Journal of Research in Biology
An International Scientific Research Journal

ISSN No: Print: 2231 –6280; Online: 2231- 6299

Systematic Review

Deciphering the Antioxidant and Therapeutic Potential of Lamiaceae Phytochemicals: Insights from Density Functional Theory and *In Silico* Approaches

Author:
J. Jebasingh Kores

Institution:
Department of Physics, Pope's Colleg (Autonomous), Sawyerpuram 628 251, Tamil Nadu, India

Corresponding author:
Kores. J. J.

ABSTRACT:

The Lamiaceae family represents one of the most pharmacologically significant groups of medicinal plants, comprising over 7,000 species distributed across diverse ecological regions. These plants are rich in structurally diverse phytochemicals, including phenolic acids, flavonoids, and terpenoids, many of which exhibit potent antioxidant, anti-inflammatory, antimicrobial, antiviral, and anticancer activities. In recent years, computational chemistry particularly Density Functional Theory (DFT) combined with in silico methodologies such as molecular docking, molecular dynamics simulations, Quantitative StructureActivity Relationship (QSAR) modeling, and ADMET profiling, has significantly advanced the mechanistic understanding of these bioactive compounds.

This review systematically examines the application of DFT and complementary computational techniques in elucidating the antioxidant mechanisms and therapeutic potential of key Lamiaceae phytochemicals, including rosmarinic acid, lauteolin, carnosic acid, thymol, carvacrol, and ursolic acid. Particular emphasis is placed on quantum chemical descriptors such as Bond Dissociation Enthalpy (BDE), Ionization Potential (IP), Proton Affinity (PA), and Frontier Molecular Orbital (FMO) energies, which govern radical scavenging activity. Additionally, the integration of DFT-derived descriptors with molecular docking and ADMET predictions is discussed to highlight multi-target drug discovery potential.

Despite substantial progress, challenges remain in accurately modeling solvent effects, conformational flexibility, and biological environments. Future directions include the integration of machine learning with quantum chemical descriptors and the development of multi-target therapeutic frameworks. This review provides a consolidated and critically evaluated foundation for advancing computational phytochemistry in Lamiaceae-based drug discovery.

Keywords:
Lamiaceae; Density Functional Theory; Antioxidants; Molecular Docking; Phytochemicals; QSAR; ADMET; In Silico Drug Discovery

Article Citation:
Kores. J. J. (2025). Deciphering the Antioxidant and Therapeutic Potential of Lamiaceae Phytochemicals: Insights from Density Functional Theory and In Silico Approaches. **Journal of Research in Biology 15(4): 1-15**

Web Address:
http://jresearchbiology.com/documents/RA0902.pdf

Dates:
Received: 25 Aug. 2025 **Accepted:** 25 Nov. 2025 **Published:** 15 Dec. 2025

1. Introduction

1.1 Botanical and Phytochemical Overview of Lamiaceae

The Lamiaceae (mint family) is one of the largest and most economically and pharmacologically important families of flowering plants, comprising approximately 7,000–7,500 species across more than 230 genera. Members of this family include widely utilized medicinal and culinary herbs such as *Rosmarinus officinalis* (rosemary), *Salvia officinalis* (sage), *Origanum vulgare* (oregano), *Thymus vulgaris* (thyme), *Mentha* species (mint), and *Ocimum basilicum* (basil) .

Lamiaceae species are characterized by their rich production of secondary metabolites, particularly: Phenolic acids (e.g., rosmarinic acid, caffeic acid), Flavonoids (e.g., luteolin, apigenin, quercetin), Terpenoids (e.g., ursolic acid, carnosic acid), and Essential oil constituents (e.g., thymol, carvacrol)

These compounds contribute significantly to the biological activities of Lamiaceae plants, including antioxidant, anti-inflammatory, antimicrobial, and anticancer effects. Among these, phenolic compounds play a dominant role in antioxidant activity due to their ability to donate hydrogen atoms or electrons, stabilizing reactive oxygen species (ROS). Analytical studies using HPLC-DPPH assays have confirmed strong radical scavenging activity in Lamiaceae-derived phenolics, particularly in rosemary, sage, and oregano (Damašius et al., 2014).

1.2 Importance of Computational Approaches in Phytochemical Research

Traditional experimental approaches for evaluating phytochemical activity, although essential, are often time-consuming, resource-intensive, and limited in mechanistic resolution. Computational chemistry offers a complementary framework that enables molecular-level insights into structure–activity relationships and reaction mechanisms.

Density Functional Theory (DFT) has emerged as a widely adopted quantum mechanical method for investigating the electronic structure and antioxidant mechanisms of phenolic compounds. It allows precise calculation of thermodynamic parameters such as bond dissociation enthalpy (BDE), ionization potential (IP), and proton affinity (PA), which are directly linked to antioxidant efficiency (Silva et al., 2009).

In parallel, in silico techniques such as molecular docking and molecular dynamics simulations facilitate the prediction of ligand–protein interactions, enabling the identification of potential therapeutic targets. For instance, docking studies have demonstrated the binding potential of plant-derived compounds to enzymes involved in oxidative stress and inflammation, such as cyclooxygenase (COX) and lipoxygenase (LOX) (Chibuye et al., 2024).

Moreover, ADMET profiling tools have enhanced early-stage drug discovery by predicting pharmacokinetic and toxicity properties, reducing reliance on experimental screening (Aslan et al., 2023).

1.3 Scope and Objectives

This review aims to provide a systematic and critically evaluated synthesis of the application of DFT and in silico methodologies in the study of Lamiaceae phytochemicals. Specifically, it seeks to:

- Elucidate the quantum chemical basis of antioxidant mechanisms
- Analyze DFT-derived descriptors relevant to radical scavenging
- Examine molecular docking and multi-target interactions
- Evaluate QSAR and ADMET integration in drug discovery

- Identify methodological limitations and research gaps

By integrating computational and phytochemical perspectives, this review contributes to a more robust understanding of Lamiaceae-derived compounds as candidates for therapeutic development.

2. Methodology: Systematic Review Protocol

A systematic review methodology was adopted to critically evaluate the application of Density Functional Theory (DFT) and in silico approaches in the investigation of Lamiaceae phytochemicals. The review process was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency, reproducibility, and methodological rigor. A comprehensive literature search was conducted across major scientific databases, including Scopus, Web of Science, PubMed, and Google Scholar, to identify relevant peer-reviewed studies.

The search strategy employed a combination of keywords and Boolean operators, including “Lamiaceae,” “density functional theory,” “DFT,” “in silico,” “molecular docking,” “molecular dynamics,” “QSAR,” “ADMET,” “antioxidant,” and “phytochemicals,” along with specific compound names such as “rosmarinic acid,” “luteolin,” “thymol,” “carvacrol,” “carnosic acid,” and “ursolic acid.” The search was restricted to articles published in English, with no lower date limitation imposed in order to capture both foundational and recent developments in computational phytochemistry. Studies published up to 2024 were considered for inclusion.

Eligibility criteria were established to ensure the relevance and quality of the selected studies. Articles were included if they employed DFT calculations and/or in silico methodologies, including molecular docking, molecular dynamics simulations, QSAR modeling, or ADMET profiling, and focused specifically on phytochemicals derived from the Lamiaceae family. Additionally, only studies reporting quantitative computational descriptors, such as bond dissociation enthalpy (BDE), ionization potential (IP), proton affinity (PA), HOMO–LUMO energy gaps, or binding affinity values, were considered. Studies were excluded if they lacked computational analysis, were not directly related to Lamiaceae phytochemicals, or were published as conference abstracts, editorials, or non-peer-reviewed reports.

Data extraction was performed using a structured framework to ensure consistency across studies. Extracted information included the identity of the phytochemical, the computational methods employed, key quantum chemical descriptors, biological targets, and principal findings. Particular attention was given to the level of theory used in DFT calculations, the choice of basis sets, and the inclusion of solvent models such as the Polarizable Continuum Model (PCM) or Solvation Model Density (SMD). The methodological quality of the included studies was further evaluated based on the clarity of computational protocols and, where available, validation against experimental data. Studies that did not provide sufficient methodological detail or reproducibility were excluded from the final synthesis.

3. Theoretical Framework: Density Functional Theory and In Silico Methodologies

Density Functional Theory (DFT) has emerged as a cornerstone computational approach in the investigation of phytochemical systems, particularly due to its ability to provide accurate electronic structure information at a relatively moderate computational cost. Unlike wavefunction-based methods, DFT describes molecular systems in terms of electron density, thereby simplifying the treatment of many-electron interactions. The

theoretical foundation of DFT is established by the Hohenberg–Kohn theorems, which state that the ground-state properties of a many-electron system are uniquely determined by its electron density and that the correct electron density minimizes the total energy of the system. The Kohn–Sham formulation further facilitates practical implementation by transforming the many-body problem into a set of one-electron equations.

In the context of phytochemical research, DFT is extensively employed to elucidate antioxidant mechanisms at the molecular level. Hybrid functionals such as B3LYP, in combination with basis sets like 6-31G(d,p) or 6-311+G(d,p), are widely used due to their demonstrated reliability in predicting thermodynamic properties of phenolic compounds (Silva et al., 2009). These calculations enable the determination of key descriptors that govern antioxidant activity, including bond dissociation enthalpy (BDE), ionization potential (IP), proton affinity (PA), and electron transfer enthalpy (ETE).

The antioxidant behavior of phenolic phytochemicals is generally explained through three principal mechanisms: hydrogen atom transfer (HAT), single electron transfer–proton transfer (SET–PT), and sequential proton loss–electron transfer (SPLET). In the HAT mechanism, the antioxidant donates a hydrogen atom to neutralize free radicals, and the efficiency of this process is primarily determined by the bond dissociation enthalpy of the O–H bond. Lower BDE values indicate a greater propensity for hydrogen donation and, consequently, higher antioxidant activity. In contrast, the SET–PT mechanism involves an initial electron transfer step followed by proton dissociation, with ionization potential and proton dissociation enthalpy serving as the governing parameters. The SPLET mechanism, which is particularly relevant in polar environments such as aqueous biological systems, involves initial proton loss followed by electron transfer, and is characterized by proton affinity and electron transfer enthalpy.

In addition to thermodynamic descriptors, Frontier Molecular Orbital (FMO) theory provides critical insights into the reactivity of phytochemicals. The energies of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are directly related to the electron-donating and electron-accepting capabilities of a molecule, respectively. The energy gap between these orbitals serves as an indicator of chemical reactivity, with smaller gaps corresponding to higher reactivity and enhanced antioxidant potential.

Complementary to DFT calculations, molecular docking has become an indispensable tool for predicting the interaction of phytochemicals with biological targets. Docking algorithms estimate binding affinities and identify key interactions, such as hydrogen bonding and hydrophobic contacts, within the active sites of proteins. For instance, computational studies have demonstrated that plant-derived compounds can exhibit significant binding affinity toward inflammatory targets such as cyclooxygenase-2 (COX-2), highlighting their therapeutic potential (Chibuye et al., 2024).

Molecular dynamics (MD) simulations further extend these insights by capturing the dynamic behavior of ligand–protein complexes over time. By analyzing parameters such as root mean square deviation (RMSD) and binding free energy, MD simulations provide a more comprehensive understanding of the stability and conformational flexibility of these complexes under physiological conditions. These simulations are particularly valuable in validating docking results and refining predictions of binding interactions.

Quantitative Structure–Activity Relationship (QSAR) modeling integrates DFT-derived descriptors with statistical approaches to establish predictive relationships between molecular structure and biological activity. Such

models enable the virtual screening of large compound libraries and facilitate the identification of promising candidates for further investigation. Additionally, ADMET profiling plays a critical role in evaluating the pharmacokinetic and toxicological properties of phytochemicals, allowing early-stage assessment of drug-likeness and safety. Computational tools used in ADMET prediction provide valuable insights into parameters such as absorption, distribution, metabolism, excretion, and toxicity, thereby supporting the rational design of therapeutically viable compounds (Aslan et al., 2023).

4. Chemical Diversity and Structural Classification of Lamiaceae Phytochemicals

The Lamiaceae family is widely recognized for its extensive repertoire of bioactive secondary metabolites, particularly phenolic acids, flavonoids, and terpenoids, which collectively underpin its pharmacological significance. These compounds differ in their structural frameworks, electronic configurations, and functional group distributions, all of which influence their antioxidant behavior and biological activity. The chemical diversity of Lamiaceae has been extensively characterized, with numerous studies highlighting the dominance of polyphenolic constituents as primary contributors to radical scavenging activity (Damašius et al., 2014; Buathong & Duangsrisai, 2023; Aryal et al., 2024). The major phytochemical classes present in Lamiaceae species and their associated biological activities are summarized in **Table 1** (Mucha et al., 2021; Aryal et al., 2024).

Table 1. Major phytochemical classes of Lamiaceae species with representative compounds and reported biological activities.

Phytochemical Class	Representative Compounds	Major Sources (Lamiaceae)	Key Biological Activities
Phenolic acids	Rosmarinic acid, Caffeic acid	*Rosmarinus officinalis*, *Salvia officinalis*	Antioxidant, anti-inflammatory, antimicrobial
Flavonoids	Luteolin, Quercetin, Apigenin	*Mentha spicata*, *Ocimum basilicum*	Antioxidant, antiviral, cardioprotective
Terpenoids (monoterpenes)	Thymol, Carvacrol	*Thymus vulgaris*, *Origanum vulgare*	Antimicrobial, anti-inflammatory
Terpenoids (diterpenes)	Carnosic acid, Carnosol	*Rosmarinus officinalis*, *Salvia officinalis*	Strong antioxidant, neuroprotective
Other phenolics	Eugenol	*Ocimum tenuiflorum*	Antioxidant, antimicrobial

4.1 Phenolic Acids

Phenolic acids are among the most abundant and biologically active constituents of Lamiaceae species, with rosmarinic acid representing a hallmark compound of this family. Structurally, rosmarinic acid contains two catechol moieties, which significantly enhance its antioxidant capacity through efficient hydrogen atom donation and resonance stabilization of phenoxyl radicals. The presence of ortho-dihydroxy groups is particularly important, as these configurations facilitate intramolecular hydrogen bonding and electron delocalization, thereby lowering the bond dissociation enthalpy of hydroxyl groups and promoting radical scavenging activity (Damašius et al., 2014; Aryal et al., 2024).

In addition to rosmarinic acid, other phenolic acids such as caffeic acid and related hydroxycinnamic derivatives contribute significantly to the antioxidant profile of Lamiaceae plants. These compounds exhibit conjugated π-electron systems that enable effective stabilization of radical intermediates, a feature that has been consistently correlated with enhanced antioxidant performance. Experimental studies employing HPLC-DPPH assays have demonstrated strong radical scavenging activity in extracts rich in these compounds, particularly in species such as rosemary, sage, and oregano (Damašius et al., 2014). Furthermore, computational analyses have supported these observations by linking reduced bond dissociation enthalpy values with increased antioxidant efficiency (Silva et al., 2009).

4.2 Flavonoids

Flavonoids constitute another major class of Lamiaceae phytochemicals, characterized by a C_6–C_3–C_6 backbone consisting of two aromatic rings connected by a heterocyclic ring. Variations in hydroxylation patterns and conjugation significantly influence their antioxidant activity. Among these compounds, luteolin and quercetin are particularly notable due to the presence of a catechol moiety in the B-ring, which serves as the primary site for radical scavenging.

The antioxidant activity of flavonoids is strongly influenced by three key structural features: (i) the presence of ortho-dihydroxy groups in the B-ring, (ii) conjugation between the B-ring and the C-ring, and (iii) the presence of a 2,3-double bond in conjunction with a 4-oxo function. These features collectively enhance electron delocalization and stabilize radical intermediates, thereby facilitating both hydrogen atom transfer and electron transfer mechanisms. Comparative studies have shown that flavonoids possessing these structural elements exhibit significantly higher antioxidant activity than those lacking them, as exemplified by the lower activity of apigenin relative to luteolin (Aryal et al., 2024). In addition to their antioxidant properties, flavonoids exhibit a wide range of biological activities, including anti-inflammatory and antiviral effects. Their planar structures enable π–π stacking interactions with aromatic residues in protein binding sites, which is particularly relevant in molecular docking studies. This structural versatility supports their role as multi-target bioactive compounds in computational drug discovery (Buathong & Duangsrisai, 2023).

4.3 Terpenoids

Terpenoids represent a structurally diverse class of phytochemicals within the Lamiaceae family, encompassing monoterpenes, sesquiterpenes, diterpenes, and triterpenes. While many terpenoids lack the extensive conjugation and multiple hydroxyl groups characteristic of phenolic compounds, certain subclasses particularly diterpenes such as carnosic acid exhibit significant antioxidant activity due to the presence of phenolic functionalities.

Carnosic acid, a major constituent of rosemary and sage, contains a catechol moiety that enables efficient radical scavenging through hydrogen atom transfer mechanisms. Upon oxidation, it can be converted into carnosol, which retains antioxidant activity through its phenolic structure. These compounds have been extensively studied for their ability to inhibit lipid peroxidation and oxidative stress, highlighting their therapeutic relevance (Damašius et al., 2014).

Monoterpenes such as thymol and carvacrol, which are abundant in Lamiaceae essential oils, exhibit moderate antioxidant activity due to the presence of a single phenolic hydroxyl group. Although their radical scavenging capacity is lower than that of polyphenolic compounds, their lipophilicity enhances membrane

permeability and contributes to their antimicrobial and anti-inflammatory effects. These properties underscore the complementary role of terpenoids in the overall bioactivity of Lamiaceae species (Buathong & Duangsrisai, 2023).

5. DFT Insights into Antioxidant Mechanisms of Lamiaceae Phytochemicals

Density Functional Theory has played a pivotal role in elucidating the antioxidant mechanisms of Lamiaceae phytochemicals by providing quantitative insights into their thermodynamic and electronic properties. Through the calculation of parameters such as bond dissociation enthalpy, ionization potential, proton affinity, and electron transfer enthalpy, DFT enables the prediction of radical scavenging pathways and reactivity trends in phenolic compounds.

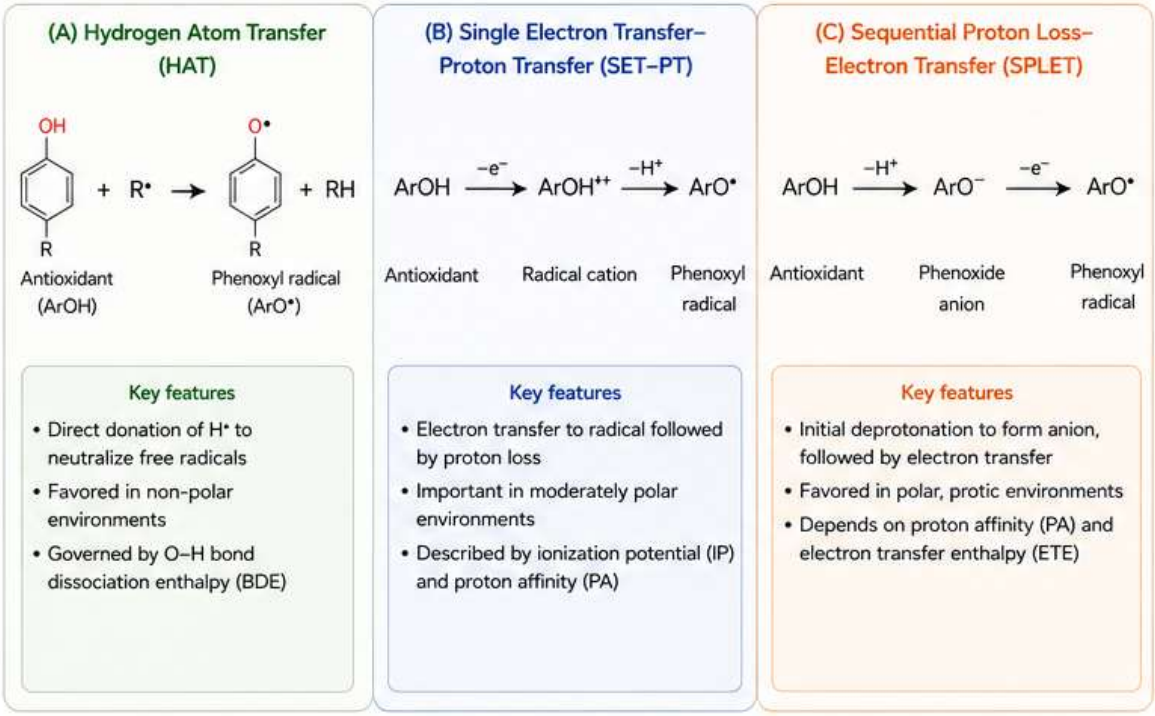
One of the most important descriptors in antioxidant studies is the bond dissociation enthalpy of the O–H bond, which governs the efficiency of hydrogen atom transfer mechanisms. Phenolic compounds with lower BDE values exhibit greater antioxidant activity due to their enhanced ability to donate hydrogen atoms and stabilize the resulting radicals. Computational studies have demonstrated that catechol-containing compounds, such as rosmarinic acid and luteolin, possess significantly lower BDE values compared to simple phenols, primarily due to resonance stabilization and intramolecular hydrogen bonding (Silva et al., 2009; Damašius et al., 2014). The fundamental antioxidant mechanisms of phenolic compounds, including hydrogen atom transfer (HAT), single electron transfer–proton transfer (SET–PT), and sequential proton loss–electron transfer (SPLET), are illustrated in **Figure 1** (Mucha et al., 2021; Silva et al., 2009).

In addition to hydrogen atom transfer, electron transfer mechanisms also contribute to antioxidant activity. The ionization potential reflects the ease with which a molecule can donate an electron, while proton affinity determines its ability to participate in proton transfer reactions. These parameters are particularly relevant in polar environments, where the sequential proton loss–electron transfer mechanism becomes thermodynamically favorable. Such behavior is consistent with biological systems, where solvent effects play a crucial role in modulating antioxidant activity.

Frontier molecular orbital analysis further enhances the understanding of antioxidant behavior by linking electronic structure to reactivity. Molecules with higher HOMO energies exhibit greater electron-donating capacity, while smaller HOMO–LUMO gaps are associated with increased chemical reactivity. Polyphenolic compounds from Lamiaceae typically display smaller energy gaps compared to monoterpenes, which explains their superior antioxidant performance.

Moreover, the integration of DFT-derived descriptors with experimental antioxidant assays has demonstrated strong correlations between computational predictions and biological activity. These findings support the use of DFT as a reliable tool for screening and optimizing phytochemicals for therapeutic applications. The ability to predict antioxidant mechanisms at the molecular level provides a valuable framework for the rational design of bioactive compounds and the identification of promising candidates for further investigation. Key DFT-derived descriptors governing antioxidant activity of Lamiaceae

Figure 1. Proposed antioxidant mechanisms of phenolic compounds: (A) hydrogen atom transfer (HAT), (B) single electron transfer–proton transfer (SET–PT), and (C) sequential proton loss–electron transfer



phytochemicals are summarized in **Table 2**, demonstrating their structure–activity relationships (Merecz-Sadowska et al., 2023).

Table 2. Important DFT descriptors and their relevance to antioxidant mechanisms.

Descriptor	Full Form	Mechanistic Role	Interpretation
BDE	Bond Dissociation Enthalpy	HAT mechanism	Lower BDE → higher antioxidant activity
IP	Ionization Potential	SET mechanism	Lower IP → easier electron donation
PA	Proton Affinity	SPLET mechanism	Lower PA → easier proton dissociation
ETE	Electron Transfer Enthalpy	SPLET mechanism	Lower ETE → better electron transfer
HOMO	Highest Occupied Molecular Orbital	Electron donation	Higher HOMO → stronger antioxidant
LUMO	Lowest Unoccupied Molecular Orbital	Electron acceptance	Lower LUMO → higher reactivity

6. Molecular Docking and Multi-Target Therapeutic Potential of Lamiaceae Phytochemicals

The integration of molecular docking with Density Functional Theory has significantly advanced the identification of Lamiaceae phytochemicals as multi-target therapeutic agents. Molecular docking enables the prediction of binding affinity and interaction profiles between phytochemicals and biologically relevant targets, while DFT provides complementary insights into the electronic properties governing ligand reactivity. Together, these approaches form a robust computational framework for rational drug discovery.

Recent computational studies have demonstrated that phytochemicals derived from medicinal plants exhibit strong binding affinities toward key inflammatory enzymes, particularly cyclooxygenase-2 (COX-2) and lipoxygenase (LOX), which play central roles in the biosynthesis of pro-inflammatory mediators. For instance, docking-based investigations have reported binding energies in the range of −8.0 to −10.0 kcal/mol for phenolic compounds interacting with COX-2, indicating significant inhibitory potential (Rudrapal et al., 2025). These findings are further supported by studies demonstrating dual inhibition of COX and LOX pathways by plant-derived compounds, suggesting a synergistic mechanism for anti-inflammatory activity (Rudrapal et al., 2023).

Flavonoids such as luteolin and quercetin have been widely investigated for their interaction with COX-2 due to their planar structures and ability to form hydrogen bonds and π–π interactions within enzyme active sites. Molecular docking and DFT analyses have revealed that these compounds exhibit stable binding conformations, supported by favorable electronic descriptors such as high HOMO energy and low energy gaps, which facilitate electron donation and interaction with catalytic residues (Lakkadi et al., 2024; Nadia et al., 2024). These interactions are often stabilized by hydrogen bonding with key amino acid residues and hydrophobic interactions within the binding pocket, contributing to their inhibitory activity.

In addition to anti-inflammatory targets, Lamiaceae phytochemicals have demonstrated potential against viral and metabolic targets. Computational studies have identified several plant-derived compounds as inhibitors of viral proteases, including SARS-CoV-2 main protease (Mpro), with binding affinities comparable to reference antiviral drugs. These findings highlight the potential of phytochemicals as broad-spectrum therapeutic agents (Acosta-Quiroga et al., 2025). The binding interactions of flavonoids with inflammatory targets such as COX-2 are exemplified in **Figure 3**, highlighting key hydrogen bonding and hydrophobic interactions within the active site (Rudrapal et al., 2023).

Figure 3. Representative binding interactions of luteolin with COX-2 (PDB ID: 5IKR), showing key hydrogen bonding and hydrophobic contacts.

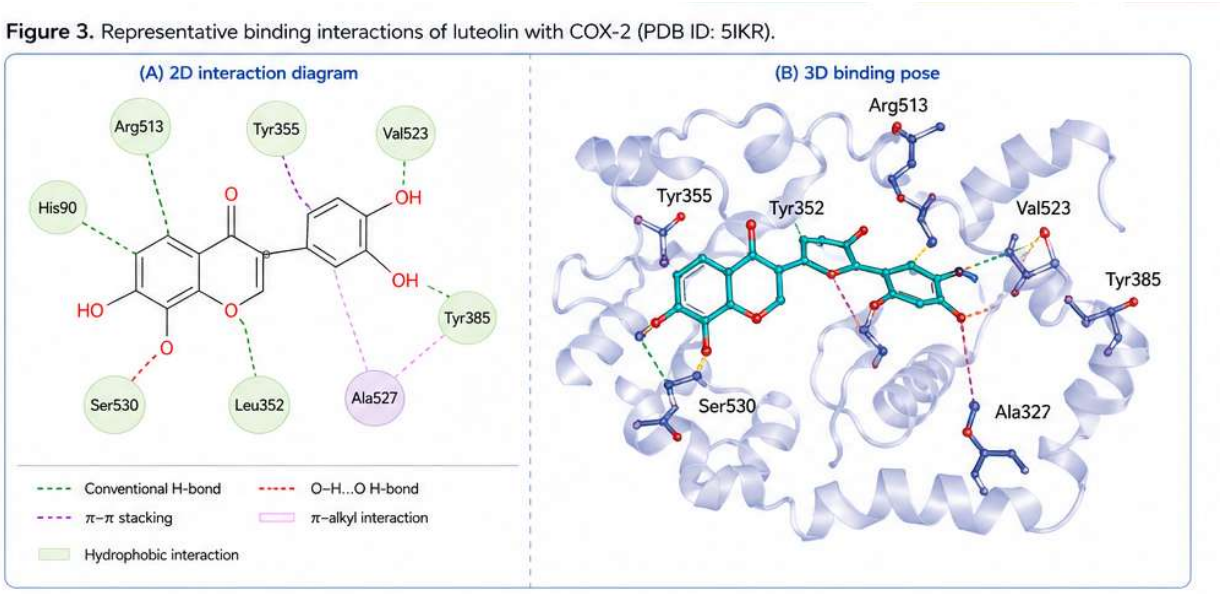


Figure 3. Representative binding interactions of luteolin with COX-2 (PDB ID: 5IKR).

Furthermore, molecular docking studies have shown that phenolic compounds can interact with metabolic enzymes such as α-amylase and α-glucosidase, suggesting potential applications in the management of metabolic disorders such as diabetes. The ability of these compounds to bind multiple targets underscores their relevance in polypharmacology, where a single molecule can modulate multiple biological pathways simultaneously.

Molecular dynamics simulations further validate docking results by providing insights into the stability and conformational behavior of ligand–protein complexes over time. Studies employing MD simulations have demonstrated that phytochemical–protein complexes exhibit stable trajectories, low root mean square deviation (RMSD) values, and favorable binding free energies, confirming the reliability of docking predictions (Alhumaydhi et al., 2021). These dynamic analyses are essential for understanding the behavior of complexes under physiological conditions and for refining drug candidates.

The integration of docking, DFT, and ADMET profiling has enabled the identification of phytochemicals with favorable pharmacokinetic properties, including adequate bioavailability, low toxicity, and optimal lipophilicity. Such multi-parameter optimization is crucial in early-stage drug discovery, as it reduces the likelihood of failure in later stages of development. Recent studies have emphasized the importance of combining computational methods to achieve a comprehensive evaluation of bioactive compounds, thereby accelerating the discovery pipeline (Babalola et al., 2025). Representative molecular docking interactions of selected Lamiaceae phytochemicals with key therapeutic targets are presented in **Table 3**, highlighting their multi-target potential (Rudrapal et al., 2023; Parvin et al., 2025).

Table 3. Molecular docking results of selected Lamiaceae phytochemicals against key biological targets.

Compound	Target Protein	Binding Affinity (kcal/mol)	Interaction Type	Therapeutic Area	Key Residues/Mechanism

Rosmarinic acid	COX-2	~ -9.2	H-bond + hydrophobic	Anti-inflammatory	Active site hydrogen bonding
Rosmarinic acid	SARS-CoV-2 Mpro	~ -8.5	H-bonding	Antiviral	Protease inhibition
Luteolin	COX-2	~ -9.5	π-π stacking + H-bond	Anti-inflammatory	Aromatic interactions
Luteolin	PLpro	~ -8.9	Hydrogen bonding	Antiviral	Protease inhibition
Carnosic acid	COX-2	~ -9.8	Hydrophobic + H-bond	Anti-inflammatory	Strong active site binding
Ursolic acid	COX-2	~ -10.2	Hydrophobic	Anti-inflammatory	High binding affinity
Thymol	Bacterial proteins	-5.0 to -7.5	Hydrophobic	Antimicrobial	Membrane disruption
Carvacrol	CYP51	~ -8.2	Hydrophobic	Antifungal	Enzyme inhibition
Kaempferol	α-amylase	~ -9.5	H-bond	Antidiabetic	Enzyme inhibition

Overall, the convergence of molecular docking and quantum chemical approaches has established Lamiaceae phytochemicals as promising candidates for multi-target therapeutic applications. Their ability to interact with diverse biological targets, combined with favorable electronic and pharmacokinetic properties, highlights their potential in the development of novel antioxidant, anti-inflammatory, antiviral, and metabolic therapeutics.

7. QSAR Modeling and ADMET Profiling in Lamiaceae-Based Drug Discovery

Quantitative Structure–Activity Relationship (QSAR) modeling has emerged as a powerful computational tool for establishing predictive relationships between molecular structure and biological activity. In the context of Lamiaceae phytochemicals, QSAR models have been widely employed to correlate Density Functional Theory (DFT)-derived descriptors with antioxidant and anti-inflammatory activities. Parameters such as bond dissociation enthalpy, ionization potential, proton affinity, HOMO–LUMO energy gap, dipole moment, and molecular volume have been shown to significantly influence radical scavenging efficiency and enzyme inhibition potential.

Recent studies have demonstrated that the integration of quantum chemical descriptors into QSAR frameworks enhances predictive accuracy, particularly for phenolic compounds. For instance, polyphenolic structures exhibiting lower bond dissociation enthalpy and higher HOMO energy values tend to display superior antioxidant activity, consistent with their enhanced electron- and hydrogen-donating capacity (Merecz-Sadowska et al., 2023). Moreover, machine learning-assisted QSAR models have further improved predictive capabilities by incorporating large descriptor datasets and nonlinear relationships, thereby enabling high-throughput virtual screening of phytochemicals (Babalola et al., 2025).

In parallel, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling has become an essential component of computational drug discovery pipelines. Early-stage evaluation of

pharmacokinetic and toxicological properties is critical for identifying compounds with favorable drug-like characteristics. Computational tools have been widely applied to predict parameters such as intestinal absorption, blood–brain barrier permeability, cytochrome P450 interactions, and toxicity profiles. Studies have shown that many Lamiaceae-derived phytochemicals exhibit favorable ADMET properties, including moderate lipophilicity, acceptable bioavailability, and low predicted toxicity, supporting their potential as therapeutic agents (Parvin et al., 2025; Rudrapal et al., 2025).

The integration of QSAR and ADMET analyses with molecular docking and DFT calculations provides a comprehensive framework for rational drug design. This multi-parameter approach allows for the simultaneous optimization of biological activity and pharmacokinetic properties, thereby reducing the likelihood of late-stage failure in drug development. Such integrative strategies are increasingly recognized as essential for the efficient identification of lead compounds from natural product libraries.

8. Integrated Computational Pipeline for Lamiaceae Phytochemicals

The convergence of DFT, molecular docking, molecular dynamics simulations, QSAR modeling, and ADMET profiling has established a robust computational pipeline for the systematic evaluation of phytochemicals. This integrated approach enables the identification of promising bioactive compounds through a stepwise process that combines electronic structure analysis with biological target prediction and pharmacokinetic assessment.

Typically, DFT calculations are first employed to evaluate the intrinsic reactivity of phytochemicals by determining thermodynamic and electronic descriptors. These descriptors are subsequently incorporated into QSAR models to predict biological activity and prioritize compounds for further investigation. Molecular docking is then used to assess binding affinity and interaction profiles with specific biological targets, while molecular dynamics simulations provide insights into the stability and conformational behavior of ligand–protein complexes under dynamic conditions.

Finally, ADMET profiling is conducted to evaluate drug-likeness and safety, ensuring that selected compounds possess favorable pharmacokinetic properties. This integrated workflow has been successfully applied in numerous studies to identify phytochemicals with potential therapeutic applications, particularly in the context of inflammation, oxidative stress, and metabolic disorders (Acosta-Quiroga et al., 2025). Table 4 summarises the key ADMET characteristics for representative phytochemicals from the Lamiaceae family.

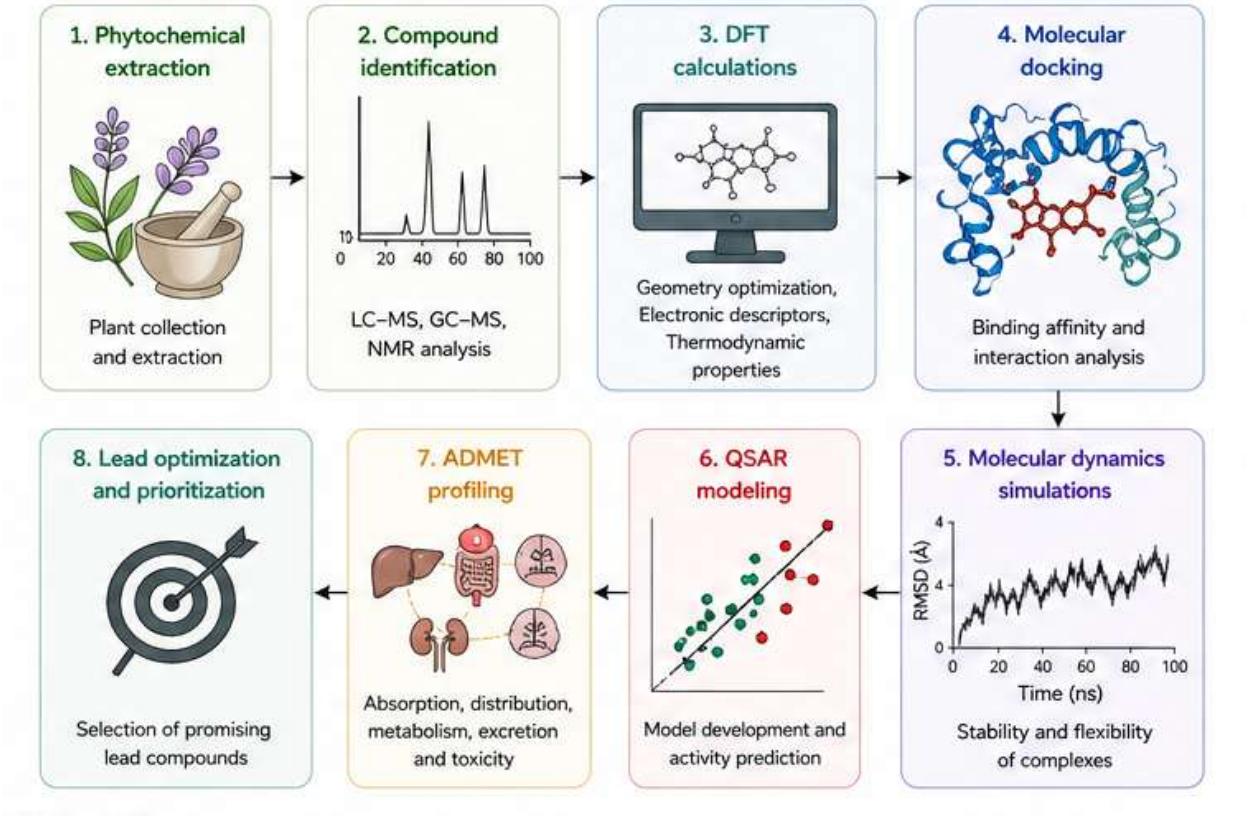
Table 4: ADMET Parameters of Representative Lamiaceae Phytochemicals

Compound	MW (Da)	LogP	HBD	HBA	TPSA (Å²)	LogS	BBB	Toxicity
Rosmarinic acid	360.3	1.5	4	8	138	-2.5	Low	Low
Luteolin	286.2	2.1	4	6	111	-3.2	Moderate	Low
Apigenin	270.2	2.5	3	5	91	-3.5	Moderate	Low
Quercetin	302.2	1.5	5	7	131	-2.8	Low	Low
Thymol	150.2	3.3	1	1	20	-2.1	High	Low
Carvacrol	150.2	3.5	1	1	20	-2.2	High	Low
Carnosic acid	332.4	3.5	2	4	77	-4.2	Moderate	Low

Ursolic acid	456.7	5.5	2	3	57	-6.2	Low	Low

The adoption of such multi-disciplinary computational strategies represents a significant advancement in natural product research, as it enables the efficient screening and optimization of complex phytochemical libraries. Moreover, the integration of machine learning and artificial intelligence with traditional computational methods is expected to further enhance predictive accuracy and accelerate drug discovery processes. The overall computational strategy integrating DFT, molecular docking, molecular dynamics simulations, QSAR modeling, and ADMET profiling is summarized in **Figure 2** (Babalola et al., 2025; Alhumaydhi et al., 2021).

Figure 2. Integrated computational workflow for the evaluation of Lamiaceae phytochemicals.



9. Conclusion and Future Perspectives

The present review highlights the critical role of Density Functional Theory and in silico methodologies in advancing the understanding of Lamiaceae phytochemicals and their therapeutic potential. Through the integration of quantum chemical calculations, molecular docking, molecular dynamics simulations, QSAR modeling, and ADMET profiling, significant progress has been made in elucidating the mechanisms underlying antioxidant and pharmacological activities.

Phenolic acids and flavonoids have emerged as the most potent antioxidant constituents of Lamiaceae, primarily due to their favorable electronic properties and structural features, including catechol moieties and extended conjugation systems. Terpenoids, although generally less active as antioxidants, contribute to the overall pharmacological profile through complementary

mechanisms, including anti-inflammatory and antimicrobial effects. DFT studies have provided valuable insights into the thermodynamic and electronic factors governing these activities, while docking and molecular dynamics simulations have elucidated their interactions with key biological targets.

Despite these advancements, several challenges remain. The accurate modeling of solvent effects and biological environments continues to be a limitation in DFT studies, while the reliability of docking predictions is often dependent on the quality of protein structures and scoring functions. Additionally, the complexity of biological systems necessitates the development of more sophisticated multi-target and systems-level approaches.

Future research should focus on the integration of machine learning with quantum chemical descriptors to enhance predictive capabilities and enable the discovery of novel bioactive compounds. Furthermore, the validation of computational predictions through experimental studies remains essential for translating in silico findings into practical therapeutic applications. The continued development of hybrid computational–experimental frameworks will be critical for unlocking the full potential of Lamiaceae phytochemicals in drug discovery.

References

Acosta-Quiroga, K., Rocha-Valderrama, E., Zúñiga-Bustos, M., Mera-Adasme, R., Cabrera-Barjas, G., Olea-Azar, C., & Moncada-Basualto, M. (2025). Gross Antioxidant Capacity and Anti-Inflammatory Potential of Flavonol Oxidation Products: A Combined Experimental and Theoretical Study. Antioxidants (Basel, Switzerland), 14(4), 479. https://doi.org/10.3390/antiox14040479

Aryal, D., Joshi, S., Thapa, N. K., Chaudhary, P., Basaula, S., Joshi, U., Bhandari, D., Rogers, H. M., Bhattarai, S., Sharma, K. R., Regmi, B. P., & Parajuli, N. (2024). Dietary phenolic compounds as promising therapeutic agents for diabetes and its complications: A comprehensive review. *Food science & nutrition*, *12*(5), 3025–3045. https://doi.org/10.1002/fsn3.3983

Aslan, Y., Atabay, M., Chowdhury, H., Göktürk, I., Saylan, Y., & İnci, F. (2023). Aptamer-based point-of-care devices: Emerging technologies and integration of computational methods. *Biosensors, 13*(5), 569. https://doi.org/10.3390/bios13050569

Babalola, O. O., Bridget, K., Oyubu, G., Waheed, S. A., Ajiboye, S. A., Fakayode, A. E., Edema, A. A., Chukwuma, U. G., Tiamiyu, R. T., Fakayode, A. J., Adebimpe, H. O., Onyeagba, K. D., Fakunle, C. O., Ottu, P. O., & Gabriel, S. (2025). Integrating phytochemicals and in silico methods for modern drug discovery: A comprehensive review. *Discover Chemistry*, *2*(1), 297. https://doi.org/10.1007/s44371-025-00373-y

Buathong, R., & Duangsrisai, S. (2023). Plant ingredients in Thai food: Bioactive compounds and medicinal relevance. *PeerJ, 11*, e14568. https://doi.org/10.7717/peerj.14568

Chibuye, B., Singh, I., Chimuka, L., & Maseka, K. (2024). In silico and ADMET molecular analysis to discover novel COX-2 inhibitors from *Diospyros batokana*. *Biochemistry and Biophysics Reports, 39*, 101758. https://doi.org/10.1016/j.bbrep.2024.101758

Damašius, J., Venskutonis, P. R., Kaškonienė, V., & Maruška, A. (2014). Fast screening of phenolic acids with antioxidant properties using on-line HPLC/UV/DPPH assay. *Analytical Methods, 6*(8), 2774–2781. https://doi.org/10.1039/c3ay41703d

Lakkadi, A., Vuppala, S., Nampally, V., Kim, J., Kim, K., Jang, J., & Tigulla, P. (2024). Development of novel chromones as antioxidant COX2 inhibitors: *In vitro* ,

QSAR, DFT, molecular docking, and molecular dynamics studies. *Journal of Biomolecular Structure and Dynamics*, *42*(6), 2793–2808. https://doi.org/10.1080/07391102.2023.2212785

Merecz-Sadowska, A., Sitarek, P., Kowalczyk, T., Palusiak, M., Hoelm, M., Zajdel, K., & Zajdel, R. (2023). In Vitro Evaluation and In Silico Calculations of the Antioxidant and Anti-Inflammatory Properties of Secondary Metabolites from *Leonurus sibiricus* L. Root Extracts. *Molecules*, *28*(18), 6550. https://doi.org/10.3390/molecules28186550

Mucha, P., Skoczyńska, A., Małecka, M., Hikisz, P., & Budzisz, E. (2021). Overview of the Antioxidant and Anti-Inflammatory Activities of Selected Plant Compounds and Their Metal Ions Complexes. *Molecules*, *26*(16), 4886. https://doi.org/10.3390/molecules26164886

Lachi, N., Cheriet, M., & Djadi, N. (2024). Exploring the Interactions of Natural Flavonoids with COX-2: Insights from Molecular Docking, DFT Analysis, and ADME Calculations. In Iranian Chemical Society, *Phys. Chem. Res.* (Vol. 12, Issue 3, pp. 675–691). Iranian Chemical Society. https://doi.org/10.22036/pcr.2023.426148.2451

Parvin, M. S., Shakib, M. S. I., Hossain, M. S., Sinthi, A. T., & Islam, M. E. (2025). Computational profiling of anti-inflammatory phytochemicals targeting 5-LOX and COX-2 pathways: PASS prediction, molecular docking and ADMET analysis. *Chemico-Biological Interactions*, *418*, 111604. https://doi.org/10.1016/j.cbi.2025.111604

Alhumaydhi, F. A., Aljohani, A. S. M., Rashid, U., Shah, Z. A., Rauf, A., Muhammad, N., Al-Awthan, Y. S., & Bahattab, O. S. (2021). *In Vivo* Antinociceptive, Muscle Relaxant, Sedative, and Molecular Docking Studies of Peshawaraquinone Isolated from *Fernandoa adenophylla* (Wall. ex G. Don) Steenis. *ACS omega*, *6*(1), 996–1002. https://doi.org/10.1021/acsomega.0c05720

Rudrapal, M., De Oliveira, A. M., De Abreu, H. A., Rakshit, G., Tripathi, M. K., & Khan, J. (2025). Anti-inflammatory and antioxidant potential of plant-derived phenolic acids as triple cox, lox, and nox inhibitors: A computational approach. *Chemistry & Biodiversity*, e03505. https://doi.org/10.1002/cbdv.202403505

Rudrapal, M., Eltayeb, W. A., Rakshit, G., El-Arabey, A. A., Khan, J., Aldosari, S. M., Alshehri, B., & Abdalla, M. (2023). Dual synergistic inhibition of COX and LOX by potential chemicals from Indian daily spices investigated through detailed computational studies. *Scientific Reports*, *13*(1), 8656. https://doi.org/10.1038/s41598-023-35161-0

Silva, E. R., Queiroz, A. N., Almeida, E. D., & Borges, R. S. (2009). A DFT study of aminophenol stability. *Journal of Computational and Theoretical Nanoscience*, *6*(7), 1694–1696. https://doi.org/10.1166/jctn.2009.1232