy models, primarily by modulating oxidative stress and neuronal excitability (1). In pentylenetetrazol (PTZ)-induced seizure models, melatonin administration has been shown to prolong seizure latency and reduce seizure duration in mice, with effects attributed to its antioxidant properties that lower brain malondialdehyde (MDA) levels (19). Similarly, in PTZ-exposed zebrafish larvae, melatonin suppressed seizure-like locomotor behaviors, including freezing and bursting, while also ameliorating comorbid anxiety- and depression-like symptoms by altering gene expression related to neuronal activity and glutathione metabolism (12).

In kainic acid (KA)-induced status epilepticus models in mice, pretreatment with melatonin at 30 or 60 mg/kg intraperitoneally dose-dependently suppressed seizure occurrence, with complete inhibition at the higher dose; this effect was mediated via melatonin receptor activation, as evidenced by blockade with luzindol (20). Complementary findings in rat models of KA-induced epilepsy showed that melatonin, combined with vigabatrin, exerted an additive anticonvulsant effect by reducing seizure severity scores and improving behavioral outcomes in beam-walking tests, while also mitigating vigabatrin-associated retinal toxicity (21). These observations highlight melatonin's efficacy across different epileptogenic triggers and underscore its role in attenuating acute seizure propagation (22).

Further exploration in N-methyl-D-aspartate (NMDA)-induced infantile spasms in prenatally stressed rats demonstrated that combined melatonin and adrenocorticotropic hormone therapy significantly decreased spasm frequency

and extended latency to onset, effects linked to normalization of hypothalamic-pituitary-adrenal axis dysregulation and restoration of brain-derived neurotrophic factor signaling (23). Such combinatorial approaches suggest synergistic mechanisms involving anti-inflammatory and neuroprotective pathways, as melatonin alone or in tandem with thiamine has been reported to enhance inhibition of oxidative stress in PTZ-challenged mice (19). Collectively, these animal studies provide robust preclinical evidence supporting melatonin's therapeutic promise, paving the way for optimized translational strategies (1).

While acute seizure models provide valuable initial insights, chronic models such as amygdala kindling more accurately replicate the progressive neuroplastic changes and epileptogenesis observed in clinical focal epilepsy. In this context, melatonin has demonstrated significant antiepileptogenic and disease-modifying properties. Studies utilizing the kindling model have revealed that chronic melatonin administration not only retards the development of kindled seizures (raising the after-discharge threshold) but also reduces seizure severity and duration in fully kindled animals. These chronic effects are largely attributed to melatonin's ability to modulate long-term synaptic plasticity, suppress maladaptive neuroinflammation, and restore the GABAergic/glutamatergic balance in the limbic structures over time. Furthermore, the evaluation of melatonin in kindling models has provided critical evidence for its synergistic potential; for instance, when combined with conventional antiseizure medications, melatonin has been shown to enhance their protective efficacy in kindled subjects, thereby highlighting its value as a disease-modifying adjunctive therapy that targets the underlying structural and functional reorganization of the epileptic brain (Table 1).

Effect of Melatonin on Seizures: Human Studies

Despite melatonin's robust, consistent anticonvulsant efficacy across diverse preclinical models, translating these findings into clinical practice remains challenging. A primary barrier lies in the inherent etiological and pathophysiological differences between experimentally induced seizures in rodents and the complex, multifactorial nature of human epilepsy. While animal models typically utilize acute chemoconvulsants or electrical stimulation to provoke seizures, human epilepsy often arises from chronic, structural, genetic, or metabolic etiologies that involve profound network-level reorganization and epileptogenesis over years. Furthermore, species-specific differences in pharmacokinetics, particularly hepatic cytochrome P450 enzyme expression and activity, can lead to vastly different melatonin bioavailability and half-lives between rodents and humans, complicating extrapolation of optimal dosing regimens. Additionally, human cohorts present with heterogeneous seizure semiologies, diverse comorbidities (such as chronic sleep disturbances and psychiatric conditions), and concurrent use of multiple antiseizure medications, all of which introduce complex pharmacodynamic and pharmacokinetic interactions rarely captured in controlled animal environments.

Table 1. Summary of Preclinical Studies Investigating the Anticonvulsant Effects of Melatonin in Animal Models of Epilepsy.

Authors (Year)	Animal Model	Seizure Induction Method	Intervention	Key Findings	Proposed Mechanism
Mehrzadi et al. (2022)	Mice	Pentylenetetrazol (PTZ)	Melatonin administration	Prolonged seizure latency; reduced seizure duration	Antioxidant activity; reduced brain malondialdehyde (MDA) levels
Ren et al. (2021)	Zebrafish larvae	PTZ exposure	Melatonin treatment	Suppressed seizure-like locomotor behaviors (freezing, bursting); ameliorated anxiety/depression-like symptoms	Modulation of gene expression related to neuronal activity and glutathione metabolism
Tchekalarova et al. (2022)	Mice	Kainic acid (KA)-induced status epilepticus	Melatonin (30 or 60 mg/kg, i.p.)	Dose-dependent suppression of seizure occurrence; complete inhibition at 60 mg/kg	Melatonin receptor (MT1/MT2) activation; effect blocked by luzindole
Wan et al. (2021)	Prenatally stressed rats	NMDA-induced infantile spasms	Melatonin + Adrenocorticotropic hormone (ACTH)	Significant reduction in spasm frequency; extended latency to spasm onset	Normalization of HPA-axis dysregulation; restoration of BDNF signaling
Ma et al. (2025)	Rats	KA-induced epilepsy	Melatonin + Vigabatrin	Additive anticonvulsant effect; reduced seizure severity scores; improved beam-walking performance; mitigated vigabatrin-induced retinal toxicity	Synergistic neuroprotection; attenuation of oxidative stress and excitotoxicity
Dehdashtian and Hosseinzadeh. (2021)	Mice	PTZ challenge	Melatonin ± Thiamine	Enhanced inhibition of oxidative stress with combination therapy	Synergistic anti-inflammatory and neuroprotective pathways

Therefore, bridging this translational gap requires a more nuanced approach that accounts for these species-specific and clinical complexities when designing and interpreting future human trials.

Human clinical trials over the past five years have provided mixed yet promising evidence for the anticonvulsant effects of melatonin as an adjunctive therapy in epilepsy, particularly in

improving seizure severity and sleep disturbances. However, impacts on seizure frequency remain inconsistent (15). In a randomized, double-blind, placebo-controlled crossover trial involving 60 adults with idiopathic generalized tonic-clonic seizures on valproic acid, add-on melatonin (3 mg nightly) significantly reduced epilepsy severity scores by 32.33% compared to 5.58% with placebo ($P<0.01$), as measured by the Chalfont Seizure Severity Scale, while also enhancing sleep quality in over half of participants ($P<0.001$) (10). Similarly, a parallel-group randomized controlled trial of 104 adults with generalized epilepsy demonstrated that melatonin supplementation (3 mg/day) alongside valproate increased responder rates ($P<0.01$) and seizure-free rates ($P<0.05$), alongside a greater reduction in seizure frequency and severity, with concurrent decreases in serum neuron-specific enolase levels indicative of reduced neuronal damage ($P<0.05$) (24).

Pediatric populations have also been a focus, with investigations highlighting melatonin's potential in infantile epileptic spasms syndrome (IESS), though results on spasm control are less conclusive (25). A double-blind, placebo-controlled trial in 70 infants aged 3 months to 2 years receiving adrenocorticotrophic hormone and magnesium sulfate found that add-on melatonin (3 mg daily) did not significantly alter the median reduction in spasm frequency (100% vs. 66.7%) or response rates at 3 or 28 days ($P>0.05$), nor improve EEG hypsarrhythmia scores or psychomotor development ($P>0.05$). Nonetheless, melatonin markedly improved sleep onset latency by 6 minutes ($P<0.05$) and sleep regularity (85.7% vs. 42.9%, $P<0.001$), elevated serum melatonin levels without adverse effects, and suggested indirect benefits for seizure management through circadian stabilization (25). These findings align with broader observations across diverse epilepsy cohorts, in which melatonin's safety profile supports its exploration despite variable efficacy in core seizure metrics (22).

A systematic review and meta-analysis of 10 randomized controlled trials further corroborates these trends, revealing that add-on melatonin significantly ameliorates seizure severity (relative risk: 0.33; 95% CI: 0.04-0.62; $P<0.05$) and sleep latency (relative risk: 0.56; 95% CI: 0.10-1.02; $P<0.05$) across 512 epilepsy patients, without notable increases in adverse events. However, no significant effect on seizure frequency was observed, underscoring the need for larger, long-term studies to delineate optimal dosing and patient subgroups (15). Collectively, these human studies indicate melatonin's adjunctive value primarily in mitigating severity and sleep comorbidities, with ongoing research essential to resolve discrepancies and enhance translational application (22).

Table 2 provides a detailed overview of these clinical trials, including study design, population, and outcomes.

Table 2. Summary of Clinical Studies Investigating the Anticonvulsant Effects of Melatonin in Human Epilepsy Cohorts

Authors (Year)	Study Design & Population	Intervention	Key Outcomes	Statistical Significance	Conclusions
Maghbooli et al. (2023)	Randomized, double-blind, placebo-controlled crossover trial; 60 adults with idiopathic generalized tonic-clonic seizures on valproic acid	Add-on melatonin 3 mg nightly vs. placebo	• Epilepsy severity score reduced by 32.33% (melatonin) vs. 5.58% (placebo • Sleep quality improved in >50% of participants	Severity: P = 0.002 Sleep: P < 0.001	Adjunctive melatonin significantly reduces seizure severity and improves sleep quality in adults with generalized epilepsy
Verma et al. (2021)	Parallel-group RCT; 104 adults with generalized epilepsy on valproate	Melatonin 3 mg/day + valproate vs. valproate alone	• Higher responder rates and seizure-free rates • Greater reduction in seizure frequency and severity • Decreased serum neuron-specific enolase (NSE) levels	Responder rate: P = 0.006 Seizure-free: P = 0.034 Frequency: P = 0.016 Severity: P = 0.032 >NSE: P = 0.024	Melatonin adjunctive therapy enhances clinical response and may reduce neuronal damage in generalized epilepsy
Sun et al. (2024)	Double-blind, placebo-controlled trial; 70 infants (3 mo–2 yr) with infantile epileptic spasms syndrome (IESS) on ACTH + magnesium sulfate	Add-on melatonin 3 mg daily vs. placebo	• No significant difference in median spasm frequency reduction or response rates • No improvement in EEG hypsarrhythmia or psychomotor development • Improved sleep onset latency (−6 min) and sleep regularity	Spasm frequency: P = 0.288 Sleep latency: P = 0.030 Sleep regularity: P < 0.001	Melatonin improves sleep parameters without significant effects on spasm control in IESS, supporting its safety and indirect benefits via circadian stabilization
Liu et al. (2024)	Systematic review and meta-analysis of 10 RCTs; 512 epilepsy patients	Add-on melatonin vs. placebo/standard care	• Significant improvement in seizure severity (RR: 0.33; 95% CI: 0.04–0.62) • Reduced sleep latency (RR: 0.56; 95% CI: 0.10–1.02) • No significant effect on seizure frequency • No increase in adverse events	Severity: P = 0.03 Sleep latency: P = 0.02	Melatonin adjunctive therapy reliably ameliorates seizure severity and sleep disturbances, though effects on seizure frequency remain inconsistent; larger trials needed

Despite the promising adjunctive role of melatonin, notable heterogeneity in clinical outcomes across trials necessitates a critical analysis of underlying discrepancies. First, dosing regimens vary significantly, with standard over-the-counter doses (e.g., 1-3 mg) potentially being insufficient to achieve the threshold concentrations required for robust anticonvulsant effects in some adult populations, whereas higher doses (e.g., 10 mg/day) have demonstrated more consistent reductions in seizure frequency (10). Second, the timing of administration is a critical yet often overlooked factor; given melatonin's exceptionally short half-life (approximately 30 minutes) (21), immediate-release preparations administered at inappropriate times may fail to sustain therapeutic levels during nocturnal or circadian seizure peaks, highlighting the necessity of chronotherapy approaches tailored to individual seizure patterns. Third, patient age strongly influences melatonin pharmacokinetics, as prepubertal children metabolize melatonin much faster than adults via hepatic cytochrome P450 1A2 (CYP1A2), often requiring weight-based dose adjustments to avoid subtherapeutic exposure (19). Fourth, the specific epilepsy syndrome plays a pivotal role; while melatonin has consistently improved sleep architecture in generalized epilepsies, its direct impact on spasm frequency in infantile epileptic spasms syndrome (IESS) remains less clear, suggesting syndrome-specific efficacy (25). Finally, concomitant use of antiseizure medications (ASMs) introduces complex drug-drug interactions. Because melatonin is predominantly metabolized by CYP1A2 (11), patients taking hepatic enzyme-inducing ASMs (e.g., carbamazepine, phenytoin) may experience accelerated melatonin clearance and reduced efficacy. In contrast, enzyme inhibitors (e.g., valproic acid, fluvoxamine) can elevate melatonin plasma levels, potentially increasing both therapeutic and adverse effects. Future clinical protocols must therefore stratify patients based on age, ASM profile, and seizure chronobiology to optimize melatonin's adjunctive potential.

Mechanisms of Melatonin in Seizure Control

To provide a structured understanding of melatonin’s pleiotropic effects, its anticonvulsant mechanisms can be categorized into a hierarchical framework comprising primary, secondary, and tertiary targets, which collectively disrupt the vicious cycle of epileptogenesis. The primary mechanisms involve direct, immediate upstream events: melatonin and its kynurenine metabolites directly scavenge reactive oxygen and nitrogen species (ROS/RNS)es, melatonin directly agonizes G-protein-coupled MT1/MT2 receptors. These primary actions trigger secondary (downstream) transcriptional and signaling cascades, notably the activation of the Nrf2 pathway (upregulating endogenous antioxidants like SOD and GPx) and the suppression of NF-κB and NLRP3 inflammasomes (attenuating neuroinflammation). Ultimately, these molecular shifts culminate in tertiary functional outcomes, specifically the restoration of the excitatory-inhibitory balance via enhanced GABAergic transmission and reduced glutamatergic excitotoxicity. Crucially, these pathways are not isolated but highly interconnected in a self-amplifying loop: oxidative stress activates microglia to release pro-inflammatory cytokines (e.g., IL-1β, TNF-α), which in turn alter the expression and function of

GABA and glutamate receptors, thereby increasing neuronal hyperexcitability and generating further ROS. Melatonin exerts its profound neuroprotective efficacy by simultaneously interrupting this interconnected triad at multiple primary and secondary nodes, thereby breaking the cycle of oxidative stress, neuroinflammation, and excitotoxicity that drives seizure propagation.

The anticonvulsant effects of melatonin are predominantly mediated through its robust antioxidant properties, which counteract the oxidative stress implicated in epileptogenesis by scavenging ROS and reactive nitrogen species (RNS) (1). By inducing the activity of endogenous antioxidative enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), melatonin reduces lipid peroxidation and mitochondrial DNA damage in seizure models, thereby preserving neuronal integrity and elevating the seizure threshold (9). These mechanisms are particularly evident in kainate- and PTZ-induced epilepsy paradigms, where exogenous melatonin administration attenuates markers of oxidative imbalance, including MDA levels, highlighting its role in mitigating seizure-induced neuronal injury (1).

Beyond antioxidative actions, melatonin modulates key neurotransmitter systems to restore the excitatory-inhibitory balance disrupted in epilepsy, primarily by enhancing GABAergic inhibition and suppressing glutamatergic excitotoxicity (9). Melatonin increases brain GABA concentrations and augments the affinity of GABAA receptors, an effect that is antagonized by bicuculline, underscoring its dependence on inhibitory neurotransmission for anticonvulsant efficacy (1). Concurrently, it inhibits glutamate-mediated excitation via NMDA receptor blockade in striatal neurons, preventing calcium influx and downstream excitotoxic cascades that propagate seizures (9).

Receptor-dependent signaling via melatonin receptors MT1 and MT2 further contributes to seizure control by influencing ion channel dynamics and circadian synchronization, with MT1/MT2 activation promoting G-protein-coupled pathways that inhibit adenylyl cyclase and modulate potassium and calcium channels (26). This receptor engagement accelerates ATP-sensitive potassium (KATP) channel conduction, leading to neuronal hyperpolarization and reduced excitability during hypoxic seizure states, while also preventing mitochondrial permeability transition pore activation (1). Additionally, melatonin's anti-inflammatory effects, including the promotion of M2 microglial polarization through the RhoA/ROCK pathway, dampen neuroinflammation and gliosis, offering a multifaceted neuroprotective strategy that aligns with the suppression of disrupted circadian rhythms and epileptiform activity (9,26).

The principal molecular and cellular mechanisms through which melatonin exerts anticonvulsant effects are illustrated schematically in Figure 1.

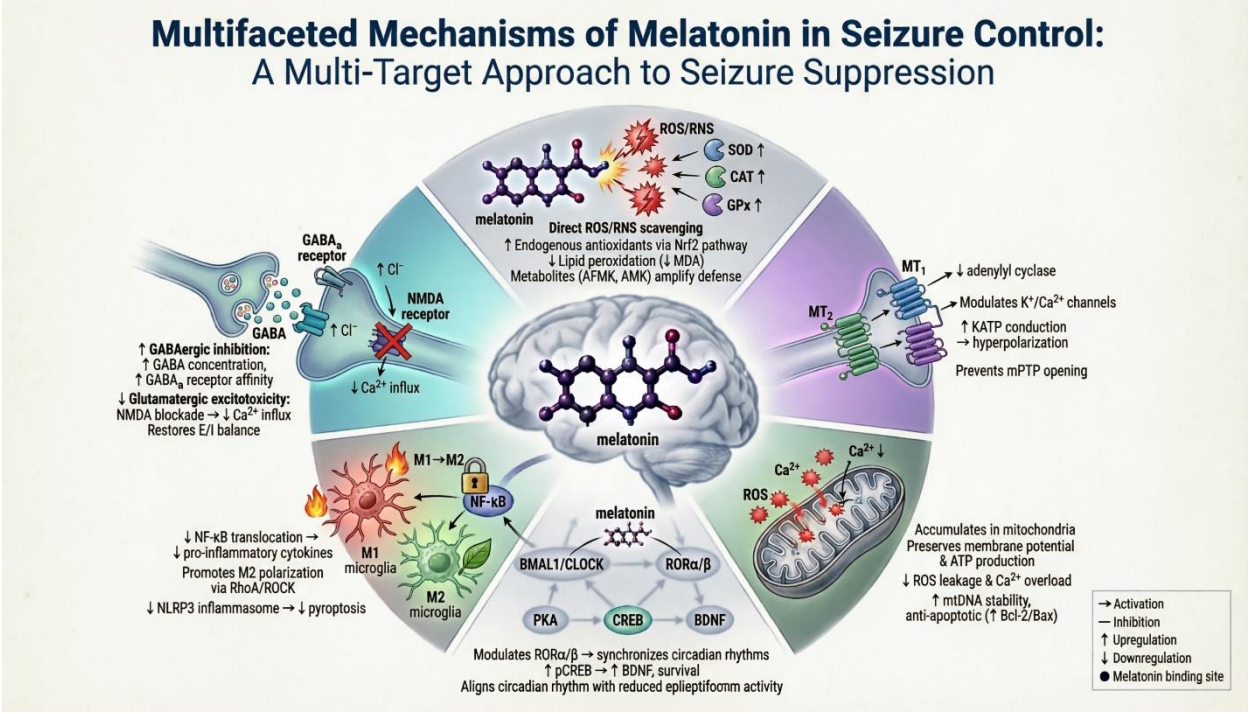


Figure 1. Schematic representation of the principal molecular and cellular mechanisms underlying the anticonvulsant effects of melatonin (1,9,26).

Melatonin demonstrates pleiotropic actions including: (1) direct and indirect antioxidant defense via ROS/RNS scavenging and upregulation of endogenous enzymes; (2) modulation of neurotransmitter balance through enhanced GABAergic inhibition and reduced glutamatergic excitotoxicity; (3) receptor-dependent signaling via MT_1/MT_2 receptors promoting neuronal hyperpolarization; (4) anti-inflammatory effects through NF-κB suppression and microglial M1-to-M2 polarization; (5) mitochondrial protection preserving bioenergetic integrity; and (6) circadian rhythm synchronization via ROR and CREB/BDNF pathways. Abbreviations: ROS/RNS: Reactive oxygen species/Reactive nitrogen species; SOD: Superoxide dismutase; CAT: Catalase; GPx: Glutathione peroxidase; MDA: Malondialdehyde; AFMK: N1-acetyl-N2-formyl-5-methoxykynuramine; AMK: N1-acetyl-5-methoxykynuramine; GABA: Gamma-aminobutyric acid; NMDA: N-methyl-D-aspartate; E/I: Excitatory/Inhibitory; MT_1/MT_2: Melatonin receptors 1 and 2; KATP: ATP-sensitive potassium channels; mPTP: Mitochondrial permeability transition pore; NF-κB: Nuclear factor kappa B; RhoA/ROCK: Ras homolog gene family member A/Rho-associated protein kinase; NLRP3: NOD-like receptor family pyrin domain containing 3; BMAL1/CLOCK: Brain and muscle ARNT-like 1/Circadian locomotor output cycles kaput; RORα/β: Retinoic acid-related orphan receptor alpha/beta; PKA: Protein kinase A; CREB: cAMP response element-binding protein; BDNF: Brain-derived neurotrophic factor; Bcl-2/B

Antioxidant Roles of Melatonin

Melatonin's antioxidant efficacy extends beyond direct radical scavenging to encompass a cascade of protective metabolites that amplify its neutralizing capacity against oxidative insults in neural tissues (28). Metabolites such as N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK) perpetuate this defense by sequentially quenching additional ROS and RNS, thereby sustaining cellular redox homeostasis in neurodegenerative environments (28). Furthermore, melatonin orchestrates transcriptional upregulation of antioxidant enzymes through activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, facilitating nuclear translocation and binding to antioxidant response elements to elevate expression of SOD, catalase (CAT), and GPx (29). This Nrf2-mediated induction not only bolsters enzymatic defenses but also mitigates protein oxidation and lipid peroxidation in vulnerable brain regions, underscoring melatonin's role as a transcriptional modulator of oxidative resilience (29).

However, it is crucial to acknowledge that under the severe conditions of neuroinflammation and chronic oxidative stress characteristic of epileptogenesis, the metabolic fate of melatonin is significantly altered. The overwhelming burden of reactive species can lead to the rapid consumption and depletion of these protective kynuramine metabolites (AFMK and AMK), thereby diminishing their sustained antioxidant capacity. Furthermore, the bioavailability and metabolic clearance of melatonin are heavily dependent on cytochrome P450 enzymes, particularly CYP1A2 in the liver and specific CYP isoforms within the brain. During neuroinflammatory states, the expression and activity of these cerebral and hepatic CYP450 enzymes are dynamically modulated by pro-inflammatory cytokines and oxidative stress, which can unpredictably alter melatonin's pharmacokinetics and reduce its effective concentration at the target sites. Consequently, the synergistic impact of accelerated metabolite consumption and enzyme-mediated metabolic shifts may compromise the overall bioavailability and therapeutic efficacy of melatonin in the highly oxidative milieu of the epileptic brain, highlighting a critical challenge that necessitates optimized delivery systems or adjusted dosing regimens (29).

In mitochondrial compartments, melatonin preferentially accumulates to safeguard bioenergetic integrity by inhibiting the permeability transition pore and enhancing electron transport chain efficiency, thereby curtailing ROS leakage during metabolic perturbations (28). Its metal-chelating prowess further attenuates Fenton-like reactions by sequestering transition metals like iron and copper, preventing hydroxyl radical generation and ferroptosis in oxidatively stressed neurons (29). These concerted actions culminate in anti-apoptotic outcomes, where melatonin preserves the Bcl-2/Bax equilibrium and suppresses caspase activation, fostering neuronal survival amid chronic oxidative challenges (28).

Collectively, these multifaceted antioxidant strategies position melatonin as a pivotal guardian against progressive neural degeneration (29).

Role of Melatonin in Nrf2 Function

Melatonin exerts a pivotal regulatory influence on the Nrf2 signaling pathway by promoting its dissociation from the Kelch-like ECH-associated protein 1 (Keap1) inhibitor, thereby facilitating Nrf2's nuclear translocation and subsequent binding to antioxidant response elements (ARE) in target gene promoters (30-33). This activation enhances the transcriptional expression of phase II detoxifying enzymes and antioxidant proteins, such as heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1), which collectively fortify cellular defenses against oxidative insults in diverse physiological contexts (34). Furthermore, through melatonin receptor-mediated mechanisms, Nrf2 induction mitigates apoptosis and mitochondrial dysfunction by modulating downstream effectors like OPA1, underscoring melatonin's therapeutic potential in oxidative stress-associated pathologies (33,35).

Effect of Melatonin on Glutathione

Melatonin protects glutathione homeostasis by increasing its synthesis and enzymatic utilization, reinforcing the tripeptide's role as a primary cellular antioxidant in mitigating oxidative perturbations. In clinical settings of generalized epilepsy, adjunctive melatonin administration has been associated with a significant elevation in serum glutathione reductase activity, which facilitates the regeneration of reduced glutathione from its oxidized form and correlates with diminished neuronal damage indicators (24). Preclinical evidence further elucidates this mechanism in seizure-induced neurodegeneration, where melatonin attenuates the depletion of GPx, preserving redox balance and curbing lipid peroxidation in vulnerable neural circuits (36). These glutathione-modulatory actions underscore melatonin's therapeutic utility in epilepsy, extending its benefits to broader oxidative stress amelioration across hepatic and systemic pathologies.

Effect of Melatonin on Mitochondrial Dysfunction

Mitochondrial dysfunction, characterized by impaired oxidative phosphorylation and excessive production of ROS, is a hallmark of epileptogenesis that exacerbates neuronal hyperexcitability and cell death. Melatonin mitigates these deficits by preserving mitochondrial membrane integrity and bioenergetic efficiency in seizure-vulnerable brain regions (9). By scavenging ROS and modulating the electron transport chain, melatonin attenuates lipid peroxidation and calcium overload within mitochondria, thereby restoring ATP levels and preventing the propagation of excitotoxic cascades in epilepsy models (22). Furthermore, melatonin's therapeutic modulation of mitochondrial DNA stability and haplogroup-specific vulnerabilities enhances its antioxidant synergy, positioning it as a multifaceted agent that alleviates seizure-

induced mitochondrial pathology and improves long-term neuronal resilience (37).

Anti-Inflammatory Roles of Melatonin

Melatonin's anti-inflammatory actions are primarily orchestrated through the suppression of nuclear factor kappa B (NF-κB) pathway activation, which inhibits the transcription of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and IL-6, thereby mitigating the cascade of neuroinflammatory responses in epilepsy (38). Additionally, melatonin fosters the shift in microglial phenotype from pro-inflammatory M1 to neuroprotective M2 states via modulation of the RhoA/ROCK signaling axis, reducing astrogliosis and hippocampal inflammation in seizure models (26). These pleiotropic effects extend to the attenuation of NLRP3 inflammasome assembly, preventing pyroptosis and further exacerbation of seizure susceptibility, thus highlighting melatonin's role in bridging inflammation resolution with anticonvulsant efficacy (17).

Effect of Melatonin on NF-κB

Melatonin attenuates neuroinflammation in epilepsy by suppressing the nuclear translocation and DNA-binding activity of NF-κB, a pivotal transcription factor that orchestrates pro-inflammatory gene expression, thereby mitigating seizure-induced hippocampal damage and gliosis (39). Through activation of sirtuin 1 (SIRT1), melatonin indirectly inhibits the NF-κB pathway, fostering an anti-inflammatory milieu that enhances neuronal survival and reduces cytokine release in models of temporal lobe epilepsy (40). In autism spectrum disorder models with comorbid epileptiform activity, chronic melatonin supplementation restores cytoplasmic localization of NF-κB in hippocampal neurons, alleviating oxidative stress-mediated inflammatory cascades and supporting GABAergic balance to curb hyperexcitability (41).

Effect of Melatonin on CREB

Melatonin modulates the cAMP response element-binding protein (CREB) signaling pathway through receptor-dependent mechanisms involving G-protein-coupled MT1 and MT2 receptors, which inhibit adenylyl cyclase and subsequently influence PKA-mediated phosphorylation of CREB, thereby exerting neuroprotective effects that may contribute to seizure suppression by enhancing neuronal survival and synaptic plasticity in epilepsy models (42,43). In rodent models of traumatic brain injury, a condition predisposing to post-traumatic epilepsy, melatonin administration at 10 mg/kg intraperitoneally activates the PKA/CREB pathway, elevating phosphorylated CREB levels in the amygdala to attenuate anxiety-like behaviors and neuroinflammation, with these effects partially reversed by PKA inhibitors such as H89 (42,44). Furthermore, in paradigms of drug-induced neurotoxicity relevant to epileptogenic processes, melatonin reverses reductions in CREB mRNA expression in the nucleus accumbens, promoting anti-addictive and neuroprotective outcomes that align with its

anticonvulsant potential by restoring transcription factor activity essential for BDNF expression and glutamatergic balance (45).

Melatonin and ROR

The retinoic acid-related orphan receptors (RORs), particularly RORα and RORβ, serve as potential nuclear transducers of melatonin's effects on circadian gene expression, with emerging evidence suggesting that melatonin acts as a ligand or modulator to influence ROR transcriptional activity in neural tissues implicated in epileptogenesis (46). In epilepsy models, dysregulation of ROR-mediated pathways disrupts the Bmal1-Clock loop, exacerbating seizure susceptibility through altered neuronal excitability and metabolic homeostasis, while melatonin supplementation restores this balance by enhancing RORα binding to response elements, thereby promoting anticonvulsant neuroprotection (47). Furthermore, genetic variations in ROR genes have been associated with altered melatonin responsiveness in refractory epilepsy cohorts, highlighting ROR's role as a therapeutic target for melatonin-based interventions that synchronize circadian rhythms and attenuate hyperexcitability (48).

Effect of Melatonin on GABAA Receptor

Melatonin potentiates the activity of GABAA receptors, enhancing chloride influx and inhibitory postsynaptic currents in neuronal populations, which contributes to its anticonvulsant efficacy by restoring the excitatory-inhibitory balance disrupted in epilepsy (49). In rodent models, subchronic melatonin administration increases the density of [^{3}H]GABA binding sites in hippocampal slices, delaying the latency and severity of pilocarpine-induced seizures through positive modulation of central GABAergic transmission (49,50). This receptor-mediated enhancement is complemented by melatonin's broader GABA-dependent mechanisms, in which exogenous supplementation attenuates seizure propagation via enhanced inhibitory signaling and mitigation of oxidative neuronal damage (1). In the PTZ model of neonatal rats, the effect of combined treatment with melatonin and phenobarbital, an antiepileptic drug that acts on GABA receptors, was investigated. The results showed that melatonin could enhance the antiepileptic effect of phenobarbital, but melatonin alone had no significant effect on seizure onset time (51,52). In Wang and co-workers' study, the sedative effect of melatonin via the GABA receptor was measured in mice. Flumazenil and picrotoxin (a benzodiazepine antagonist) reduced the sedative effect of melatonin, but bicuculline (a GABA antagonist) could not completely inhibit melatonin. These observations suggest that melatonin's neuronal inhibitory and sedative effects are mediated by binding to the benzodiazepine site of the GABAA receptor (53,54).

The circadian dynamics of epilepsy and melatonin

Beyond pharmacokinetic variables, the circadian dynamics of epilepsy and melatonin represent a critical yet underexplored dimension in clinical management. Epilepsy is inherently a chronobiological disorder, with seizure

occurrence exhibiting distinct circadian and multi-day rhythmicity; for instance, generalized tonic-clonic seizures predominantly peak in the early morning, whereas focal seizures often cluster during the night. This temporal pattern is intricately linked to the endogenous circadian system, where disruptions in the sleep-wake cycle or melatonin secretion can lower the seizure threshold and exacerbate epileptiform activity. Conversely, melatonin, characterized by its robust nocturnal peak, exerts a bidirectional influence on this dynamic: it not only synchronizes circadian rhythms but also modulates neuronal excitability in a time-dependent manner. Consequently, the concept of chronotherapy, optimizing the timing of drug administration to align with the body's biological rhythms, becomes paramount. Administering melatonin at inappropriate circadian phases may fail to coincide with peak seizure vulnerability, thereby attenuating its anticonvulsant efficacy and contributing to the clinical heterogeneity observed across trials. Future clinical protocols must therefore incorporate chronotherapeutic principles, tailoring the timing of melatonin administration to individual seizure chronotypes to maximize therapeutic synergy and restore disrupted circadian-neuronal homeostasis (55,56).

Safety Profile and Potential Adverse Effects

Although melatonin is generally well-tolerated and has a favorable safety profile, a comprehensive clinical evaluation must address potential adverse effects and pharmacokinetic interactions that may affect its therapeutic utility. The most frequently reported adverse effect is daytime somnolence, which is often dose-dependent and can be exacerbated by inappropriate timing of administration relative to the individual's circadian phase (57). Furthermore, melatonin's influence on the hypothalamic-pituitary axis requires careful monitoring of endocrine parameters; prolonged supplementation has been shown to modulate hormone secretion patterns, such as prolactin and cortisol, potentially disrupting basal neuroendocrine homeostasis in susceptible individuals (58). More critically, significant drug-drug interactions exist between melatonin and conventional ASMs. Classical hepatic enzyme-inducing ASMs, notably phenobarbital, carbamazepine, and phenytoin, upregulate cytochrome P450 enzymes (particularly CYP1A2), which are primarily responsible for melatonin metabolism (59). Consequently, co-administration of these ASMs accelerates melatonin clearance, substantially lowering its systemic bioavailability and potentially compromising its anticonvulsant efficacy. Therefore, when melatonin is prescribed as an adjunctive therapy, clinicians must carefully consider these endocrine and pharmacokinetic variables, which may require dose adjustments or the selection of non-enzyme-inducing ASMs to optimize therapeutic outcomes and minimize adverse effects.

Conclusion

Over the past five years, converging evidence has robustly established the anticonvulsant

potential of the melatonergic system. By simultaneously modulating oxidative stress, neuroinflammation, and GABAergic transmission, melatonin consistently reduces seizure severity across both preclinical models and human cohorts. Clinically, its most profound impact lies in its dual capacity to improve sleep architecture and mitigate seizure severity, particularly in pediatric populations and adults with comorbid sleep disturbances while maintaining an exceptional safety profile. However, inconsistent effects on overall seizure frequency highlight critical translational barriers, necessitating standardized dosing protocols and chronotherapeutic strategies. Ultimately, integrating melatonin into precision-medicine frameworks, tailored to individual circadian profiles and specific epilepsy syndromes, holds the potential to revolutionize adjunctive management strategies for refractory epilepsy.

Declarations

Acknowledgments

The author would like to thank the Vice-Chancellor for Research and Technology of Baqiyatallah University of Medical Sciences for their support and collaboration.

Author Contributions

Mahdi Mashhadi Akbar Boojar: Conceptualization, literature search and selection, data analysis and interpretation, writing – original draft, writing – review & editing, and final approval of the manuscript. The author meets all ICMJE criteria for authorship and is solely responsible for the integrity of the work.

Conflict of Interest

The author declares that there is no conflict of interest.

Funding

This research received no specific funding.

Ethical Approval / Protection of Human and Animal Subjects

This article is a narrative review based on previously published literature and does not involve any original research with human participants or animal subjects. Therefore, ethical approval was not required.

Data Availability

No new data were generated or analyzed in this study. All data supporting the findings of this review are available in the published articles cited in the reference list.

Use of Artificial Intelligence

The author declares that a generative artificial intelligence tool (Gamma AI) was used solely for the creation of the schematic illustration presented in Figure 1. No generative artificial intelligence tools were used in the writing, editing, data interpretation, literature synthesis, or any other aspect of the scientific content of this manuscript. The author takes full responsibility for the accuracy, integrity, and originality of the entire work, including the content and interpretation of Figure 1.

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