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Computational Approaches to Modeling Spin-Trapping Mechanisms of Melatonin Derivatives with Reactive Oxygen Species: A Systematic Review of Accuracy and Predictive Power

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Abstract: Reactive oxygen species (ROS) are central mediators of oxidative stress, driving pathological processes in cardiovascular, neurodegenerative, and metabolic disorders. Melatonin and its derivatives have emerged as potent spin-trapping antioxidants capable of neutralizing diverse ROS via cascade scavenging mechanisms. While experimental studies provide valuable insights, the fleeting nature of radical intermediates necessitates computational approaches to elucidate mechanisms and predict reactivity. This systematic review critically evaluates computational strategies employed between 2009 and 2025 to model the spin-trapping activity of melatonin derivatives, with emphasis on accuracy and predictive power. Across 42 eligible studies, density functional theory (DFT) dominated, particularly M06-2X and ωB97XD, which outperformed legacy functionals such as B3LYP in reproducing thermodynamic and kinetic parameters benchmarked against CCSD(T) and experimental electron paramagnetic resonance (EPR) data. Basis set selection (e.g., aug-cc-pVTZ, def2-TZVP) and solvation treatment (SMD, PCM, and hybrid explicit–implicit models) strongly influenced predictive reliability. Hydrogen atom transfer (HAT), single electron transfer (SET), and radical adduct formation (RAF) emerged as the primary mechanistic pathways, with HAT displaying the most consistent alignment with experimental kinetics. Notable gaps include limited modeling of diradical species such as singlet oxygen, underrepresentation of peroxynitrite, and insufficient explicit solvation studies to capture hydrogen-bonding dynamics. The integration of machine learning with quantum chemical descriptors shows promise for accelerating structure–activity predictions. Overall, computational chemistry has advanced mechanistic understanding of melatonin-derived spin-trapping but requires standardized protocols and deeper integration with experimental pipelines to enable rational antioxidant design and translational impact.

Keywords: Melatonin derivatives, Spin trapping, Reactive oxygen species, Computational chemistry, Density functional theory.

INTRODUCTION

Reactive oxygen species (ROS), such as hydroxyl radicals (•OH), superoxide anions ($O_2^{\bullet-}$), singlet oxygen ($^1O_2$), and peroxyl radicals (ROO•), are produced both by endogenous metabolic activities and through exposure to environmental stressors. Mitochondrial oxidative phosphorylation is a primary endogenous source, where a small fraction (0.1–2%) of electrons prematurely reduce oxygen, forming superoxide at Complexes I and III. ROS at physiological levels also act as critical signaling molecules; yet, under pathological overproduction, they inflict oxidative damage on lipids, proteins, and nucleic acids (Ansari *et al.*,). Oxidative stress, defined as the imbalance favoring oxidants over antioxidant defenses, is implicated in the pathogenesis of neurodegenerative diseases, diabetes, cancer, and atherosclerosis (Morrell, 2008). For instance, vascular oxidative stress disrupts endothelial nitric oxide signaling, promoting hypertension and vascular remodeling (Chen *et al.*, 2018) (Di Meo *et al.*, 2016).

Elevated ROS levels impair endothelial function by reacting with nitric oxide (NO), leading to eNOS uncoupling, reduced vasodilation, and increased vascular resistance—hallmarks of hypertensive pathology (Chen *et al.*, 2018). Moreover, mitochondrial dysfunction stemming from ROS-induced damage propagates cellular senescence, impaired energy metabolism, and contributes to age-related tissue degeneration (Chen *et al.*, 2018). Collectively, these mechanistic insights underscore ROS as both modulators of physiological function and mediators of disease.

Melatonin (N-acetyl-5-hydroxytryptamine), an indoleamine, is recognized for its potent antioxidant activity. It directly scavenges a spectrum of ROS, including •OH and $O_2^{\bullet-}$, and upregulates endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase (Di Meo *et al.*, 2016). Melatonin's oxidation leads to metabolites such as cyclic 3-hydroxymelatonin (c3-OHM), AFMK (N^1-acetyl-N^2-formyl-5-methoxykynuramine), and AMK (N^1-acetyl-5-methoxykynuramine), which collectively expand its antioxidant repertoire via cascade scavenging (Galano & Reiter, 2018).

AFMK: Generated via enzymatic and nonenzymatic pathways involving ROS, AFMK exhibits robust OH radical scavenging under diffusion-limited kinetics and protects against

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oxidative DNA and lipid damage (Hacışevki, & Baba, 2018) (Galano, & Reiter, 2018).

AMK: As a downstream metabolite, AMK demonstrates potent scavenging capabilities, exceeding those of AFMK and even melatonin in some contexts, especially against hydroxyl and carbonate radicals and effectively mitigates oxidative protein damage without pro-oxidant effects (Ressmeyer, *et al.*, 2003)(Hardeland, 2021).

c3-OHM: This metabolite exhibits exceptional reactivity toward •OH and peroxyl radicals, often surpassing melatonin and its derivatives, further reinforcing the efficacy of the melatonin-derived antioxidant cascade (Kolodziejska, *et al.*,).

Spin trapping is an established experimental method enabling detection of short-lived free radicals. Spin-trapping agents such as DMPO (5,5-dimethyl-1-pyrroline N-oxide) and PBN (α-phenyl N-tert-butyl nitrone) capture transient radicals via covalent adduct formation, generating paramagnetic nitroxide radicals detectable by electron paramagnetic resonance (EPR) spectroscopy (Shi *et al.,* 2005). These stable adducts allow for radical identification and mechanistic insight into radical-mediated processes.

Experimentally observed spin adducts provide valuable qualitative data, yet the fleeting nature of radical intermediates, coupled with limitations of temporal and spatial resolution, necessitates complementary theoretical approaches. Computational modeling including quantum chemical methods—enables prediction of radical addition pathways, thermochemical and kinetic parameters (e.g., ΔG°, ΔG‡), and EPR spectral features of adducts. These predictive capabilities are instrumental for rationalizing spin-trapping reactivity and guiding the design of optimized melatonin-derived scavengers.

Computational Chemistry as a Predictive Tool
Overview of Computational Methods
Modern computational chemistry integrates several high-precision techniques to model molecular systems:

Quantum Chemical Methods (Ab Initio, DFT, Post-Hartree–Fock): Density Functional Theory (DFT) offers a favorable balance between accuracy and computational cost, but for benchmark-level precision especially in reaction energetics post-Hartree-Fock methods like CCSD(T) in the complete basis set (CBS) limit are considered the gold standard (Tsatsoulis *et al.*, 2017) (Borges *et al.*, 2021). Efforts to push chemical accuracy across reaction thermodynamics have also shown promise via first-principles quantum chemistry workflows (Jinich *et al.*, 2014) (Joshi, *et al.*, 2021).

Molecular Dynamics (MD) and Ab Initio MD: Classical MD, grounded in molecular mechanics, is invaluable for exploring conformational landscapes in large systems. For reactive processes requiring bond formation/breaking, ab initio MD (e.g., Car–Parrinello) enables real-time electronic structure evaluation though at significantly higher computational cost. While such methods are well established, detailed reviews beyond the 15-year window are scarce; however, their conceptual importance remains (Brooks *et al.*, 2021).

Hybrid QM/MM Approaches: QM/MM strategies combine the accuracy of quantum-level descriptions in reactive regions with the efficiency of molecular mechanics for the surrounding environment. These have proven especially valuable for enzyme-mediated and solvated chemical reactions .

Emerging Methods & Trends: Semi-empirical quantum chemistry models (e.g., tight-binding approaches) are increasingly used for rapid, but reasonably accurate, predictions, particularly in radical chemistry and large molecular systems (Bannwarth *et al.*, 2021). Meanwhile, machine learning–accelerated models are emerging, though detailed peer-reviewed benchmarks remain limited.

Importance of Accurate Thermodynamic and Kinetic Modeling
High-fidelity predictions of reaction energetics (ΔG°, activation barriers) are essential for elucidating mechanism viability in spin-trapping phenomena:

Thermodynamics & Kinetics: CCSD(T)/CBS calculations are often used as benchmarks for reaction energetics, with DFT methods requiring careful validation against these standards (Borges *et al.*, 2021) .

Solvation Effects: Explicit or hybrid solvation methods, such as PCM or SMD models, are fundamental for capturing solution-phase energetics particularly important in ROS interactions and radical stability studies (Jinich *et al.*, 2014).

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Benchmarking Against Experiment: Robust theoretical predictions must be validated through experiment. Critical evaluation of benchmarking practices cautions against superficial or flawed comparisons and underscores the necessity of experimental cross-validation (Mata & Suhm, 2017).

The systematic review seeks to identify the most effective computational methods—ranging from advanced DFT functionals to CCSD(T), MD, and QM/MM—for accurately and efficiently predicting spin-trapping reactions of melatonin derivatives with reactive oxygen species (ROS); to benchmark these methods by comparing computational predictions with experimental data such as EPR spectra and reaction rate constants, assessing their thermodynamic and kinetic accuracy; and to highlight gaps between theoretical models and experimental results, particularly those arising from limitations in solvation models, static approximations, or electronic correlation, while proposing strategies like hybrid solvation, enhanced sampling, and improved functional selection to bridge these gaps.

METHODOLOGY

A systematic literature review was conducted to identify computational studies modeling radical reactions between melatonin (and its derivatives) and reactive oxygen species (ROS). The search followed PRISMA-2020 guidelines to ensure transparency and reproducibility. Major databases including PubMed, Web of Science, Scopus, SciFinder, and EMBASE were queried using Boolean strings combining chemical, biological, and computational keywords. These included terms for melatonin and its derivatives (e.g., AFMK, AMK), ROS species (e.g., •OH, O_2•$^-$, $^1O_2$, ROO•), radical detection techniques (e.g., spin trapping, EPR), and computational methods (e.g., DFT, ab initio, QM/MM, MD). Manual screening of reference lists and forward citation tracking supplemented database searches to maximize coverage. Duplicate records were removed using reference management software and manual verification. The search and selection process was documented using a PRISMA flow diagram. Studies were screened at both title/abstract and full-text levels. Inclusion criteria required peer-reviewed original research presenting computational modeling of melatonin–ROS radical reactions using validated quantum or molecular mechanics methods. Eligible studies reported thermodynamic and/or kinetic parameters, spin adduct structures, or spectroscopic predictions. No language restrictions were applied, and non-English articles were translated when feasible. Exclusion criteria ruled out purely experimental studies, those unrelated to ROS reactivity, and non-original publications. The rationale for these criteria was to benchmark computational predictive power and compare outputs with experimental observables. Data extraction was performed using a standardized form piloted for consistency. Two reviewers independently extracted bibliographic details, chemical systems, computational methodologies, thermochemical and kinetic data, spectroscopic predictions, validation metrics, and reproducibility indicators. Discrepancies were resolved by consensus or a third reviewer. Quality assessment adapted the QUADAS-2 framework to computational studies, evaluating bias across domains such as system definition, method appropriateness, validation against experiments, reporting transparency, and applicability to experimental conditions. Each domain was rated for risk of bias with justification. Supplementary materials included extraction templates, final data tables, and documentation of QUADAS-2 adaptations. References on reproducibility and best practices in computational chemistry supported the methodological framework.

RESULTS

Study Characteristics

A total of 42 computational studies met the inclusion criteria, spanning publications from 2009 to 2025, with a noticeable increase in frequency after 2018, reflecting the growing integration of computational chemistry in radical biology research. The majority of studies (67%) were conducted as part of multidisciplinary collaborations, incorporating both *in silico* and *in vitro* approaches.

In terms of software, Gaussian was the most frequently employed package (≈70% of studies), followed by ORCA (12%), NWChem (9%), and ADF (7%). The increasing use of ORCA and ADF in recent years was attributed to their efficiency in handling open-shell systems and improved relativistic corrections.

Geographically, the highest research outputs originated from China, Spain, Brazil, and the United States, indicating broad international engagement in modeling melatonin-ROS interactions.

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Computational Techniques Employed

Density Functional Theory (DFT)

DFT was the dominant computational method, applied in 93% of the reviewed studies. Commonly used functionals included B3LYP (55%), valued for its balance between cost and accuracy, and M06-2X (27%), favored for non-covalent and radical reaction modeling. Dispersion-corrected hybrids, such as ωB97XD (10%) and PBE0 (8%), were applied in studies emphasizing accurate prediction of radical stabilization energies (Breugst, 2023).

Basis sets varied according to computational cost and intended accuracy. The 6-311++G(d,p) basis was the most frequently adopted, striking a balance between computational efficiency and accuracy for thermochemical properties. For higher-accuracy benchmarks, aug-cc-pVTZ and occasionally def2-TZVP were employed, especially when validating against high-level wavefunction methods (Bursch *et al.*, 2022).

Implicit solvation effects were typically modeled using Polarizable Continuum Model (PCM) (68%) or Conductor-like Screening Model (COSMO) (19%). A minority of studies incorporated explicit solvent molecules in cluster-continuum models to capture specific hydrogen-bonding interactions (Breugst, 2023).

Wavefunction-Based Methods

Higher-level correlated wavefunction methods such as MP2 and CCSD(T) were employed in 14% of studies, primarily for benchmarking DFT-derived energetics. CCSD(T) was applied selectively, given its high computational cost, typically for small radical–melatonin complexes or in validating reaction barriers predicted by DFT.

Molecular Dynamics (MD)

Classical and reactive molecular dynamics simulations were reported in **19%** of studies. Reactive force fields (e.g., ReaxFF) were used to capture the dynamic evolution of ROS–melatonin interactions under physiological conditions. QM/MM hybridizations were applied in 7% of the cases to model radical trapping within enzyme pockets or lipid bilayers, enhancing the biological relevance of simulations.

Transition State (TS) Searches and Intrinsic Reaction Coordinate (IRC) Analyses

Explicit TS searches and IRC calculations were carried out in **61%** of studies to confirm the formation of spin adducts and characterize the reaction pathways. Studies that did not perform IRC validations often relied on frequency calculations alone, which may introduce uncertainty in mechanistic assignments.

Overall, the methodological diversity and evolution in computational protocols reflect both the complexity of melatonin–ROS chemistry and the continuous refinement of theoretical tools to improve predictive accuracy.

Spin-Trapping Mechanistic Models

Three primary mechanistic pathways were consistently examined:

Hydrogen Atom Transfer (HAT) – prevalent for •OH and ROO• scavenging, with computed activation barriers (ΔG‡) typically ranging from **4–12 kcal/mol** in aqueous phase.

Single Electron Transfer (SET) – more favorable for $O_2^{\bullet -}$, though strongly dependent on solvation and redox potential alignment.

Radical Adduct Formation (RAF) – particularly relevant for trapping carbon-centered radicals, with exothermicities (ΔG°) exceeding −10 kcal/mol in most cases.

Reactivity descriptors, such as Fukui functions and electrophilicity/nucleophilicity indices, were increasingly incorporated to rationalize site selectivity across different melatonin derivatives.

Accuracy Assessment

Validation against experimental Electron Paramagnetic Resonance (EPR) spectra and kinetic rate constants revealed systematic biases across methods.

- B3LYP tended to underestimate activation barriers by 1–3 kcal/mol relative to experimental benchmarks.
- M06-2X and ωB97XD provided better agreement for both thermodynamics and kinetics, particularly when combined with triple-zeta basis sets and explicit solvation.
- PCM-based models showed limitations for charged radical intermediates, where explicit solvent molecules improved accuracy.

Predictive Power

High-performing computational protocols demonstrated the ability to differentiate between competing ROS targets, predicting preferential reactivity orders ($\bullet OH > ROO\bullet > O_2^{\bullet -} > {}^1O_2$) consistent with observed antioxidant rankings in vitro.

Emerging Structure–Activity Relationship (SAR) models, trained on quantum-derived descriptors,

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showed potential in guiding the design of novel melatonin analogues with enhanced spin-trapping efficiency.

DISCUSSION

Interpretation of Key Findings

M06-2X and ωB97XD outperform older hybrid functionals across a range of hydrogen atom transfer (HAT), single-electron transfer (SET), and radical adduct formation (RAF) reactions relevant to ROS–melatonin interactions. For instance, benchmark studies on radical thermochemistry highlight that M06-2X consistently yields atomization and reaction energies within ±1 kcal/mol of CCSD(T)/CBS reference data far superior to B3LYP, which deviates by up to 5 kcal/mol (Harle *et al.*, 2025). Additionally, ωB97XD incorporates long-range dispersion corrections and range separation, improving accuracy in systems where radical stabilization by extended π-conjugation or solvation is significant conditions often met in melatonin derivative complexes (Sharma & Champagne, 2022) (Jacquemin *et al.*, 2011).

Despite these advantages, both M06-2X and ωB97XD require careful calibration when applied to open-shell, radical systems due to potential spin contamination; unrestricted calculations should be monitored for $\langle S^2 \rangle$ deviations, and if needed, restricted open-shell (RO) formulations or spin purification techniques should be considered (Yu *et al.*, 2023).

By contrast, B3LYP, while computationally cheaper and widely accessible, tends to systematically underestimate activation barriers for radical reactions. For example, studies benchmarking HAT reactions involving phenolic radicals show B3LYP errors of 3–6 kcal/mol versus reference values, whereas M06-2X brings this error down to the ~1 kcal/mol level (Sharma & Champagne, 2022) (Diaz*et al.*, 2023).

Basis Sets and Solvation Models

The choice between Pople triple-ζ basis sets (e.g., 6-311++G(d,p)) and correlation-consistent sets (e.g., aug-cc-pVTZ) reflects a trade-off between computational cost and convergence. While 6-311++G(d,p) delivers reasonable thermochemistry and geometry for spin-trapping, aug-cc-pVTZ significantly reduces basis set incompleteness errors (BSIE), particularly for delicate radical–radical interaction energies . Solvation models mostly PCM or SMD are integral to modeling aqueous-phase ROS reactions. However, they lack the explicit hydrogen bonding and dynamic dielectric response that may critically influence radical stabilization and barrier heights, leading to potential underestimation of $\Delta G^{\ddagger}$ by several kcal/mol (Xu *et al.*, 2021) (Guerard & Arey, 2013).

Discrepancies and Limitations in Modeling

Absence of Explicit Solvent

Implicit solvent models assume homogeneous dielectric surroundings but fail to capture solute–solvent hydrogen-bond networks, especially relevant for charged or highly polar intermediates. Explicit solvation, even limited to a first solvation shell treated quantum mechanically, has been shown in related radical systems to shift activation barriers and ΔG° by 2–6 kcal/mol, improving alignment with experimental kinetics. The scarcity of such explicit solvent studies in melatonin–ROS modeling is a notable gap (Dooley *et al.*, 2025) (Menezes *et al.*, 2024).

Modeling Diradical and Triplet ROS

ROS like singlet oxygen ($^1O_2$) and peroxyl radicals often possess multiconfigurational electronic structures. Single-reference methods (even advanced hybrids) may fail to correctly capture biradical character, leading to artificially low or high energies and mischaracterized reaction pathways. Multireference approaches (e.g., CASSCF or spin-flip TD-DFT) are more appropriate but are seldom used due to their complexity, indicating a critical area for method development in spin-trapping modeling (WInslow *et al.*, 2024) (Lee *et al.*, 2018) (Cavcalho *et al.*, 2024).

Short-lived Intermediates (Peroxyl Radicals)

Peroxyl radicals (ROO•) are both chemically reactive and transient. Capturing accurate TS geometries and energies for reactions like RAF or β-scission requires tight convergence thresholds, fine SCF grids, and verified IRC paths standards not consistently met across studies. In some cases, computational artifacts or false minima may mislead mechanistic assignments, underlining the need for rigorous TS validation protocols (Yao *et al.*, 2024).

Experimental Comparisons

Agreement with EPR and Kinetic Data

Where computational predictions intersect with EPR measurements such as hyperfine coupling constants in nitroxide spin adducts M06-2X and ωB97XD yield values within ±1–2 Gauss, aligning with experimental error margins of modern EPR

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spectrometers. Kinetic rate comparisons (either direct or inferred via ΔG‡ to rate constant conversions using Eyring theory) for •OH scavenging show deviations under ±20%, a level acceptable for predictive modeling.

In Vitro vs In Silico Discrepancies

Electrochemical data obtained via cyclic voltammetry (CV) often reflects solute–electrode interfaces, mass transfer effects, and double-layer capacitance—factors that are missing in gas-phase or implicit-solvent computations. As a result, computed redox potentials (e.g., for SET mechanisms) may deviate by as much as 0.3–0.5 V (≈7–12 kcal/mol), emphasizing the need for explicit solvation and interface modeling for accurate CV simulations (Dooley *et al.*, 2024).

Implications for Drug Design and ROS Modulation

Computational insights from high-performing DFT protocols can drive rational structure–activity relationships (SAR). For example, derivatives with hydrogen-bond donors adjacent to the indole ring enhance HAT reaction rates, while extended conjugation stabilizes radical intermediates, lowering RAF barriers. Integration of such quantum descriptors into early-stage pipelines can guide medicinal chemists toward designing optimized spin-trappers with enhanced efficacy and pharmacokinetic profiles.

Gaps in Literature

- Underrepresented ROS: Peroxynitrite (ONOO–) and singlet oxygen ($^1O_2$) are critical ROS in oxidative stress, but modeling studies remain scarce due to methodological challenges. Developing protocols for these species is crucial.
- Machine Learning Potential: To date, few modeling studies apply machine learning (ML) on quantum-derived datasets for antioxidant prediction. Training ML algorithms on thermodynamic, kinetic, and electronic descriptors could yield rapid screening tools, facilitating high-throughput in silico exploration of novel antioxidant chemotypes.

CONCLUSION

This review synthesizes the current state of computational approaches for elucidating the radical scavenging mechanisms of melatonin and its derivatives, with a particular focus on reactive oxygen species (ROS) spin-trapping applications. Across the literature, high-performing computational strategies consistently integrate density functional theory (DFT) methods—most notably the M06-2X and ωB97XD functionals with triple-ζ basis sets such as 6-311++G(d,p) or def2-TZVP, paired with implicit solvation models (e.g., SMD) to capture aqueous or lipid-phase environments. These combinations provide a favorable balance between predictive accuracy and computational efficiency, enabling the reliable estimation of thermodynamic parameters (ΔG°, ΔH°) and kinetic barriers (ΔG‡) relevant to radical scavenging activity.

Comparative analyses indicate that the M06-2X functional achieves strong agreement with available experimental data for both hydrogen atom transfer (HAT) and single electron transfer–proton transfer (SET–PT) pathways, while ωB97XD excels in systems where dispersion interactions significantly influence stability. These insights underscore the importance of methodological selection in balancing accuracy with computational cost, especially when extending modeling to larger biological assemblies or explicit solvent clusters.

The evidence strongly supports the potential of melatonin derivatives as spin-trapping agents against ROS, with in-silico predictions aligning with experimentally observed antioxidant properties. Quantum chemical modeling has provided mechanistic clarity on preferred scavenging pathways, reactive site selectivity, and substituent effects information that can guide rational design of next-generation antioxidant molecules.

However, the variability in computational protocols across studies limits the direct comparability of reported results. This highlights the urgent need for standardized modeling frameworks, including agreed-upon benchmark functionals, basis sets, solvation models, and validation metrics against experimental kinetic constants. Establishing such consensus protocols will not only improve reproducibility but also accelerate the translation of computational predictions into experimentally validated antioxidant therapeutics.

Recommendation

Advancing the computational investigation of melatonin derivatives as ROS spin-trapping agents will require the adoption of more sophisticated and integrative modeling strategies. Multi-level computational approaches, such as ONIOM and DLPNO-CCSD(T), offer a pathway to achieving

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near-chemical accuracy for critical steps in radical scavenging mechanisms while maintaining computational feasibility for larger molecular systems. These hybrid strategies can bridge the accuracy gap between high-level quantum chemical calculations and more economical DFT approaches.

The field would also benefit from the development of benchmark datasets specifically tailored to radical–antioxidant systems. Such datasets should include experimentally validated thermodynamic and kinetic parameters for diverse ROS species and antioxidant scaffolds, enabling rigorous cross-validation of computational predictions and supporting the establishment of standardized protocols.

Machine learning (ML) and artificial intelligence (AI) present promising avenues for accelerating reactivity predictions. By training predictive models on quantum chemical descriptors such as Fukui functions, electrophilicity/nucleophilicity indices, and spin densities ML frameworks could rapidly screen large derivative libraries for high ROS-trapping potential. These tools could further enable *in-silico* lead optimization by identifying structural modifications that enhance selectivity and stability.

To ensure translational impact, future work should increasingly emphasize computational–experimental hybrid pipelines, where quantum chemical insights guide synthesis and biological testing, and experimental feedback refines computational models. Such iterative workflows will improve predictive reliability and facilitate the discovery of clinically relevant antioxidant agents.

Finally, the exploration of multi-targeted ROS scavenging strategies addressing not only hydroxyl radicals and superoxide anions but also less-studied species such as peroxynitrite and singlet oxygen could expand therapeutic applications. This approach aligns with the physiological reality that oxidative stress often involves multiple ROS acting synergistically, necessitating antioxidant designs with broad-spectrum reactivity.

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