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# Python-Based Mechanistic Evaluation of Antioxidant Activity Using DFT Calculations

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**Abstract: Cardiovascular disease, chronic inflammation, neurodegeneration, aging, and cancer are largely associated with oxidative stress due to the accumulation of reactive oxygen species (ROS). Hydrogen Atom Transfer (HAT) and Single Electron Transfer (SET) are the strategies adopted by antioxidants to neutralize ROS, both of which can be examined using quantum-chemical descriptors, including bond dissociation enthalpy (BDE), ionization potential (IP), and the energies of frontier molecular orbitals (FMOs). This study evaluates twelve phenolic and aromatic compounds, including phenol, catechol, hydroquinone, pyrogallol, caffeic acid, ferulic acid, gallic acid, and resveratrol, using Density Functional Theory (DFT) at the B3LYP/6-31G(d,p) level in Gaussian 09. Although DFT calculations have been employed to investigate antioxidants, most studies are limited to individual compounds and rely on manual extraction of computational descriptors. Automated workflows that help to integrate the extraction of descriptors, classification of mechanistic pathways, and comparative evaluation across a range of antioxidants remain unexplored. Geometry optimization and vibrational frequency analysis confirmed structural stability; BDEs and IPs, along with energy gaps between the FMOs, were useful for analyzing mechanistic antioxidant behavior. A Python-based automation workflow for extracting quantum-chemical descriptors from Gaussian output files was useful for calculating antioxidant parameters and generating structured datasets and visualizations. Molecules rich in hydroxyl groups (-OH) exhibited stronger HAT activity via radical stabilization and effective hydrogen donation, whereas conjugated systems such as resveratrol and ferulic acid preferred SET pathways due to lower IPs and effective electronic delocalization. The study demonstrates the integration of a computational framework connecting DFT-based mechanistic studies with automated extraction of descriptors to obtain antioxidant analysis that are reproducible.**

***Keywords:*** *Antioxidants, Density Functional Theory (DFT), Hydrogen Atom Transfer (HAT), Single Electron Transfer (SET), Bond Dissociation Enthalpy (BDE), Ionization Potential (IP), Python Workflow.*

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## I. INTRODUCTION

The oxygen atoms released from living cells during routine metabolic activities contribute to the formation of reactive oxygen species (ROS) [1]. These species, including singlet oxygen, hydrogen peroxide, hydroxyl radicals, and superoxide radicals, are among the most chemically reactive ROS[2]. Moderate concentrations of ROS participate in cellular functions, such as the activation of immune responses against pathogens and the regulation of intracellular signaling cascades under physiological conditions [3]. Oxidative stress is induced when ROS production overwhelms the body's antioxidant defenses. Such an imbalance causes extensive damage to molecules by disrupting lipid concentration in cellular membranes. Essential proteins that help the functioning of enzymes and nucleic acids that store genetic information are also affected. Such instances of persistent oxidative stress are manifested in diseases ranging from type 2 diabetes and cancer to Alzheimer's, ailments of the heart, and several other long-standing inflammatory illnesses[4].

Antioxidants are significant because they interrupt the torrent of oxidative damage by engaging with free radicals and neutralizing their reactivity at the source before allowing them to propagate further damage [5]. Phenolic compounds have always invited significant scientific attention due to their demonstrable radical scavenging capacity among the existing compounds known to have antioxidant activity. Phenolic compounds are present in plenty within foods that are plant-based and in conventional medicines[5]. The hydroxyl groups attached to the aromatic ring are the strongest characteristic suitable for phenolic antioxidants, and the radical intermediates are stabilized by resonance stemming from the aromatic rings. The unpaired electron density is distributed across the aromatic ring

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through resonance rather than concentrating it around a single atom regarded as a reactive site. The antioxidant effectiveness of phenolic compounds doesn't rely only on the number of hydroxyl groups attached to them. The extent of delocalization in the molecules, the location of the -OH moieties, and their interactions with each other and with the rest of the molecule are pertinent [7].

The antioxidant activity of phenolic compounds is governed by two fundamental mechanistic pathways, such as (i) Hydrogen Atom Transfer (HAT) and (ii) Single Electron Transfer (SET). HAT favors the direct donation of hydrogen atoms to ROS within an antioxidant [6]. This effectively terminates the radical chain reaction by converting the highly reactive radical into a stable molecule, while the antioxidant itself becomes a much less reactive radical.

$$ArOH \rightarrow ArO^{\cdot} + H^{\cdot}$$

SET is operative when a single electron is donated by the antioxidant to the radical species rather than a full hydrogen atom. The antioxidant is converted into a radical cation by this process.

$$ArOH \rightarrow ArOH^{\cdot+} + e^{-}$$

The bond dissociation enthalpy (BDE) is the primary metric in the HAT pathway. As the BDE decreases, the chosen O-H bond can be broken with minimal energy, thereby facilitating hydrogen donation. The ionization potential (IP) sets the stage for the SET pathway by measuring the energy essential for the removal of one electron from the molecule [9]. When a molecule transfers electrons more readily, it is due to a lower IP, and thus the SET mechanism is established.

Density Functional Theory (DFT) can be considered as one of the most consistent tools with computational efficacy to analyze the electronic composition of molecules[7]. The accuracy and efficiency of DFT, compared with post-Hartree-Fock calculations, strike a trade-off between the complexity of phenolic antioxidants and the suitability for analyzing phenolic molecules of varied sizes and complexity[8]. DFT is a useful tool for calculating BDE, IP, and frontier molecular orbital (FMO) energies, as well as parameters that provide a thorough description of a molecule's antioxidant potential, such as electronegativity, chemical hardness, and electrophilicity indices [11]. FMO is about the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) to explain how molecules interact with radical entities like ROS, during electron transfer.

The extraction of data from the DFT calculations in the Gaussian output files is a tedious process that must be performed manually. When the research concerns a set of molecules that require calculation of their neutral, radical, and cationic forms, it is prone to transcription errors, which limits the number of molecules that can be studied with this type of investigation. Automation of workflows with Python is a plausible solution to mitigate human error when extracting data from output files. This study aims to present a thorough evaluation of the antioxidant mechanisms of twelve phenolic-aromatic molecules using DFT calculations. A scientific understanding of the structure-activity relationships existing within these molecules will be analyzed, and a methodological toolkit that favors the automation of the computational workflow will be presented to the researchers.

## II. COMPUTATIONAL METHODOLOGY

The compounds chosen for this study are 12 in number and exhibit structural diversity among phenolic antioxidants. The selected compounds include phenol[9], salicylic acid[10], catechol[11], caffeic acid[12], ferulic acid[13], vanillic acid[14], hydroquinone[15], syringic acid[16], pyrogallol[17], anisole[18], resveratrol[19], and gallic acid[20]. The selection of these compounds was deliberate, as this research aims to analyze these molecules thoroughly, given their diverse number of -OH groups, varying degrees of conjugation, and side chains of varying lengths attached to the aromatic core. Thus, a meaningful comparison of the molecules that ensures the connection between explicit structural properties and antioxidant nature is established. Anisole is chosen as the control (without a free -OH group), providing a reference point for comparison. This makes it easy to draw meaningful comparisons between molecules and to connect structural features to specific patterns of antioxidant activity, thereby enabling detailed study of the HAT and SET mechanisms.

The calculations concerning the electronic structure were carried out using the Gaussian 09 program package[21]. The B3LYP hybrid density functional, combined with the 6-31G(d,p) basis set, was chosen and has been extensively validated in the literature. This combination also provides a practical trade-off between computational needs and accuracy[22–24]. Geometry optimization was followed by vibrational frequency calculations, ensuring attainment of the global minimum for the structures. Those frequency calculations that yielded zero imaginary frequencies were considered valid for further analysis, as they ensure the formation of true minima. Calculations were performed on the neutral ground state, the radical species formed by removing a hydrogen atom from a -OH group, and the cationic species formed by removing one electron from the neutral molecule, where the neutral state serves as the reference point for all descriptor calculations. The unrestricted DFT method correctly treated unpaired electrons in open-shell systems for radical and cationic species.

BDE values were calculated using the standard thermodynamic definition. The enthalpy of the radical species after the cleavage of the O-H bond is regarded as the enthalpy of a free hydrogen atom (H(H$^{\bullet}$)), and the enthalpy of the neutral parent molecule was combined according to the following relation.

$$BDE = H(ArO^{\bullet}) + H(H^{\bullet}) - H(ArOH)$$

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This calculation gives the energy cost of homolytic cleavage of the O-H bond, the key step in the HAT mechanism. As BDE lowers, the breakage of the bond becomes easier, indicating that the molecule is capable of donating a hydrogen atom more readily, and thus is an effective HAT antioxidant.

The difference in total electronic energy between the cationic and neutral forms of each molecule constitutes IP and reflects the possibility of losing an electron by a molecule. Low IP moleciules facilitates easy oxidisatuon and thus are active SET antioxidants.

$$IP = E(ArOH^{+\bullet}) - E(ArOH)$$

The HOMO-LUMO energy gap (ΔE) was then calculated with the following relation.

$$\Delta E = E_{(LUMO)} - E_{(HOMO)}$$

The HOMO energy level is directly related to the IP via Koopmans' theorem and indicates how readily the molecule can donate electrons. The LUMO energy level is associated with EA, which reflects the molecule's capacity to accept electrons. The magnitude of ΔE indicates molecular reactivity, with smaller values of ΔE corresponding to increased reactivity and a greater tendency for charge transfer.

The Python-based automation workflow developed in this study was built to locate, read, and organize data from large numbers of Gaussian log files. The regular expression capabilities of the Python workflow help to systematically parse each log file and extract the relevant numerical values, including thermal enthalpy corrections, SCF energies, dipole moments, HOMO and LUMO energies, and the energies of radical and cationic states. Once extracted, these values were passed to calculation routines that computed BDE and IP automatically. The following script demonstrates automated extraction of quantum chemical descriptors for Phenol.

➢ *SCF Energy*

```
import re

def extract_scf_energy(text):

    pattern = r'SCF Done:\s+E\([RU]B3LYP\)\s+=\s+(-?\d+\.\d+)'

    matches = re.findall(pattern, text)

    if matches:
        return float(matches[-1])

 return None
```

➢ *HOMO-LUMO Energy with BDE and IP Calculation*

```
def extract_homo_lumo(text):

    homo = None
    lumo = None

    lines = text.splitlines()

    for line in lines:

        if "Alpha  occ. eigenvalues" in line:
            values = line.split("--")[1].split()
            homo = float(values[-1])

        if "Alpha virt. eigenvalues" in line and lumo is None:
            values = line.split("--")[1].split()
            lumo = float(values[0])

    return homo, lumo

BDE_hartree = E_radical + E_H - E_neutral

IP_hartree = E_cation - E_neutral
```

## III. RESULTS AND DISCUSSION

The successful optimization of all twelve molecules was calculated with the B3LYP/6-31G(d,p) level. The frequency calculations confirmed the stable energy minima of the structures (Figure 1). Additional optimization cycles were required for the highly hydroxylated molecules and their open-shell derivatives. Molecules such as pyrogallol and gallic acid possess packed networks of intramolecular hydrogen bonds. Those bonds cooperate strongly with the electronic redistribution when a molecule is ionized or when the hydroxyl group is converted to a radical. Finding the true minimum energy of these molecules is essential, as they are sensitive to electronic changes.

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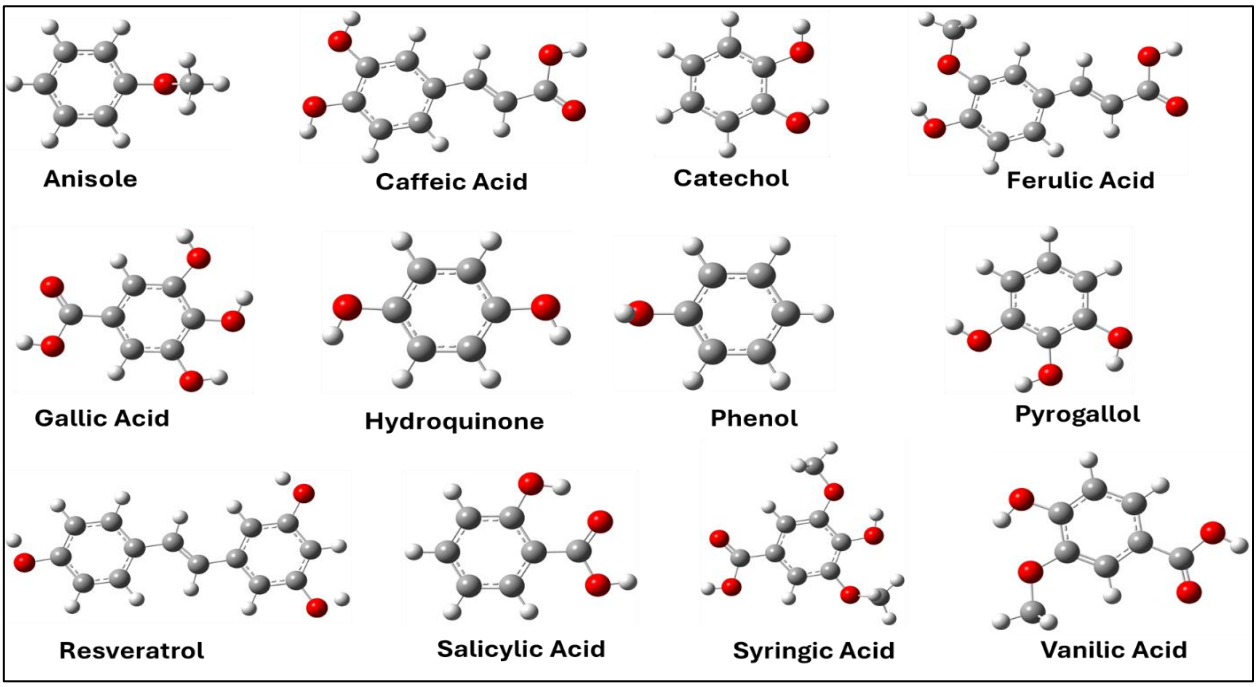


Fig 1 DFT-Optimized Geometries of the Investigated Antioxidant Molecules Calculated at the B3LYP/6-31G(d,p) Level

The optimized geometries reflected the expected structural trends. The molecules rich in -OH groups exhibited stabilizing hydrogen-bonding interactions, while conjugated systems such as resveratrol displayed planar geometry due to extended π-electron delocalization across their aromatic rings. The $H_{BDE}$ calculations reveal how structural features decide the ability to donate hydrogen atoms. A meaningful spread in BDE values across the twelve molecules was observed, and this variation correlated in an interpretable way with the molecular structures involved (Figure 2).

Table 1 Comparative Quantum Chemical Descriptors Including BDE, IP, and ΔE for Mechanistic Antioxidant Evaluation.

| **Molecule** | **HOMO (Hartree)** | **LUMO (Hartree)** | **ΔE (eV)** | **BDE (Kcal mol$^{-1}$)** | **IP (eV)** |
|---|---|---|---|---|---|
| Phenol | -0.22322 | -0.00055 | 6.059162 | 84.2 | 11.19006 |
| Salicylic acid | -0.23597 | -0.06529 | 4.644442 | 82.5 | 8.527345 |
| Catechol | -0.21274 | 0.00374 | 5.890724 | 87.3 | 11.18538 |
| Caffeic acid | -0.21876 | -0.07168 | 4.002253 | 82.3 | 7.771902 |
| Ferulic Acid | -0.21595 | -0.06898 | 3.999259 | 86.6 | 7.638975 |
| Vanillic acid | -0.22577 | -0.04966 | 4.7922 | 89.5 | 8.109759 |
| Hydroquinone | -0.20609 | -0.00562 | 5.455069 | 80.9 | 7.823305 |
| Syringic acid | -0.22274 | -0.04927 | 4.720362 | 85.9 | 7.906381 |
| Pyrogallol | -0.21314 | 0.01196 | 6.125286 | 89.1 | 12.06986 |
| Anisole | -0.21744 | 0.0028 | 5.993039 | NA | 8.038003 |
| Resveratrol | -0.20216 | -0.05257 | 4.070553 | 79.6 | 7.030936 |
| Gallic acid | -0.22894 | -0.05358 | 4.771791 | 92 | 8.022138 |

Table 1 conveys that resveratrol and hydroquinone are the most efficacious HAT antioxidants based on BDE values. In both cases, the ease of O-H bond cleavage is a function of the stability of the radical species formed after donating hydrogen atoms. The remaining unpaired electron is spread across the aromatic π system through resonance after the breakage of the O-H bond. This delocalization lowers the energy of the radical state, thereby minimizing the energy cost and yielding a low BDE value. Catechol and pyrogallol, which carry adjacent hydroxyl groups on the aromatic ring, exhibit intermediate BDE values. Their radical species are also stabilized by resonance. However, a different electronic environment is introduced by multiple interacting -OH groups and intramolecular hydrogen bonding. The parent molecule is stabilized by intramolecular hydrogen bonding in the neutral form, relative to the radical, resulting in an elevated BDE.

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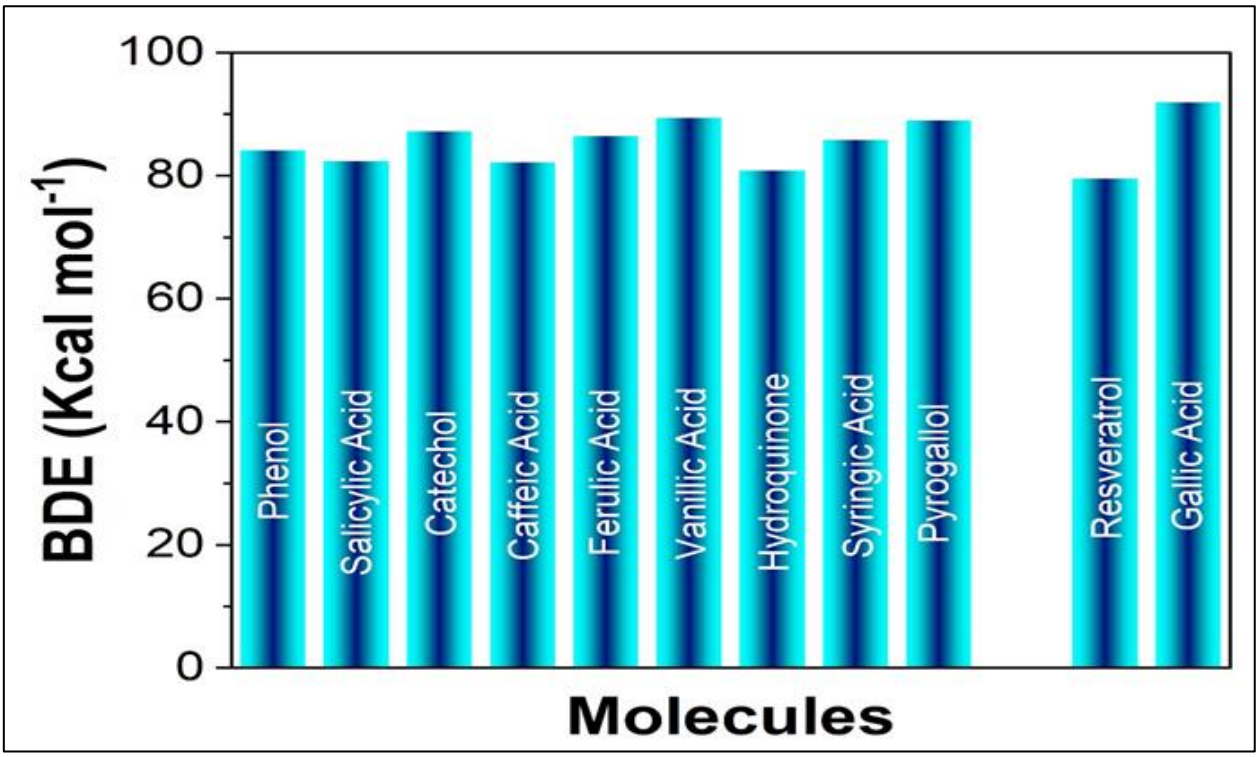


Fig 2 Calculated BDE Values for Evaluation of HAT Antioxidant Activity.

The BDE value of gallic acid is 92 kcal/mol for the -OH position under investigation, which is a potential antioxidant. The BDE value represents the energy of a specific O-H bond within a specific electronic and structural context. The local environment around that -OH group, the nature of any hydrogen bonding, and the orientation of neighboring substituents can influence the result[25]. Thus, interpreting BDE alongside other structural and electronic data is more pertinent than treating it as a definitive classification of antioxidant potential. Anisole could not partake in the HAT mechanism at all. The $-OCH_3$ group in place of a -OH group does not have a dissociable O-H bond, so BDE calculation wasn't applicable. This confirmed its value as a control compound that delineates the boundaries of what can and cannot participate in HAT-based antioxidant activity.

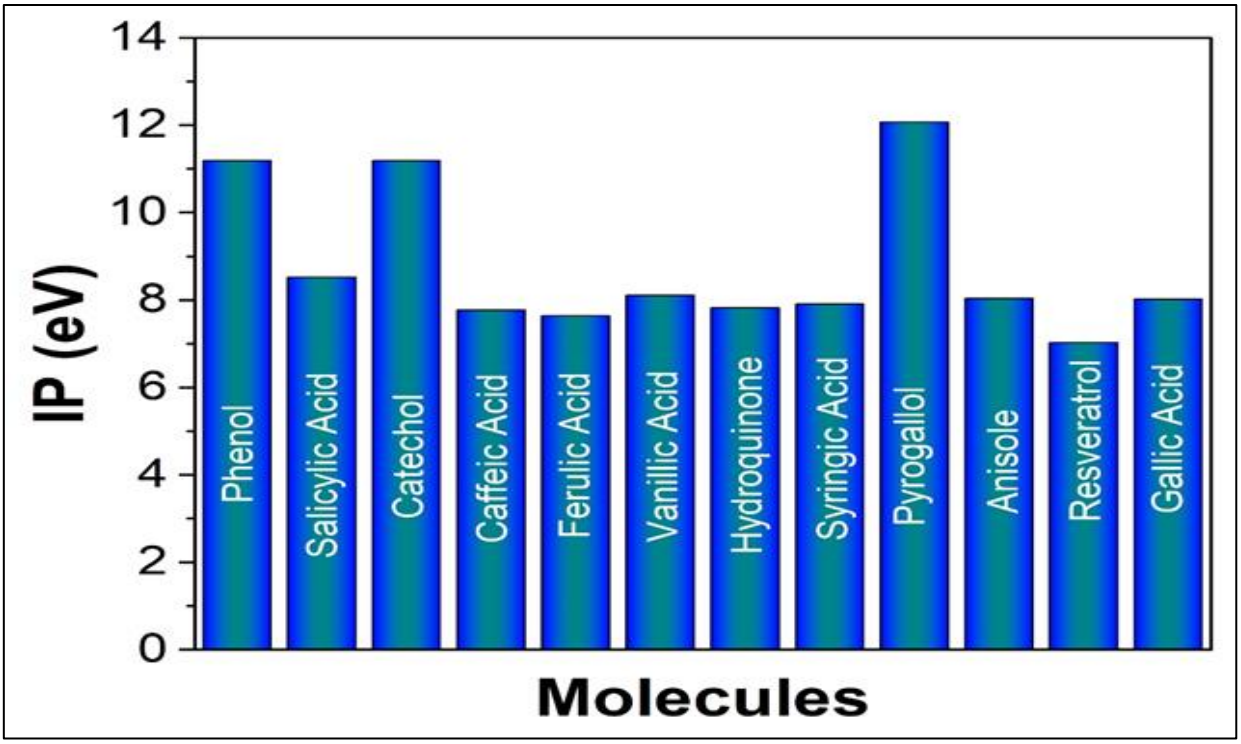


Fig 3 Calculated IP to Evaluate SET Mechanism of Antioxidant Activity.

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The IP gives a complementary picture of antioxidant behavior, which is governed by the degree of conjugation and electron delocalization rather than by hydrogen-donating groups (Figure 3). Resveratrol has the lowest IP among the molecules in the study, confirming its outstanding electron-donating capabilities. The architecture of the resveratrol molecule consists of two aromatic rings coupled by a conjugated double bond, with -OH groups located in such a way as to provide electron density to this extended π framework. During the event of SET, as resveratrol is oxidized to its radical cation, the positive charge is delocalized across the entire conjugated system. The cation attains stability through charge delocalization, which lowers its energy and consequently lowers the IP of the neutral molecule. Ferulic acid and caffeic acid can be considered stronger SET antioxidants in this series as they exhibit stronger IPs. The structural framework is similar to hydroxycinnamic acids, where -COOH groups as well as conjugated double bonds are connected through an aromatic ring substituted by -OH groups, which facilitate electron delocalization. Charge delocalization is lower for smaller π systems such as phenol and catechol, which exhibit elevated IPs compared to conjugated systems [26].

The complementary descriptors, such as BDE, IP, and the HOMO-LUMO energy gap, aid in evaluating the mechanistic classification of antioxidant activity (Table 1, Figure 4). HAT pathways are favorable for molecules with low BDE, as they can donate a hydrogen atom without energy expenditure. Molecules with low IPs and small HOMO-LUMO gaps, on the other hand, are suited for SET since they possess an electronic structure that gives up electrons readily.

The IP of resveratrol is calculated to be 7.03 eV, which is the lowest recorded in the entire series. Its ΔE, which is calculated to be 4.07 eV, was among the smallest. Resveratrol has a stilbene framework in which two aromatic rings bearing -OH groups are conjugated through a double bond. Thus, charges are spread evenly, leading to the stabilization of the extended π framework. The cation formed by electron removal makes the initial electron transfer energetically accessible. Ferulic acid and caffeic acid narrate a similar story. Their IPs of 7.64 eV and 7.77 eV, respectively, combined with a ΔE of ~4.00 eV, result in SET activity. The molecular π system and electron-donating substituents conjugated to the side chain connecting the aromatic ring to a -COOH group favor electron delocalization. Hydroquinone appears to be a strong performer in the HAT pathway. Its BDE of 80.9 kcal/mol reflects its readiness to release hydrogen atoms, a characteristic attributable to its symmetrical para-dihydroxy framework. When a radical forms on the oxygen after hydrogen donation, the two -OH groups work together to delocalize electrons through resonance. The delocalization of these electrons thereby lowers the energy of the radical state. Resveratrol, though apt for SET profile, also recorded a low BDE of 79.6 kcal/mol, adding it to a list of molecules that are competitive through both mechanistic pathways instantaneously. The radical intermediate in HAT and the cationic species in SET can be stabilized by these molecules. Phenol and catechol occupied a middle ground. Their IPs of 11.19 eV and ΔE values exceeding 5.8 eV make them less suitable as SET antioxidants than the conjugated systems discussed above. The larger gap indicates a more constrained, less reactive electronic structure. Their BDE values remain adequate, indicating that hydrogen atom donation remains a viable strategy for antioxidant activity for these molecules. They are better classified as HAT-active compounds with sufficient electronic flexibility.

Pyrogallol, despite carrying three hydroxyl groups, recorded the highest IP in the series at 12.07 eV and the largest ΔE at 6.13 eV, contributing to a poor SET antioxidant. Its BDE of 89.1 kcal/mol was also on the high side, suggesting that the O-H bond examined does not cleave particularly easily either. The number of hydroxyl groups a molecule carries does not determine its antioxidant effectiveness. The position of those groups relative to each other and the pattern of radical stabilization they enable are contributing factors. The dense clustering of -OH groups around the ring results in an intramolecular hydrogen-bonding of pyrogallol, which works against radical formation. Gallic acid with a BDE of 92 kcal/mol was the highest in the series at the investigated hydroxyl position, suggesting poor antioxidant performance. Its IP of 8.02 eV and ΔE of 4.77 eV leave room for a fractional contribution to SET. The three -OH groups in gallic acid and the elaborate network of intramolecular hydrogen-bonding interactions facilitate radical stabilization and electronic redistribution, making the molecule's antioxidant behavior difficult to capture with a single descriptor. Thus, descriptor-based analysis proves to be beneficial by considering multiple values together rather than any one metric in isolation. Anisole served as a mechanistic control with clarity, as it replaces the phenolic -OH group with a -$OCH_3$ group; it has no O-H bond available for hydrogen donation, allowing the HAT pathway. Its IP values were moderate, but without the ability to donate hydrogen atoms, it cannot function as an antioxidant. Its inclusion in the study therefore confirmed a point that is easy to state but important to demonstrate directly: the hydroxyl group is not merely one structural feature among many in phenolic antioxidants; it is the functional core that makes antioxidant activity through these mechanisms possible in the first place.

The descriptor analysis reveals that antioxidant behavior in phenolic compounds is best studied as the product of two competing structural tendencies. The molecules rich in -OH groups tend to favor HAT due to their structural features that support radical stabilization after hydrogen donation. SET is favored by conjugated aromatic molecules with extended π systems, as their electronic structure facilitates easy electron removal and efficient charge delocalization. Molecules such as resveratrol and caffeic acid are notable for exhibiting favorable characteristics for both SAT and HAT, providing mechanistic versatility that contributes to biological potency.

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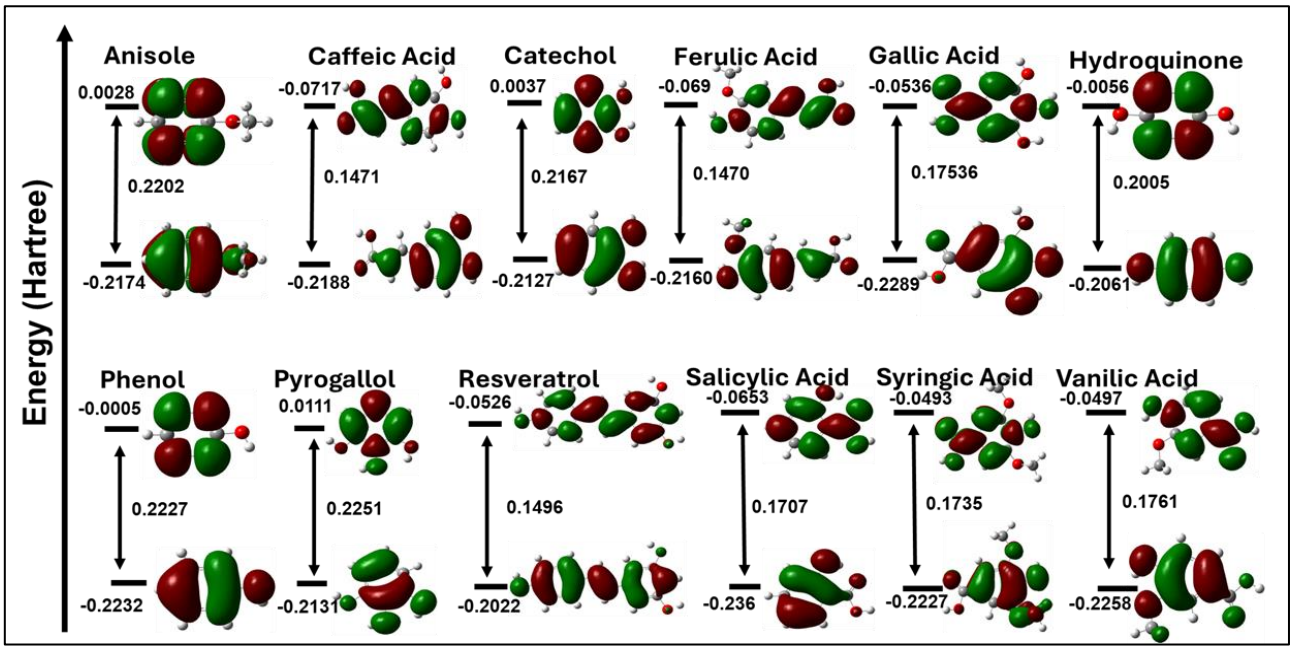


Fig 4 Frontier Molecular Orbital Energies (HOMO, LUMO) and ΔE of the Antioxidant Molecules.

Ferulic acid, caffeic acid, and resveratrol displayed the smallest ΔE, which indicates that relatively little energy is required to promote electrons from the HOMO to the LUMO (Figure 4). This suggests that the molecules are electronically flexible and capable of engaging in charge-transfer interactions with external reactants. This electronic flexibility is desirable because small ΔE values are consistent with their SET behavior. Phenol, pyrogallol, and anisole sat at the other end of the spectrum, displaying the largest ΔE in the series. These larger ΔE reflect more rigid and less reactive electronic structures. Their activity through the HAT mechanism does not depend on a small ΔE but on the stability of their radical forms. For anisole, the large ΔE and the absence of a -OH group together confirm its inertness as a reference compound. Extended conjugation lowers the ΔE and increases SET activity, while compact -OH-rich structures tend to favor HAT activity.

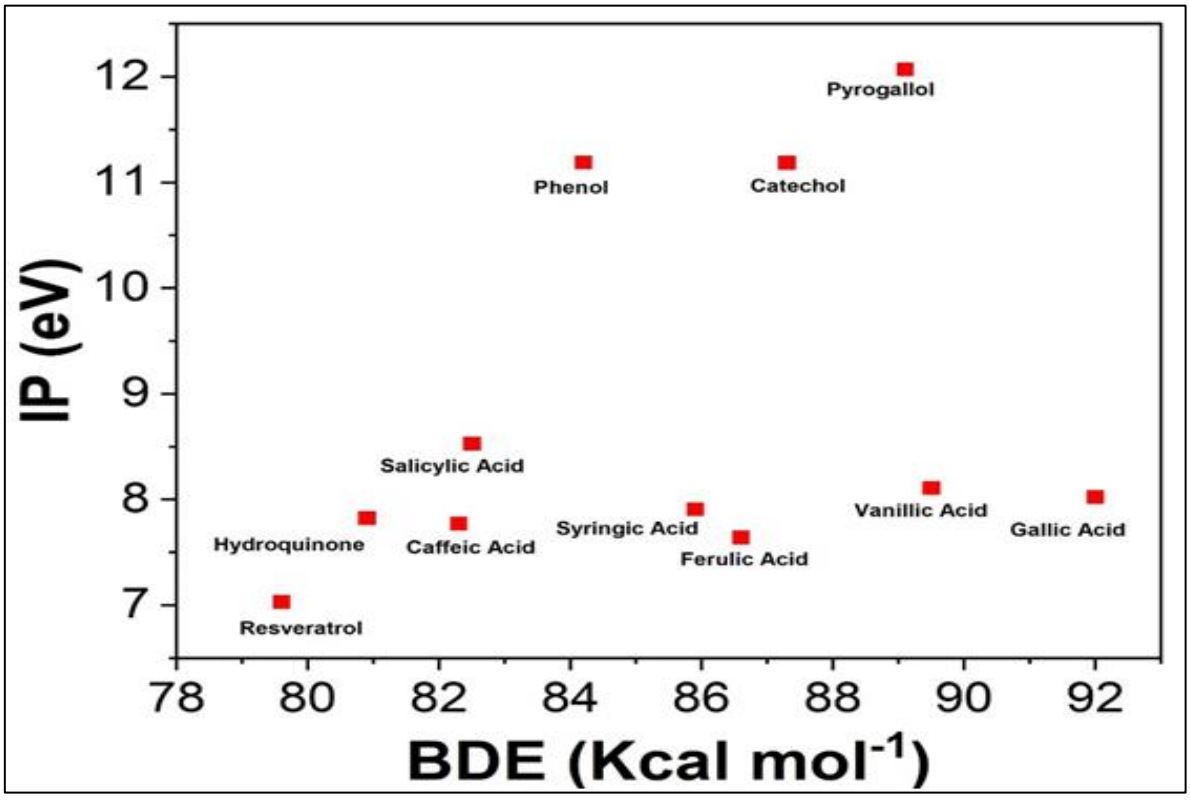


Fig 5 Mechanistic Classification Based on HAT and SET Tendencies.

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The assignment of a mechanistic profile to each of the twelve molecules in the study reveals that these profiles are not absolute. This is because antioxidant mechanisms can vary with respect to solvent, pH, the specific radical species present, and other environmental factors (Figure 5). Hydroquinone and pyrogallol were identified as primarily HAT-active antioxidants. Their structures support hydrogen donation and radical stabilization, and their IPs are not low enough to make them particularly competitive in the SET category. Resveratrol, ferulic acid, and caffeic acid were classified as predominantly SET-active. Their extended π systems, low IPs, and small ΔE collectively indicate that these molecules are outstanding electron donors. Caffeic acid presents an interesting intermediate case. Its structure combines a significant degree of π-conjugation with -OH group in a position that supports efficient HAT, resulting in meaningful activity through both pathways. This kind of dual-mechanism behavior may actually be advantageous in biological contexts, where multiple types of radical species are present simultaneously, and different mechanisms may be more effective against different targets.

The Python-based automation workflow performed reliably throughout the study and delivered the efficiency gains that motivated its development. Given the volume of data involved, with twelve molecules each requiring calculations in three electronic states and analysis of multiple descriptors per state, the manual alternative would have required a substantial and error-prone effort. The automated workflow completed descriptor extraction for all molecules in a fraction of the time that manual processing would have demanded, and did so with a reproducibility that manual transcription cannot match. Beyond the immediate efficiency gains, the automation framework also made it much easier to compare results across molecules and to generate visualizations that clearly communicate trends in the data. Plots of BDE values, ionization potentials, ΔE, and other descriptors across all twelve molecules were generated automatically, making the comparative analysis far more accessible than it would have been from raw numerical tables alone. The development of this workflow also serves a broader purpose within the field. As computational chemistry studies grow in scope and the number of molecules studied in a single investigation increases, automation becomes not merely a convenience but a practical necessity. The framework developed here can be adapted for other antioxidant studies or extended to include additional descriptors, different levels of theory, or larger molecular libraries with relatively modest additional programming effort.

## IV. CONCLUSION

This research realises the investigation of the antioxidant mechanisms of twelve structurally diverse phenolic and aromatic molecules. Calculation of BDE, IP, and FMO descriptors at the B3LYP/6-31G(d,p) level of theory enables a coherent understanding of how molecular structure governs antioxidant activity through both the HAT and SET pathways. Molecules that carry multiple -OH groups supporting resonance stabilization of radicals, such as hydroquinone and pyrogallol, are conducive to HAT activity, whereas molecules with extended π conjugation, such as resveratrol, ferulic acid, and caffeic acid, are suitable for SET activity. Their low IP and the ease with which their electrons can delocalize facilitate the SET pathway effectively. Molecules such as caffeic acid follow both pathways and may function as antioxidants in intricate biological settings. The automation of these calculations, demonstrated using a Python workflow, reduced manual effort in computational antioxidant research without negotiating with the accuracy or depth of analysis. The quantum-chemical descriptors extracted directly from Gaussian output files were automatically used to calculate antioxidant parameters through the proposed workflow.

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