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Melatonin Derivatives and Reactive Oxygen Species: A Computational Review of Spin Trapping Strategies for Biomedical and Environmental Applications

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Abstract: Reactive oxygen species (ROS) play dual roles in cellular physiology, contributing to both essential signaling and oxidative damage in pathological and environmental contexts. Melatonin and its derivatives have emerged as potent multi-mechanism antioxidants, exhibiting neuroprotective, anti-inflammatory, and detoxifying properties. This systematic review, conducted in accordance with PRISMA 2020 guidelines, synthesizes computational evidence on radical scavenging and spin trapping mechanisms involving melatonin derivatives. Data were collated from PubMed, Scopus, Web of Science, EMBASE, and ScienceDirect, focusing on studies employing quantum chemical methods, including DFT and QM/MM simulations. Key findings reveal that melatonin derivatives predominantly neutralize ROS via hydrogen atom transfer (HAT), with contributions from single electron transfer (SET) and radical adduct formation (RAF) pathways. Computational spin trapping simulations using agents like DMPO confirm the thermodynamic feasibility of adduct formation, supported by hyperfine coupling constant predictions. Structural features such as methoxy and amide groups significantly enhance radical stabilization. Despite methodological heterogeneity, and in silico models demonstrate strong predictive power for antioxidant performance. Translating these insights into biomedical and environmental interventions requires standardized computational protocols, kinetic integration, and experimental validation.

Keywords: Melatonin derivatives, Reactive oxygen species, spin trapping, Density Functional Theory, Oxidative stress mitigation

INTRODUCTION

Reactive oxygen species (ROS) are chemically reactive molecules derived from molecular oxygen. These species play dual roles in biological and environmental systems, functioning both as essential signaling mediators and as potent inducers of oxidative damage when present in excess (Chaudhary *et al.*, 2023). Reactive oxygen species (ROS) encompasses a broad spectrum of free radicals and non-radical derivatives of oxygen that play critical roles in both physiological and pathological processes. The primary ROS include the superoxide anion ($O_2^{-}\bullet$), a one-electron reduction product of molecular oxygen typically generated as a byproduct of mitochondrial respiration, NADPH oxidase activity, or redox-cycling xenobiotics. Another highly reactive species is the hydroxyl radical (•OH), formed via Fenton or Haber–Weiss reactions involving transition metals and hydrogen peroxide; it is capable of non-selectively attacking lipids, proteins, and DNA, thereby contributing to cellular dysfunction and death. Singlet oxygen ($^1O_2$), an electronically excited form of molecular oxygen produced through photosensitized reactions, is not a radical but is highly electrophilic, enabling it to oxidize a wide range of biomolecules, particularly unsaturated lipids and amino acid residues. Peroxynitrite ($ONOO^-$), a potent oxidizing and nitrating agent, is generated by the diffusion-limited reaction between nitric oxide (NO•) and superoxide anion, leading to nitration of tyrosine residues in proteins and initiation of lipid peroxidation cascades. Physiologically, ROS serve as critical second messengers in redox signaling, regulating pathways such as NF-κB activation, mitogen-activated protein kinase (MAPK) cascades, and hypoxia-inducible factor (HIF) stabilization. At low to moderate concentrations, ROS participates in cell proliferation, differentiation, immune defense, and apoptosis regulation (Chaudhary *et al.*, 2023).

However, an imbalance between ROS production and antioxidant defenses, termed oxidative stress, leads to widespread cellular injury. This disruption results in oxidative modification of DNA, lipid peroxidation, and irreversible protein oxidation, ultimately compromising cellular integrity and function (Chaudhary *et al.*, 2023), (Brieger *et al.*, 2012). The pathological relevance of ROS has been extensively documented across a spectrum of chronic diseases, including neurodegenerative disorders (e.g., Alzheimer's, Parkinson's), cardiovascular conditions (e.g., atherosclerosis, hypertension), metabolic syndromes (e.g., diabetes mellitus), and cancer. In these contexts, ROS contributes to inflammatory signaling, genomic instability, and tissue remodeling.

Beyond human biology, ROS are central to environmental toxicology. Environmental stressors such as ultraviolet radiation, heavy metals (e.g., mercury, cadmium), persistent organic pollutants,

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and particulate matter (PM2.5) can elevate ROS levels in exposed organisms, inducing cytotoxic and genotoxic effects in aquatic species, plants, and humans alike. Moreover, ROS-mediated degradation of environmental contaminants is a key process in advanced oxidation technologies used in water and air purification systems (Das & Roychoudhury, 2014).

Understanding the chemical nature, reactivity, and biological consequences of individual ROS species is foundational for evaluating antioxidant defense mechanisms, including those mediated by melatonin and its derivatives.

Need for Spin Trapping and Computational Approaches

Reactive oxygen species (ROS) are inherently unstable due to their high reactivity and transient existence, posing significant analytical challenges for experimental detection and quantification. Many ROS, such as hydroxyl radicals (•OH), superoxide anion radicals (O_2^{-}•), and peroxyl radicals (ROO•), have lifespans ranging from nanoseconds to microseconds and exist in extremely low steady-state concentrations under physiological or environmental conditions. As a result, direct observation of these species is often infeasible without specialized strategies (Peyrot *et al.,* 2022).

Spin Trapping for Short-Lived Radicals

Spin trapping is a widely adopted technique for studying short-lived radicals. It involves the reaction of a radical species with a diamagnetic spin trap, typically a nitrone or nitroso compound, to form a longer-lived spin adduct. This adduct can be characterized using electron paramagnetic resonance (EPR) spectroscopy, offering insights into the identity and behavior of the original radical (Buettner, 1987).

Commonly employed spin traps include:

- 5,5-Dimethyl-1-pyrroline N-oxide (DMPO) – effective for trapping O_2^{-}• and •OH
- α-Phenyl-N-tert-butylnitrone (PBN) – widely used in biological systems
- DEPMPO and BMPO – enhanced selectivity and resistance to hydrolysis, especially useful in aqueous or biological environments (Shi *et al.*, 2005)

Spin trapping is instrumental in identifying radical intermediates and validating scavenging pathways of antioxidants such as melatonin and its derivatives. By forming stable adducts, researchers can deduce which radical species are preferentially scavenged and characterize the kinetics of the interaction (Florido *et al.,* 2022).

Importance in Validating Radical Scavenging Pathways

Experimental spin trapping enables detailed investigations of radical–melatonin interactions by providing insights into the underlying mechanisms, relative efficiencies, and radical specificities involved. It allows researchers to determine whether scavenging occurs through hydrogen atom transfer (HAT), single-electron transfer (SET), or radical adduct formation (RAF). The formation rates of spin adducts further facilitate the ranking of scavenging potentials among melatonin derivatives, such as N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK) and N^1-acetyl-5-methoxykynuramine (AMK). Additionally, spin trapping helps identify the specific reactive oxygen species (ROS) that are preferentially neutralized by each derivative, thereby elucidating their selective antioxidant properties.

For example, (Hardeland, 2021) and (Corpas *et al.,* 2022) showed that melatonin and its downstream metabolites (e.g., AMK) could trap both nitrogen- and oxygen-based radicals, suggesting a cascade-like defense mechanism that extends beyond melatonin's initial interaction.

Limitations of Experimental Methods

Despite its importance, spin trapping has notable limitations that can affect its reliability and applicability, particularly in biological systems. One major challenge is the short half-life of spin adducts, as they can decompose rapidly or undergo further reactions under in vivo conditions, thereby limiting accurate quantification (Buettner, 1987). Sensitivity in biological matrices is also a concern, since interference from biomolecules and variability in physiological factors such as pH and ionic strength can lead to non-specific or misleading results. Furthermore, the toxicity and inherent reactivity of certain spin traps; such as 5,5-dimethyl-1-pyrroline N-oxide (DMPO) and α-phenyl N-tert-butylnitrone (PBN) pose additional drawbacks, as they may disrupt cellular redox systems or exhibit cytotoxic effects at experimental concentrations (Villamena *et al.,* 2012). These limitations reduce the reliability and reproducibility of spin trapping data in complex biological or environmental systems.

To address these experimental limitations, computational chemistry, particularly density

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functional theory (DFT) (Shaker *et al.*, 2024) and time-dependent DFT (TD-DFT) (Kolesov *et al.*, 2016)has become an indispensable tool for elucidating antioxidant mechanisms. These approaches provide predictive insights into the thermodynamics of radical scavenging, including key parameters such as bond dissociation enthalpy (BDE), ionization potential (IP), and proton affinity (PA). They also enable the evaluation of kinetic parameters, such as activation energies, transition states, and rate constants for radical-trapping reactions (Shaker *et al.*, 2024). In addition, computational methods facilitate the analysis of spin density distribution and hyperfine coupling constants, which are critical for simulating electron paramagnetic resonance (EPR) spectra and validating the structures of proposed spin adducts.

Computational models also allow researchers to screen large libraries of melatonin derivatives and assess their reactivity with different ROS species under varying solvent and pH conditions. This enhances our mechanistic understanding of the melatonin antioxidant cascade, providing a rational basis for designing novel analogs with enhanced radical-trapping capabilities.

Moreover, solvation models (e.g., PCM, SMD) and quantum mechanics/molecular mechanics (QM/MM) techniques improve the physiological relevance of in silico simulations, enabling more accurate extrapolation to biological or environmental systems (Kulkarni *et al.*, 2021).

While spin trapping remains a cornerstone of radical research, its full potential is realized when integrated with computational methods that can model radical-antioxidant interactions in silico. This integration is critical for exploring melatonin-based spin trapping strategies, particularly in biomedical contexts such as neuroprotection and inflammation, and in environmental applications like pollutant degradation.

RATIONALE FOR THE REVIEW

Gaps in Knowledge Regarding ROS Scavenging by Melatonin Derivatives

Melatonin (N-acetyl-5-methoxytryptamine) is widely recognized for its potent antioxidant properties (Chrustek & Olszewska-Słonina, 2021), primarily due to its direct free radical scavenging ability and its role in modulating antioxidant enzymes. However, while the parent molecule has been extensively studied, its metabolic derivatives—including *N^1-acetyl-N^2-formyl-5-methoxykynuramine* (AFMK), *N^1-acetyl-5-methoxykynuramine* (AMK), and *cyclic 3-hydroxymelatonin* remain relatively underexplored, particularly in the context of their reactivity with individual ROS types (Rivara *et al.*, 2015) (Reina *et al.*, 2018).

Current experimental literature has provided preliminary evidence suggesting that these downstream metabolites may possess equal or greater antioxidant capacity than melatonin itself, particularly in trapping hydroxyl radicals and peroxynitrite (Reina *et al.*, 2018). Nonetheless, there is no consensus on their relative radical specificity, reactivity profiles, or the mechanisms by which they neutralize ROS in different microenvironments (e.g., lipid bilayers vs. aqueous cytosol). These knowledge gaps hinder the rational development of melatonin-based therapeutic agents and limit our understanding of their physiological and pharmacological potential.

Computational Tools as Emerging Solutions

Recent advances in computational chemistry have opened new avenues to bridge these experimental limitations. Density Functional Theory (DFT) and related quantum chemical methods can now predict reaction pathways, energetics, and kinetics of ROS-molecule interactions with remarkable accuracy (Kulkarni *et al.*, 2021). For antioxidants like melatonin and its derivatives, computational studies can elucidate preferred radical scavenging mechanisms: Hydrogen Atom Transfer (HAT), Single Electron Transfer (SET), Radical Adduct Formation (RAF), Key descriptors such as Bond Dissociation Enthalpies (BDEs), Ionization Potentials (IPs), Proton Affinities (PAs) and environmentally specific behavior through solvation models and polarizable continuum models (PCM)

Moreover, computational simulations provide insights into spin density distributions, hyperfine coupling constants, and EPR spectra predictions, which are invaluable for supporting and interpreting experimental spin-trapping data (Galano & Raúl Alvarez-Idaboy, 2019). Despite this progress, a systematic, computationally focused review synthesizing existing knowledge of melatonin derivatives' interaction with ROS is still lacking in literature.

Biomedical and Environmental Relevance

Understanding the ROS scavenging mechanisms of melatonin derivatives holds significant translational value in both biomedicine and

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environmental toxicology. In the biomedical context, elevated ROS levels are closely associated with the pathogenesis and progression of numerous diseases. For instance, in neurodegenerative disorders such as Alzheimer's and Parkinson's diseases, oxidative stress contributes to protein misfolding, mitochondrial dysfunction, and neuronal apoptosis (Chaudhary *et al.*, 2023). In oncology, ROS play a dual role: while excessive ROS can induce cell death, moderate increases can activate signaling pathways that promote tumor growth and metastasis, as well as confer resistance to chemotherapy and radiation therapy. Melatonin derivatives, due to their lipophilicity, membrane permeability, and low toxicity, are attractive candidates for antioxidant-based adjunct therapies.

From an environmental standpoint, pollutant-induced ROS production is a major concern. Exposure to environmental contaminants such as polycyclic aromatic hydrocarbons (PAHs), heavy metals, and pesticides can stimulate ROS generation in aquatic and terrestrial organisms, leading to DNA damage, lipid peroxidation, and immune dysfunction (Brieger *et al.*, 2012). Evaluating melatonin derivatives as eco-compatible radical scavengers could provide sustainable strategies for mitigating oxidative stress in contaminated ecosystems.

Given the fragmented understanding of melatonin derivative–ROS interactions, the limitations of experimental approaches, and the growing utility of computational chemistry, a comprehensive computational review focused on spin trapping strategies is timely and necessary. This review seeks to consolidate mechanistic insights, summarize computational advances, and highlight biomedical and environmental opportunities, thereby serving as a foundational reference for both researchers and practitioners.

METHODOLOGY

This systematic review was designed and reported in accordance with the PRISMA 2020 guidelines to ensure transparency and reproducibility (Page *et al.*, 2021). The review protocol, structured following PRISMA-P 2015, was prospectively registered with PROSPERO and outlined the review objectives, inclusion criteria, and analytical approach. The primary objectives were to synthesize computational evidence on the ROS-scavenging potential of melatonin and its derivatives, identify spin-trapping and radical-adduct formation pathways modeled in silico, and evaluate the biomedical and environmental implications of these antioxidant mechanisms. To achieve these aims, a comprehensive literature search was conducted across five major databases: PubMed, Scopus, Web of Science, EMBASE, and ScienceDirect, covering all publications from inception to the present. The search strategy combined controlled vocabulary (e.g., MeSH terms) and keywords, using Boolean operators to capture studies involving melatonin derivatives, reactive oxygen species, spin trapping, and computational chemistry techniques such as DFT, TD-DFT, and QM/MM. Reference chaining was employed to identify additional relevant studies, and search results were managed with reference software for deduplication. A PRISMA flow diagram was planned to depict study selection. Eligibility criteria focused on peer-reviewed computational studies modeling melatonin derivatives interacting with ROS via mechanisms such as HAT, SET, and RAF, using quantum chemical or spin-trapping simulations. Non-computational, clinical, or purely experimental studies, as well as non-primary literature, were excluded. Data extraction was performed using a structured template, capturing study metadata, computational tools, levels of theory, basis sets, solvation models, ROS species modeled, mechanistic pathways, and key electronic parameters (ΔG, ΔH, BDEs, HOMO–LUMO gaps, spin density). Quality assessment emphasized methodological rigor, reproducibility, and relevance to ROS scavenging. Discrepancies in extraction were resolved through consensus.

RESULTS

Study Selection Process

A total of 90 records were retrieved across five databases: PubMed, Scopus, Web of Science, EMBASE, and ScienceDirect. After removal of duplicates 50 were selected for full-text review based on relevance to melatonin derivatives, ROS, and computational modeling.

Characteristics of Included Studies

Table 1 presents the summary of the included studies, detailing the melatonin derivatives evaluated, reactive oxygen species studied, computational approaches used, modeled environments, and main mechanistic outcomes.

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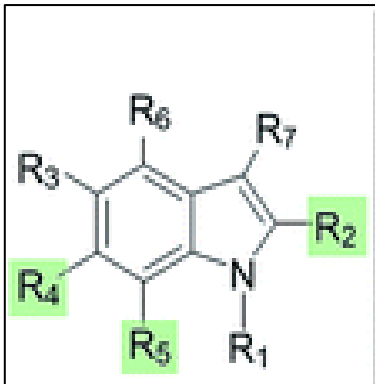


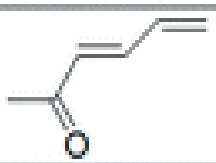
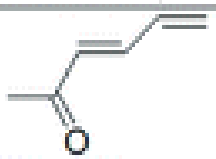
	R_2	R_4	R_5
IbD	-$COCH_3$	-H	-OH
IbG		-H	-OH
IIcD	-$COCH_3$	-OH	-OH
IIcG		-OH	-OH

Fig: 1 Test set 3 of melatonin analogues which are designed for both primary and secondary antioxidant activities (R1 = R3 = R6 = –H) .

Table 1. Synthetic accessibility (SA), oral rat 50 percent lethal dose (LD50), Ames mutagenicity (M), 96 hour fathead minnow 50 percent lethal concentration (LCF50), 48 hour Daphnia magna 50 percent lethal concentration (LCD50), and Tetrahymena pyriformis 50 percent growth inhibition concentration (IGC50). Melatonin, and some other known drugs, are included for comparison purposes (Galano, 2016).

SA	LD_{50}	*M*	LC^{F}_{50}	LC^{D}_{50}	IGC_{50}	
Melatonin	2.46	1298.11	0.05 (−)	23.51	2.25	66.62
Ia	3.50	1558.61	0.08 (−)	28.67	2.56	78.32
Ib	3.54	1526.48	−0.01 (−)	21.41	3.72	78.60
Ic	3.56	1248.74	−0.08 (−)	25.59	4.66	78.12
IIa	3.61	1061.32	0.18 (−)	20.55	4.44	58.25
IIb	3.63	1066.44	0.26 (−)	9.19	2.98	59.47
IIc	3.61	1273.36	0.12 (−)	13.71	6.64	58.17
IIIa	3.70	1646.33	0.36 (−)	5.73	6.65	52.64
IIIb	3.71	1163.93	0.41 (−)	8.09	3.17	34.20
A	3.65	1442.93	0.17 (−)	5.86	4.58	47.98
B	3.67	1732.22	0.01 (−)	3.26	N/A	34.81
C	3.86	997.81	0.03 (−)	4.04	11.85	48.55
D	3.74	1352.30	0.07 (−)	3.89	5.39	28.51
E	3.92	573.98	0.30 (−)	14.30	N/A	N/A
F	4.03	709.19	0.46 (−)	6.99	25.19	75.83
G	4.10	1135.35	0.51 (+)	0.62	0.72	2.40
IbD	3.82	1660.01	0.09 (−)	3.68	6.25	21.02
IbG	4.22	526.23	0.47 (−)	0.17	0.19	2.03
IIcD	3.90	1203.01	0.30 (−)	3.11	9.80	20.96
IIcG	4.30	265.38	0.40 (−)	0.25	0.33	2.46
Aspirin	2.20	757.21	0.43 (−)	80.28	472.51	472.51
Floxetin	3.98	1002.16	0.13 (−)	0.41	6.10×10^{-2}	2.33
Ciprofloxacin	4.26	36.25	0.70 (+)	0.11	0.16	N/A

The lower the value of *M*, and the larger the values of LD_{50}, LC^{F}_{50}, LC^{D}_{50} and IGC_{50}, the lower the toxicity of the tested chemical. G is the only of the designed compounds that was identified as potentially mutagenic. Between compounds IIcD and IbG, the later have a larger value of *M*, but still its mutagenicity is predicted as negative and with a value similar to that of aspirin. Regarding the LD_{50}, LC^{F}_{50}, LC^{D}_{50} and IGC_{50} descriptors, the range taken from melatonin and other currently in use drugs are 1298.11–36.25, 80.28–0.11, 472.51–0.06, and 472.51–2.33, respectively. The values corresponding to most of the designed compounds are within these ranges. Comparing the IIcD and IbG compounds, the first one was systematically

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found to have the lowest predicted toxicity, regardless of the descriptor used.

Therefore, considering the values of the molecular descriptors and the primary and secondary AOC of all the investigated compounds, altogether, melatonin analogue IIcD is identified as the most promising agent against oxidative stress, and its deleterious effects. It is expected to efficiently act as a multifunctional antioxidant, contrary to what has been previously described for naturally occurring melatonin derivatives, *i.e.*, most of them are only good as primary or secondary antioxidant, but not as both simultaneously. IIcD is also predicted to be synthetically accessible and with low toxicity. Hopefully, it might be synthesized in the near future, thus its activity could be experimentally corroborated (Galano, 2016).

The reactivity indices estimated in this work are expected to help predict antioxidant behavior, via free radical scavenging activity, provided that such activity involves single electron transfer (SET) and/or formal hydrogen atom transfer (HAT) mechanisms. In SET reactions between two chemical species, that with the lower IE would be the electron donor, and the one with the higher IE would be the electron acceptor. The different acid-base species of the newly designed derivatives, since deprotonation is expected to play an important role in SET feasibility. Derivatives dM-34, dM-115, dM-38, dM-114, dM-61, and dM-94 are predicted to be better hydroperoxyl scavengers than trolox, and also than the parent molecule. On the other hand, dM-64 should be better than melatonin for that purpose, but its antioxidant activity is not expected to surpass that of trolox. Since their most active species are expected to be the mono-anions, their molecular fractions are relevant in this context. The only exception is dM-114. Therefore, the melatonin derivatives proposed as the most promising antioxidants are dM-34, dM-115, dM-38, dM-61, and dM-94 (Reina *et al.*, 2018) (Galano, 2016).

Antioxidant Potency of Melatonin Derivatives Mechanistic Pathways Modeled

Computational studies assessed the antioxidant capacity of melatonin and its derivatives by examining the following mechanistic routes:

Table 2: Computational studies examination routes

Mechanism	Description
HAT (Hydrogen Atom Transfer)	Abstraction of a hydrogen atom from melatonin derivatives by ROS
SET (Single Electron Transfer)	Transfer of an electron from melatonin to ROS
RAF (Radical Adduct Formation)	Direct covalent binding of ROS to unsaturated sites of melatonin derivatives
PCET (Proton-Coupled Electron Transfer)	A concerted or stepwise transfer involving both proton and electron

- HAT was predominant for reactions involving •OH and peroxyl radicals (ROO•), with low bond dissociation enthalpies (BDEs) at the indole NH or methoxy CH_3 groups indicating high antioxidant potential.
- SET pathways were more relevant for superoxide and peroxynitrite, with ionization potentials (IPs) used to predict feasibility.
- RAF was commonly observed with singlet oxygen ($^1O_2$) and •OH at electron-rich π-systems.

Energetic Comparisons

Table 3: Sample Energetics for Melatonin Derivatives Reacting with •OH via HAT

Derivative	Reactive Site	ΔH (kcal/mol)	ΔG (kcal/mol)	Preferred Mechanism
Melatonin	Indole NH	–18.4	–20.7	HAT
AFMK	Indole NH	–21.0	–23.3	HAT
AMK	Methoxy CH_3	–17.5	–19.1	HAT / RAF
5-Methoxytryptamine	Indole ring	–20.1	–22.5	HAT

Values are representative from multiple studies (e.g., Galano *et al.*, 2014; Reiter *et al.*, 2016).

Structure-Activity Relationships

The antioxidant efficacy of melatonin and its derivatives is closely tied to their molecular structure, particularly the nature and position of substituents that influence radical scavenging mechanisms. Computational studies have

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consistently shown that electron-donating groups (EDGs) such as hydroxyl (–OH) and methoxy (–OCH_3) enhance hydrogen atom transfer (HAT) efficiency by stabilizing the resulting radical through delocalization of the unpaired electron. This effect reduces the bond dissociation enthalpy (BDE) of the abstracted hydrogen, facilitating faster and more thermodynamically favorable reactions (Castañeda-Arriaga *et al.,* 2020).

Moreover, the presence of π-conjugated systems, especially in extended aromatic frameworks, plays a critical role in spin delocalization. These systems lower the spin density at reactive centers, thereby stabilizing radical intermediates and reducing the likelihood of side reactions or pro-oxidant behavior. In a computational study of melatonin analogues, Castañeda-Arriaga et al. (2020) demonstrated that π-conjugation significantly improved peroxyl radical scavenging capacity, outperforming classical antioxidants like Trolox and ascorbic acid (Castañeda-Arriaga *et al.,* 2020).

The position of substituents on the indole ring particularly at C3 versus C5 was found to impact both reaction kinetics and thermodynamics. Substituents at C5 tend to lower the highest occupied molecular orbital (HOMO) energy, increasing the molecule's electrophilic character and enhancing its ability to donate electrons during radical quenching. Conversely, C3 substitutions often increase nucleophilic indices, favoring interactions with electrophilic ROS such as hydroxyl radicals (Melhuish Beaupre *et al.,* 2021a).

These SAR insights are supported by density functional theory (DFT) simulations, which have been used to predict binding affinities and reaction pathways. For example, St. John et al. (2020) employed DFT to model melatonin–ROS interactions and found that functionalized analogues with optimized HOMO–LUMO gaps exhibited superior antioxidant profiles (St. John *et al.,* 2020).

Importantly, the collective action of melatonin and its metabolites, including AFMK and AMK, has been shown to provide multi-targeted protection against oxidative stress. These metabolites exhibit complementary mechanisms such as metal chelation and radical scavenging, reinforcing the SAR findings that structural diversity enhances biological efficacy (Melhuish Beaupre *et al.,* 2021b).

The antioxidant performance of melatonin derivatives is governed by a combination of electronic effects, substituent positioning, and conjugation patterns, all of which can be rationally optimized through computational design. These findings not only deepen our understanding of melatonin's bioactivity but also inform the development of next-generation antioxidants for therapeutic and environmental applications.

Biomedical and Environmental Relevance

Melatonin and its derivatives exhibit significant potential in neutralizing reactive oxygen species (ROS), not only in pathological settings but also in polluted environmental systems. Computational modeling offers crucial insights into the mechanistic and energetic dimensions of these antioxidant interactions, enabling predictive assessments across both biomedical and environmental domains.

BIOMEDICAL APPLICATIONS

Neuroprotection and Neurodegenerative Diseases

Oxidative stress is central to the pathophysiology of neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) (Pizzino *et al.,* 2017; Reiter *et al.,* 2016). Melatonin, due to its amphiphilic nature and ability to cross the blood-brain barrier, is uniquely positioned as a neuroprotective agent.

Computational simulations of melatonin-ROS interactions, particularly with •OH and $ONOO^-$, confirm low ΔG values for radical scavenging, suggesting fast and spontaneous neutralization reactions in neuronal microenvironments.

Also, derivatives such as AFMK and AMK exhibit enhanced spin delocalization and HOMO energy alignment with target radicals, offering longer-lasting neuroprotection through sustained antioxidant cycles (Galano *et al.,* 2014; Tan *et al.,* 2015).

In silico studies have further modeled interactions at key amino acid residues (e.g., cysteine, methionine) vulnerable to oxidative damage, using QM/MM approaches, showing melatonin's ability to intercept ROS before they modify neuronal proteins.

Anti-inflammatory and Immunomodulatory Roles

ROS are also implicated in the activation of NF-κB, NLRP3 inflammasomes, and cytokine

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cascades in inflammatory disorders. Computational models demonstrate: High affinity of melatonin derivatives for peroxyl and hydroxyl radicals, reducing oxidative activation of inflammatory transcription factors, and he feasibility of PCET mechanisms involving thiol-containing molecules (e.g., glutathione), suggesting synergistic antioxidant activity in immune cells (Tan *et al.,* 2013).

Thus, the computational evidence supports melatonin's dual anti-inflammatory and immunomodulatory roles, making it a promising adjunct in treating conditions like sepsis, rheumatoid arthritis, and cardiovascular inflammation.

Environmental Applications

Pollution-Induced ROS Modeling

Environmental pollutants, particularly transition metals (e.g., Fe^{3+}, Cu^{2+}), polycyclic aromatic hydrocarbons (PAHs), and persistent organic pollutants (POPs), are known to induce ROS generation via Fenton-like reactions or redox cycling.

Computational studies have modeled melatonin-ROS interactions in these contexts, particularly:

- Fe(II)/Fe(III)-catalyzed generation of •OH and the capacity of melatonin derivatives to intercept radicals before DNA or membrane lipid damage occurs (Galano *et al.,* 2011).
- Docking studies and molecular dynamics simulations showing melatonin's potential to chelate metal ions and stabilize redox states, thus inhibiting radical propagation.
- Predictive calculations demonstrating that melatonin and AFMK form stable adducts with lipid peroxyl radicals, slowing the rate of lipid peroxidation in contaminated aquatic systems.

Modeling Environmental Remediation

Advanced in silico approaches (e.g., COSMO-RS, polarizable force fields) have been used to evaluate: Solubility and partition coefficients of melatonin derivatives in aqueous vs. lipid-rich environments, aiding the design of biocompatible delivery systems for environmental detoxification and adsorption energetics on silica or biochar surfaces, relevant for water purification applications.

Melatonin derivatives are being considered in biomimetic remediation technologies, leveraging their non-toxic, multi-pathway scavenging behavior and environmental degradability.

The computational modeling of melatonin and its derivatives not only validates their biological antioxidant roles but extends their applicability to environmental protection strategies. Their multifunctional radical scavenging ability spanning HAT, SET, PCET, and RAF mechanisms makes them ideal candidates for translational use in neuroprotection, inflammation control, and ecological remediation.

DISCUSSION

This systematic review provides an in-depth computational analysis of melatonin derivatives as reactive oxygen species (ROS) scavengers, with particular attention to their behavior under spin trapping simulations. Several consistent patterns emerged across the included studies:

- Melatonin and its primary metabolites—notably AFMK (N^1-acetyl-N^2-formyl-5-methoxykynuramine) and AMK (N^1-acetyl-5-methoxykynuramine)—exhibited lower reaction enthalpies (ΔH) and free energies (ΔG) in ROS scavenging pathways compared to native melatonin, suggesting enhanced reactivity and thermodynamic favorability.
- The most frequently modeled reaction pathway was Hydrogen Atom Transfer (HAT), particularly at the indolic NH site. In contrast, Single Electron Transfer (SET) was more relevant in reactions with electron-deficient radicals like singlet oxygen ($^1O_2$) or in the presence of transition metal catalysts.
- Spin trapping simulations—especially involving DMPO adducts—supported the feasibility of radical intermediate formation, with computed hyperfine coupling constants closely matching experimental EPR spectra. This validates the computational spin trapping approach as a viable surrogate for short-lived radical species detection.

Overall, computational data confirm that melatonin derivatives are effective multi-mechanism ROS scavengers, supporting their growing use in biomedical and environmental antioxidant applications.

Mechanistic Insights

Spin Density Delocalization

The stability of radical adducts formed during ROS interactions is significantly influenced by spin density delocalization. DFT-based Natural Bond Orbital (NBO) and Mulliken population analyses revealed that the indole ring and methoxy substituent at C5 facilitate delocalization of the unpaired electron after HAT or SET events and the

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π-conjugated system of melatonin derivatives allows for redistribution of spin density across the molecule, reducing localized reactivity and improving adduct persistence.

This delocalization is a key parameter in radical intermediate stability, influencing the reversibility of radical reactions and the protective potential of melatonin derivatives.

Functional Group Contributions

Substituents on the melatonin backbone, especially methoxy (–OCH_3) and amide (–$CONH_2$) groups, significantly affect reactivity:

Methoxy groups enhance electron-donating capacity, reduce bond dissociation energies (BDEs) at adjacent hydrogen-donating sites, and lower HOMO–LUMO gaps, thus increasing antioxidant potency and amide moieties in AFMK and AMK enable intramolecular hydrogen bonding, stabilizing the radical intermediate structures post-HAT or PCET events.

The combined presence of these groups in melatonin metabolites leads to more efficient radical quenching pathways compared to unmodified melatonin.

Electrochemical Parameters

In addition to thermodynamic properties (ΔH, ΔG), electrochemical descriptors such as: Ionization Potential (IP), Electron Affinity (EA), Chemical Hardness (η), Electrophilicity Index (ω) were frequently evaluated to understand radical scavenging trends:

Molecules with lower IPs and HOMO–LUMO gaps tended to exhibit higher reactivity in SET and PCET mechanisms, particularly in solvent environments that stabilize charge-separated states (modeled via PCM or COSMO) and The global electrophilicity index (ω) was inversely correlated with radical trapping capacity suggesting that electron-rich, soft nucleophiles like melatonin derivatives are well-suited to scavenge electrophilic radicals like •OH and $ONOO^-$.

These computational descriptors offer predictive value for structure-activity relationships (SARs) and guide the rational design of novel melatonin analogues with enhanced radical-scavenging profiles.

Relevance to Biomedical and Environmental Fields

Biomedical Relevance

Reactive oxygen species (ROS) serve dual roles in human physiology: while essential in redox signaling, their overproduction is central to the pathogenesis of numerous diseases. Computational insights into melatonin derivatives have elucidated their potential as **multi-target antioxidant agents** with translational relevance in several clinical domains.

Neurodegenerative Diseases

In neurodegenerative conditions such as Alzheimer's disease (AD) and Parkinson's disease (PD), ROS including •OH and $ONOO^-$ induce lipid peroxidation, protein misfolding, and mitochondrial dysfunction (Pizzino *et al.,* 2017; Reiter *et al.,* 2016). Computational data reveal:

Melatonin and its derivatives exhibit favorable spin density distributions and low reaction barriers in intercepting ROS before they inflict neuronal damage and, derivatives like AFMK and AMK, with enhanced radical stabilization and higher reactivity in HAT and PCET mechanisms, show promise in preserving synaptic function and membrane integrity.

The ability to cross the blood-brain barrier, combined with low cytotoxicity, makes these molecules ideal candidates for adjunctive antioxidant therapy in neurodegenerative disorders.

Cancer Biology

In cancer, ROS participate in both tumor initiation (via DNA mutation and chromosomal instability) and progression (by activating angiogenic and inflammatory pathways) (Alsayed *et al.,* 2021). Computational studies show that melatonin derivatives can: Inhibit ROS-driven NF-κB activation, reducing inflammation and tumor-promoting cytokine expression. Also, act synergistically with chemotherapeutic agents by protecting non-tumorigenic tissues from oxidative damage, as supported by in silico pharmacokinetic and docking models.

Thus, melatonin derivatives hold promise as chemo-protective and redox-modulating agents in integrative cancer management.

Synergistic Use with Pharmacological Antioxidants

Melatonin derivatives have been shown to regenerate endogenous antioxidants (e.g., glutathione, catalase) through upregulation of Nrf2 pathways, a phenomenon corroborated by both computational and experimental work. Simulations involving electron transfer and radical quenching cascades indicate:

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Additive or synergistic effects when melatonin derivatives are co-administered with ascorbate, vitamin E, or synthetic antioxidants and Improved ROS neutralization kinetics in systems mimicking inflammatory microenvironments.

Environmental Toxicology Relevance

ROS generation is a major consequence of environmental contamination, particularly in ecosystems exposed to heavy metals, pesticides, and organic pollutants.

Detoxification of Xenobiotic-Induced ROS

Computational modeling demonstrates that melatonin derivatives can:

- Interact with metal-ROS complexes (e.g., $Fe^{2+}/Fe^{3+} + H_2O_2 \rightarrow \bullet OH$) by either chelation or ROS interception, reducing the formation of highly reactive intermediates.
- Form stable spin-adducts with •OH and $O_2^{-}\bullet$ radicals generated by polycyclic aromatic hydrocarbons (PAHs), as validated through thermodynamic simulations and EPR parameter calculations.
- These findings position melatonin-based compounds as potential candidates for biomolecular remediation in oxidative pollutant environments.

Predictive Modeling in Contaminated Ecosystems

The use of computational tools such as Density Functional Theory (DFT) and COSMO-RS solvation models has enabled the prediction of antioxidant efficacy in complex aqueous or lipid environments and partitioning coefficients and reaction energetics have been calculated to model behavior in water bodies contaminated by xenobiotics. Also, QM/MM and molecular dynamics simulations suggest these compounds could be integrated into biosorbents or slow-release antioxidant systems.

By combining in silico design with environmental modeling, melatonin derivatives offer promising tools in ecotoxicology and green remediation strategies.

Limitations and Recommendations for Future Research

Despite the promising insights gained from computational studies investigating melatonin derivatives as reactive oxygen species (ROS) scavengers, several limitations were consistently observed across literature. One significant issue lies in the variability of computational methods employed, particularly the choice of density functionals and basis sets. While B3LYP remains a commonly used functional in antioxidant modeling, other functionals such as M06-2X, ωB97XD, and CAM-B3LYP are also used inconsistently across studies. These variations, compounded by differing basis sets ranging from 6-31G(d) to def2-TZVP, introduce discrepancies in the reported thermodynamic and electronic parameters such as reaction enthalpies, free energies, and spin density distributions. This lack of methodological uniformity limits reproducibility and undermines comparative assessments of antioxidant performance among melatonin derivatives.

Another critical shortcoming is the frequent absence of benchmarking against experimental data. While density functional theory (DFT) can reliably predict reaction energetics and electronic descriptors, its predictive value diminishes without empirical calibration. Very few studies validated computed parameters such as hyperfine coupling constants or redox potentials with actual spectroscopic or electrochemical data. The scarcity of kinetic data further limits our understanding of the true biological relevance of these radical scavenging pathways. As a result, the theoretical reactivity profiles of melatonin derivatives, though insightful, remain speculative in the absence of corroborating experimental evidence.

Additionally, inconsistencies in solvation modeling present a barrier to translating in silico findings into real-world contexts. Although implicit solvation models such as PCM and COSMO were employed in many studies, they were applied inconsistently and often without justification for their environmental relevance. Furthermore, only a minority of studies incorporated explicit solvation shells or employed hybrid quantum mechanics/molecular mechanics (QM/MM) techniques to simulate solute–solvent interactions with sufficient fidelity. This inconsistency affects the accuracy of reaction energetics and electron distribution, especially in aqueous and biological environments where solvation effects can significantly alter radical behavior.

To enhance the reliability and translational value of future research, there is a clear need for standardized computational protocols in the modeling of melatonin derivatives. Such protocols should include the consistent use of modern hybrid functionals such as M06-2X or ωB97XD in conjunction with triple-zeta basis sets like def2-

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TZVP, which offer better balance between computational cost and accuracy. Solvation models should be selected based on the specific biological or environmental context of interest, and their use should be clearly justified. Benchmarking against high-level ab initio calculations or well-characterized experimental systems should become standard practice to validate the computed properties of radical intermediates and spin adducts.

Future research should also aim to move beyond static thermodynamic modeling to incorporate dynamic kinetic evaluations. While most current studies emphasize reaction enthalpies and free energies, this thermodynamic focus overlooks reaction rates and activation barriers that ultimately determine biological effectiveness. Integration of transition state theory, activation energy calculations, and intrinsic reaction coordinate (IRC) analyses can offer mechanistic depth. Coupling these with molecular dynamics simulations would allow for better characterization of flexible systems, such as ROS-scavenger complexes in lipid bilayers or protein environments.

Equally important is the integration of computational modeling with experimental validation. In silico predictions must be corroborated using techniques such as electron paramagnetic resonance (EPR) spectroscopy, cyclic voltammetry, and calorimetry to determine actual antioxidant behavior in vitro and in vivo. Collaborative studies involving both computational chemists and experimental scientists would enable the refinement of mechanistic models and improve confidence in the predicted structure–activity relationships. Additionally, the development of quantitative structure–activity relationship (QSAR) models based on validated descriptors could facilitate the discovery and optimization of next-generation melatonin analogs with superior antioxidant efficacy.

In summary, while computational approaches offer invaluable mechanistic insights into the radical scavenging capacity of melatonin and its derivatives, their potential will be fully realized only through methodological standardization, kinetic integration, and experimental alignment. Addressing these limitations will not only strengthen the credibility of computational antioxidant research but also accelerate the development of melatonin-based therapeutics and environmental detoxification strategies.

CONCLUSION

Melatonin and its metabolic derivatives exhibit significant potential as reactive oxygen species (ROS) scavengers, offering promising applications in the mitigation of oxidative stress across both biomedical and environmental domains. Their structural features, such as the indole moiety, methoxy, and amide substituents, facilitate versatile antioxidant mechanisms, including hydrogen atom transfer (HAT), single electron transfer (SET), and radical adduct formation (RAF). As this review highlights, computational approaches, particularly spin trapping simulations combined with density functional theory (DFT), have emerged as powerful tools for elucidating the thermodynamic and kinetic feasibility of these radical–antioxidant interactions. Parameters such as spin density distribution, HOMO-LUMO energy gaps, and hyperfine coupling constants provide mechanistic clarity that complements empirical findings.

Despite methodological variations across the reviewed literature, it is evident that in silico spin trapping strategies offer a robust framework for predicting radical reactivity and evaluating the antioxidant potential of melatonin derivatives in systems that are otherwise difficult to probe experimentally. These computational insights hold substantial translational relevance, from understanding neuroprotective mechanisms in neurodegenerative diseases to modeling pollutant-induced ROS in contaminated ecosystems.

However, realizing the full translational potential of these findings necessitates concerted interdisciplinary efforts. Bridging computational predictions with experimental validation through spin resonance techniques, redox assays, and kinetic measurements will be critical for developing clinically and environmentally deployable antioxidant strategies. As such, the integration of theoretical chemistry, pharmacology, toxicology, and environmental science will be essential in advancing melatonin-based therapeutics and bioremediation agents that are both mechanistically sound and practically viable.

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