

Deciphering antioxidant activities and mechanisms of catechol analogues through a DFT study

Sefren Geiner Tumilaar

`sefren.geiner.tumilaar@brin.go.id`

National Research and Innovation Agency (BRIN)

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Abstract

Allyl-pyrocatechol and hydroxychavicol are catechol analogues abundant in *Piper betle* that differ only in the position of the allyl group but exhibit distinct antioxidant activities. Density functional theory (DFT) calculations were employed to elucidate their antioxidant behavior and underlying mechanisms. The study was conducted using the B3LYP functional with the 6-31 + G(2d,2p) basis set, incorporating frontier molecular orbital (FMO) analysis, global reactivity descriptors, and evaluation of antioxidant mechanisms including hydrogen atom transfer (HAT), single electron transfer-proton transfer (SET-PT), sequential proton loss electron transfer (SPLET), and transition metal chelation (TMC). Allyl-pyrocatechol exhibits a smaller HOMO–LUMO gap (0.18959 eV) than hydroxychavicol (0.20302 eV), indicating higher reactivity. It predominantly follows HAT (BDE = 3.550 eV) and TMC ($\Delta H_{\text{acidity}} = 14.984$ eV), whereas hydroxychavicol favors SPLET (PA = 15.594 eV). Overall, allyl-pyrocatechol is more reactive, while hydroxychavicol is relatively more stable.

1. Introduction

Catechol are important plant phenolics compounds obtained from the phenylpropanoid pathway of plants that are widely distributed in the leaves and other parts of many plant species belonging to the *Piperaceae* family.^[1–2] They are most abundant in *Piper betle* but are also present in appreciable amounts in *Piper longum* and *Piper nigrum*. In the mid twentieth century, several isolates of catechol compounds namely allyl-pyrocatechol (**1**) and hydroxychavicol (**2**), were first discovered.^[3–4] Allyl-pyrocatechol (**1**) is essentially another name for hydroxychavicol (**2**), featuring its catechol structure with an allyl group.^[5] Hydroxychavicol (**2**) (4-allylpyrocatechol) is a catechol derivative with an allyl side chain.^[6] These compounds have diverse pharmacological effects, especially as antimicrobials, antioxidants, anti-inflammatories, and anticancer.^[7–10] These compounds are very promising for development in pharmaceuticals, cosmetics, and health supplements.^[11–12]

The antioxidant potential of allyl-pyrocatechol (**1**) and hydroxychavicol (**2**) is strongly related to their chemical structure.^[13] The basic structure of these compounds which have two hydroxyl groups (OH) in ortho position (next to each other) on the benzene ring is very effective in scavenging free radicals.^[14–15] In addition, these two structures have allyl ($-\text{CH}_2-\text{CH}=\text{CH}_2$) is a hydrocarbon chain directly attached to the benzene ring that can strengthen bioactivity and increase membrane penetration.^[16] Due the presence of these allyl and OH positions that these two compounds have the potential to be superior free radical scavengers.^[17] Their antioxidant properties, which stem from their ability to neutralize free radicals, help prevent lipid peroxidation and minimize the impact of transition metal ions.^[18] However, despite the well-established role of hydroxyl groups in antioxidant activity, the effect of subtle structural variations, particularly the positional difference of the allyl substituent, on the electronic properties and antioxidant mechanisms of catechol analogues remains poorly understood at the molecular level. Previous studies have largely focused on general antioxidant behavior without providing a detailed,

mechanism-resolved comparison between closely related isomers such as allyl-pyrocatechol and hydroxychavicol.

Free radicals are unstable molecules that contain one or more unpaired electrons and can cause cellular damage if not controlled.^[19–21] Examples include superoxide radical anions ($\text{O}_2^{\bullet-}$) and hydroxyl radicals ($\bullet\text{OH}$). In addition, reactive oxygen species (ROS) also encompass non-radical but highly reactive molecules, such as hydrogen peroxide (H_2O_2), singlet oxygen ($^1\text{O}_2$), and ozone (O_3).^[22] The body has natural antioxidant defense mechanisms, but lifestyle factors can increase oxidative stress, which occurs when ROS production exceeds the antioxidant capacity, leading to cellular damage and physiological disorders.^[23–24] Therefore, extensive research is required to study the antioxidant activity of catechol.^[25]

Nowadays, computational chemistry has become an effective approach to investigate the antioxidant activity of catechol compounds.^[26–29] Compared to experimental and clinical studies, computational methods provide valuable insights at lower cost and shorter time.^[30–31] They can not only help explain debatable experimental results but also predict the chemical behavior and antioxidant activity of new compounds.^[32] In particular, density functional theory (DFT) calculations, as part of quantum chemical methods, play a central role in analyzing the structural, electronic, and reactivity properties of molecules.^[33–36] In such analyses, it is important to consider various factors, including global reactivity parameters, molecular orbital energies, and specific antioxidant mechanisms.^[37]

DFT has been extensively applied in the study of antioxidant mechanisms due to its balance between computational efficiency and accuracy in predicting thermodynamic and electronic properties of small organic molecules. In this study, calculations were performed using the B3LYP functional, which incorporates Becke's exchange functional and the Lee–Yang–Parr correlation functional, known for its reliable performance in modeling radical reactions and hydrogen atom transfer processes.^[38–39] Although newer functionals exist, B3LYP remains widely used for qualitative studies of organic antioxidant molecules due to its reliable geometries and computational efficiency. Recent studies continue to employ B3LYP for evaluating antioxidant activity and metal chelation in phenolic compounds, providing consistent qualitative trends while maintaining computational efficiency.^[40–41] These precedents support the suitability of our approach for analyzing the antioxidant potential of allyl-pyrocatechol (**1**) and hydroxychavicol (**2**).

Although B3LYP is a well-established functional developed earlier, its use remains relevant in contemporary computational studies. Recent research continues to demonstrate its reliability in predicting molecular properties and reactivity. For example, a 2025 study employed B3LYP to investigate the antioxidant activity of *Cola acuminata* phytochemicals, obtaining results consistent with experimental observations.^[42] Similarly, B3LYP has been successfully applied in predicting ^{19}F NMR chemical shifts, showing favorable performance.^[43] These examples highlight that, despite the

availability of newer functionals, B3LYP still provides a reliable balance between computational efficiency and accuracy for small organic molecules, including in antioxidant studies.

It is important to note that while B3LYP is commonly used in computational studies of organic molecules, previous studies have demonstrated that it tends to underestimate ionization potentials and electron affinities when compared to range-separated functionals.^[44–46] Therefore, although B3LYP was used in this study, we acknowledge that for more accurate highest occupied molecular orbital-lowest unoccupied molecular orbital (HOMO-LUMO) energy predictions, range-separated functionals may be preferable.

In general, the mechanism of interaction between free radicals and antioxidants can be explained through four main mechanisms, namely hydrogen atom transfer (HAT), single electron transfer-proton transfer (SET-PT), sequential proton loss electron transfer (SPLET), transition metal chelation (TMC).^[47–48] Nevertheless, a systematic understanding of how minor structural differences influence the preference of specific antioxidant mechanisms (HAT, SET-PT, SPLET, and TMC) is still lacking. In particular, there is limited computational evidence explaining why structurally similar catechol derivatives may exhibit different dominant pathways and reactivity profiles. This gap highlights the need for a comprehensive theoretical investigation that integrates electronic structure analysis with mechanism-based evaluation. Therefore, in this research we aim to obtain and compare in-depth knowledge of structural aspects, conformational features, and electronic analyses of allyl-pyrocatechol (**1**) and hydroxychavicol (**2**), primarily based upon B3LYP functional with 6–31 + G (2d,2p) basis set in the gas phase.^[49] In addition, this study focused on analyzing four antioxidant mechanisms centered on one OH group and discussing the influence of the position difference of the allyl group on the OH group. In continuation of our previous works, the results of this study will be compared with the results of previous studies on in vitro antioxidants. We deciphering distinct about the structure activity relationship between allyl-pyrocatechol (**1**) and hydroxychavicol (**2**) based on computational chemistry.

2. Computational method

The calculations were performed using Gaussian 09 software.^[50–51] Geometry optimization and frequency calculations were performed using the DFT method with the B3LYP functional and the 6–31 + G(2d,2p) basis set without symmetry restrictions. This basis set was chosen due to its well-established balance between computational efficiency and accuracy in predicting thermochemical and electronic properties of small organic molecules, especially in radical-based antioxidant mechanisms. The diffuse functions (+) and polarization functions (2d,2p) are essential to accurately describe electron delocalization and bond dissociation processes relevant in all antioxidant mechanism. A similar approach was successfully applied by Ma and Wang,^[52] in studying the antioxidant activity of polyphenolics, where the use of this basis set allowed for reliable calculation of bond dissociation enthalpy (BDE), which showed a strong correlation with antioxidant potency. The minimum structure was confirmed to be the real state as no imaginary frequencies were found. Furthermore, single point

energies were calculated for the most stable geometry in the gas phase using the DFT method with the B3LYP functional and the 6-31 + G(2d,2p) basis set. The 6-31 + G(2d,2p) basis set is a split-valence double- ζ basis that includes diffuse functions to account for electron delocalization and anion/radical states, as well as double sets of polarization functions (d for heavy atoms and p for hydrogen) to better describe molecular flexibility and reactivity. This level of theory has been demonstrated to provide a computational cost for structural optimization, orbital analysis, and reactivity descriptors of antioxidant compounds.^[53] This functional and basis set level of theory was employed as it balances computational efficiency and accuracy and is commonly used in antioxidant and structure–activity studies. However, this basis set has notable limitations that must be acknowledged. It does not reach basis set convergence and may yield less reliable thermochemical and noncovalent interaction energies compared with larger triple- ζ sets.^[54] Benchmarking studies also indicate notable errors in properties such as electron affinity.^[55] Therefore, the energies reported here should be regarded as qualitative indicators of trends rather than precise quantitative predictions. All visualizations were performed using GaussView 9.0. Additionally, the computations were executed on an Intel® Core™ i7-9700K with 32 GB RAM running Windows 10 Pro OS.

2.1. Chemical structure refinement

Firstly, to refine the chemical structures, a limited conformational analysis was carried out by rotating the OH group at position 1 (O-H rotation) in both allyl-pyrocatechol (**1**) and hydroxychavicol (**2**) and the lowest-energy geometries without imaginary frequencies were retained for subsequent calculations. Figure 1 is a structural drawing of allyl-pyrocatechol (**1**) and hydroxychavicol (**2**). Figure 2 shows the optimized chemical structures of allyl-pyrocatechol (**1**) and hydroxychavicol (**2**). The presence of intramolecular hydrogen bonding is one feature that contributes to the stability of the selected structures.^[56]

2.2. Frontier molecular orbital (FMO) analysis

FMO which are vital in establishing a compound's electronic and chemical characteristics, are specifically formed by the HOMO and LUMO.^[57] Using density functional theory (DFT), FMO in catechol have been analyzed, and their energy gap have been computed. A greater degree of molecular reactivity is indicated by a smaller HOMO–LUMO gap.^[58] The energy gap (E_{gap}) is calculated using Eq. 1:

$$E_{\text{gap}} = E_{\text{LUMO}} - E_{\text{HOMO}} \quad (1)$$

Higher HOMO values suggest stronger electron donor ability, whereas lower HOMO values indicate weaker electron donor ability. This is the relationship between HOMO and the mechanism of action of antioxidants. Furthermore, HOMO-LUMO studies are vital for comprehending antioxidant activity since electron transfer contributes to the hydrogen abstraction process.^[59]

2.3. Global reactivity electronic descriptors

Global reactivity electronic descriptors are those that describe catechol's reactivity and its link to changes in external environments.^[60–61] By computing these characteristics, the reactivity of allyl-pyrocatechol (**1**) may be compared to that of hydroxychavicol (**2**), making this method useful for understanding the reactive properties of diverse compounds.

The global reactivity descriptors employed include ionization potential (I), electron affinity (A), hardness (η), softness (S), electronegativity (χ), chemical potential (μ), and electrophilicity index (ω). These characteristics are determined by the quantity of electrons and the electron density, both of which can vary due to external factors.^[62–63] Global reactivity descriptors can be calculated by energy vertical method. The energy vertical technique considers the overall energy difference between neutral molecules and the corresponding anions and cations. The equations for calculating ionization potential (I), electron affinity (A), and the global reactivity descriptors were computed by using the equations given below:

$$I = E_{\text{cation}} - E_{\text{neutral}} \quad (2)$$

$$A = E_{\text{neutral}} - E_{\text{anion}} \quad (3)$$

$$\eta = (I - A)^{1/2} \quad (4)$$

$$S = 1/(2\eta) \quad (5)$$

$$\chi = (I + A)^{1/2} \quad (6)$$

$$\mu = -\chi \quad (7)$$

$$\omega = \mu^2/2 \quad (8)$$

2.4. Antioxidant activity mechanism

The four methods of action of catechol antioxidants can be explained using the following equation. To simplify the explanation, the term ArOH is utilized to denote antioxidant molecules.^[56] We used the published enthalpy values of 3.145 kJ/mol for $H(e^-)$ and 6.197 kJ/mol for $H(H^+)$ during computation.^[64]

2.4.1. Hydrogen atom transfer (HAT)

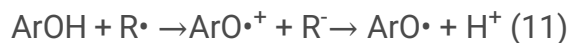
In this method, the antioxidant component combines directly with the free radical, neutralizing it, while the phenolic antioxidant changes to a radical form. This mechanism involves HAT (Eq. 9), in which the antioxidant molecule (ArOH) contributes a hydrogen atom to the free radical. This mechanism's numerical parameter is the BDE. A lower BDE score implies that the antioxidant is better at neutralizing free radicals (Eq. 10).^[65]



$$\text{BDE} = H(\text{ArO}^\bullet) + H(\text{H}^\bullet) - H(\text{ArOH}) \quad (10)$$

2.4.2. Single electron transfer–proton transfer (SET-PT)

This process takes place in two stages. In the initial stage, free radical cations are formed due to electron transfer from neutral species (Eq. 11). In the next stage, the phenolic radical cation undergoes decomposition into phenolic radicals and protons (Eq. 11).^[66]



The numeric parameter connected with this stage is ionization potential (IP) (Eq. 12) and proton dissociation energy (PDE) (Eq. 13).

$$\text{IP} = \text{H}(\text{ArO}^{\bullet+}) + \text{H}(\text{e}^-) - \text{H}(\text{ArOH}) \quad (12)$$

$$\text{PDE} = \text{H}(\text{ArO}^\bullet) + \text{H}(\text{H}^+) - \text{H}(\text{ArO}^{\bullet+}) \quad (13)$$

2.4.3. Sequential proton loss electron transfer (SPLET)

Phenolic antioxidants split into protons and anions in the first stage of the SPLET process. Additionally, free radicals will react with the ions created in the initial stage (Eq. 14). The proton affinity (PA) is represented by the first step, which may be computed using Eq. 15. The next parameter for the second step electron transfer enthalpy (ETE) can be calculated by the Eq. 16.^[67]

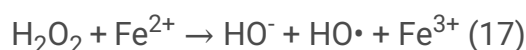


$$\text{PA} = \text{H}(\text{ArO}^-) + \text{H}(\text{H}^+) - \text{H}(\text{ArOH}) \quad (15)$$

$$\text{ETE} = \text{H}(\text{ArO}^\bullet) + \text{H}(\text{e}^-) - \text{H}(\text{ArO}^-) \quad (16)$$

2.4.4. Transition metal chelation (TMC)

The mechanism is based on the Fenton reaction for example in Eq. 17,^[56, 68] which occurs when hydrogen peroxide (H_2O_2) is present and metals in a low oxidation state can produce free radicals.



Polyphenols anions have a strong propensity to chelate, or bind, with heavy metals. The generation of H^+ ions in this mechanism is considered since the chelation process is linked to the synthesis of anion by deprotonation. The deprotonation of OH groups in the polyphenol structure is what causes the metal chelation process.^[69] Thus, the following formula can be used to define a molecule's capacity to release protons (H^+) (Eq. 18). The numeric parameter connected with this mechanism is enthalpy alterations of acidity ($\Delta\text{H}_{\text{acidity}}$) (Eq. 19).



$$\Delta H_{\text{acidity}} = H(\text{ArO}^-) - H(\text{ArOH}) \quad (19)$$

3. Result and discussions

3.1. Chemical structure refinement

Prior to optimization, this study only examined the activity and mechanism of one OH group in these two compound structures. This is because the catechol structural system, which in fact has two OH groups, can contribute to antioxidant activity but only one OH group is usually more dominant in releasing hydrogen, depending on the environment and other substituents.^[27] According to research by Apak et al.^[65], which describes the difference in antioxidant activity of phenolic compounds with two OH groups through BDE values. The OH group with lower BDE will more easily release hydrogen and act as the main antioxidant. This is also in line with other studies which state that in SET-PT and SPLET mechanisms, both OH groups can play a role, but one group may be more effective in releasing protons than the other.^[66] Therefore, analysis is often focused on the more reactive OH group to understand the antioxidant mechanism more specifically.

Next, possible spatial structures were drawn and optimized individually. The potential energy of each conformer was determined, and the conformer with the lowest potential energy was chosen for additional calculations. Figure 2 shows the optimal chemical structure of allyl-pyrocatechol (**1**) and hydroxychavicol (**2**). The presence of intramolecular hydrogen bonding could add to the stability of the chosen structure.^[70]

Intramolecular hydrogen bonding was observed in both allyl-pyrocatechol (**1**) and hydroxychavicol (**2**), particularly of the OH groups at position one. The optimized geometries showed H $\cdots$ O distances in the range of 1.78–1.90 Å and H $\cdots$ O at position one with angles of approximately 150–170°, which are consistent with moderate to strong intramolecular hydrogen bonding. These interactions contribute to the stabilization of the lowest-energy conformers and slightly reduce the HOMO-LUMO, thereby enhancing the electron-donating ability of the OH groups. As a result, intramolecular hydrogen bonding plays a crucial role in modulating the reactivity descriptors and antioxidant potential of both compounds.

According to research, chemical structural features such as stereochemistry, bond length, and, in particular, one OH group interactions play an important role in free radical scavenging methods.^[71] In this study, we present the results of molecular geometry calculations performed on two catechol derivatives: allyl-pyrocatechol (**1**) and hydroxychavicol (**2**), using the DFT method with the B3LYP functional and the 6–31 + G(2d,2p) basis set.

It should be noted that all calculations in this study were carried out in the gas phase. Although this approach allows us to capture the intrinsic structural and electronic features of the molecules, it neglects solvent effects that can significantly influence thermochemistry and reactivity, especially in biological environments. Continuum solvation models such as Polarizable Continuum Model (PCM) or

Solvation Model based on Density (SMD) have been shown to provide more realistic predictions in gas phases.^[72–73] Therefore, the present results should be interpreted as qualitative indicators of intrinsic reactivity, with the inclusion of solvation models reserved for future work.

The present work focused on reactivity indexes and global electronic descriptors, which provide a preliminary insight into the antioxidant potential of allyl-pyrocatechol (**1**) and hydroxychavicol (**2**). However, this approach does not explicitly account for the properties of radical counterparts (e.g., $\cdot\text{OH}$, $\text{O}_2\cdot^-$, $\text{ROO}\cdot$) or the kinetic aspects of the reactions, which are crucial for predicting antioxidant efficiency and determining the relative importance of different mechanisms and reaction sites. Therefore, the present results should be interpreted as intrinsic indicators of reactivity. The primary goal of this study was to elucidate the structural and electronic differences between allyl-pyrocatechol (**1**) and hydroxychavicol (**2**), rather than to provide a complete quantitative prediction of antioxidant activity. Future studies will extend the scope to radical-specific reaction pathways and kinetic modeling for a more comprehensive assessment.

Before and after optimization.

3.2. Frontier molecular orbital (FMO) analysis

According to the frontier molecular orbital theory, interaction of HOMO and LUMO orbitals plays an important role in the development of transition states.^[74] The negative HOMO energy value corresponds to the vertical ionization potential, whereas the negative LUMO value reflects vertical electron affinity. The presence of various functional groups on the phenyl ring also has an effect on the HOMO and LUMO energy.^[75]

Based on Fig. 3 the HOMO-LUMO calculation results, the E_{gap} value can be used to examine the reactivity and stability of allyl-pyrocatechol (**1**) and hydroxychavicol (**2**). If the E_{gap} value is small, the molecules react more easily. But if the E_{gap} value is large, the molecule is more stable and less prone to change. Allyl-pyrocatechol (**1**) has an E_{gap} of 0.18959 eV, which is lower than hydroxychavicol (**2**) at 0.20302 eV, indicating that this compound is more reactive. In addition, the HOMO values for both compounds are similar – 0.21878 eV for allyl-pyrocatechol (**1**) and – 0.21866 eV for hydroxychavicol (**2**), indicating that their electron donor capacity is essentially equivalent. However, the difference in LUMO values is more significant, with allyl-pyrocatechol (**1**) having a lower value (–0.02919 eV) than hydroxychavicol (**2**) (–0.01564 eV), indicating a greater ability to accept electrons. Thus, it can be concluded that allyl-pyrocatechol (**1**) has more reactivity or can be used as an antioxidant, but hydroxychavicol (**2**) has greater stability, making it more appropriate for applications that require higher chemical resistance.

using the DFT method with the B3LYP functional and the 6–31 + G(2d,2p) basis set.

3.3. Global reactivity electronic descriptors

The electronic properties of allyl-pyrocatechol (**1**) and hydroxychavicol (**2**) are studied by looking at several things, such as how easy it is to give off electrons (I), how good it is at accepting electrons (A), how strong it is at surviving changes (η), how good it is at attracting electrons (χ), how easy it is to change shape (S), how easy it is to lose electrons (μ), how good it is at accepting electrons in reactions (ω), how good it is at giving electrons (ω^-). All of this contributes to a better understanding of the two molecules' reactions and stability as shown in Fig. 4.

Global hardness (η) is like a shield for the molecule so that it doesn't change easily when there is a charge transfer.^[76] Thus, the higher the hardness value, the stronger the molecule is to resist changes due to electron attack. If the hardness is high, the molecule is more stable and less likely to be reactive when a small disturbance occurs during a chemical reaction. According to Fig. 4, hydroxychavicol (**2**) (4.33 eV) has a higher hardness than allyl-pyrocatechol (**1**) (3.42 eV). Thus, hydroxychavicol (**2**) is more resistant to electromagnetic interference and has a higher chemical stability.

Electron affinity (A) and hardness (η) are closely related to a molecule's electronic characteristics. In general, molecules with higher electron affinity (more positive values) have lower hardness, indicating a better ability to take electrons. Molecules with lower electron affinity (more negative values) have higher hardness, indicating greater resistance to electronic interference and chemical stability.^[77] As presented in Fig. 4, a clear difference can be observed: hydroxychavicol (**2**) has a negative electron affinity (-0.74 eV), indicating a lower propensity to accept electrons, while allyl-pyrocatechol (**1**) has a positive electron affinity (1.00 eV), indicating a higher ability to accept electrons. This correlation confirms the inverse relationship between electron affinity and molecular hardness, where an increase in the ability to accept electrons is inversely proportional to the level of molecular hardness.

Softness (S), the reciprocal of hardness (η), indicates how readily a molecule can accept or donate electrons. It reflects the chemical reactivity of the molecule, and is influenced by its functional groups.^[78] Because it is softer than hydroxychavicol (**1**) (0.12 eV), allyl-pyrocatechol (**1**) (0.15 eV) combines with other substances more readily. Additionally, allyl-pyrocatechol (**1**) has a higher value (9.80 eV) than hydroxychavicol (**2**) (6.41 eV) when examining the electrophilicity index (ω). This indicates that allyl-pyrocatechol (**1**) is an electrophile that is more active in reactions and prefers to receive electrons. The electrophilicity index indicates how intensely a molecule wants to attract electrons.^[61]

Instead of referring to molecular electronegativity, the electronic distribution and polarity of the molecule were analyzed to assess its tendency to donate or accept electrons, which relates to antioxidant reactivity.^[79] Allyl-pyrocatechol (**1**) (4.43 eV) is higher than hydroxychavicol (**2**) (3.58 eV), so allyl-pyrocatechol (**1**) prefers to attract electrons. The chemical potential (μ) also says the same thing. Chemical potential is analogous to the ease with which electrons can escape equilibrium.^[80] Allyl-pyrocatechol (**1**) has a lower chemical potential (-4.43 eV) than hydroxychavicol (**2**) (-3.58 eV), so it is easier to meet and react with compounds that like to give electrons (nucleophiles).

The capacity to donor electrons (ω^-) and acceptor electrons (ω^+) demonstrates how molecules interact.^[81] Allyl-pyrocatechol (**1**) donates electrons better than hydroxychavicol (**2**) because it gives electrons at a higher energy (5.50 eV). Allyl-pyrocatechol (**1**) is also more effective at collecting electrons (1.08 eV) than hydroxychavicol (**2**) (0.23 eV), making it an easier electrophile.

Ionization potential is similar to the energy required to remove an electron from a molecule.^[82] Hydroxychavicol (**2**) has a slightly greater ionization potential (7.91 eV) than allyl-pyrocatechol (**1**) (7.85 eV). This indicates hydroxychavicol (**2**) that requires more energy to lose electrons, making it more stable than allyl-pyrocatechol (**1**).

molecules using the DFT method with the B3LYP functional and the 6–31 + G(2d,2p) basis set.

3.4. Antioxidant activity mechanism

3.4.1. Hydrogen atom transfer (HAT)

In this method, each chemical contributes a hydrogen atom to the HAT process, which uses homolytic cleavage to trap free radicals. BDE is a key quantity for understanding how the HAT mechanism operates. If the BDE is minimal, the HAT reaction happens quickly, increasing the compound's antioxidant activity. The OH bond in phenolic compounds contributes significantly to antioxidant action.^[83–84] From Table 1, The BDE value of allyl-pyrocatechol (**1**) is 3.550 eV, which is lower than that of hydroxychavicol (**2**), which is 3.906 eV. This suggests that allyl-pyrocatechol (**1**) can transfer hydrogen atoms more easily, making it more effective in neutralizing free radicals than hydroxychavicol (**2**). Thus, according to the HAT mechanism, allyl-pyrocatechol (**1**) is expected to have more antioxidant activity than hydroxychavicol (**2**).

Table 1

Numerical parameters relate to all conceivable antioxidant processes of catechol molecules in the gas phase using the DFT method with the B3LYP functional and the 6–31 + G(2d,2p) basis set level of theory.

Molecules	Energy (eV)						
	Bond	BDE	IP	PDE	PA	ETE	$\Delta H_{\text{acidity}}$
Allyl-pyrocatechol (1)	1-OH	3.550	7.629	17.229	15.049	2.213	14.984
Hydroxychavicol (2)	1-OH	3.906	7.623	9.993	15.594	2.022	15.529

3.4.2. Single electron transfer-proton transfer (SET-PT)

Antioxidants can also trap free radicals via SET-PT.^[85] This procedure involves two steps. Step one: Antioxidant molecules emit electrons, which can be detected using IP. Step two: After losing an electron, the molecule transforms into a cation radical, which releases a proton. This process can be quantified using PDE.^[30, 86] Table 1 shows the IP and PDE values for 1 O-H in the cation radicals of the investigated compounds. Both compounds had relatively similar IP values, 7.629 eV for allyl-pyrocatechol (**1**) and

7.623 eV for hydroxychavicol (**2**), showing no major difference in electron donation ability in the SET mechanism. The PDE parameter shows that hydroxychavicol (**2**) has a lower PDE of 9.993 eV than allyl-pyrocatechol (**1**) (17.229 eV). A smaller PDE indicates quicker proton dissociation, implying that Hydroxychavicol (**2**) could be more effective in radical stabilization via proton donation.

3.4.3. Sequential proton loss electron transfer (SPLET)

SPLET is critical for trapping free radicals in polyphenolic compounds, particularly in polar settings. This method involves two steps: In the step one, the molecule loses a proton, as determined by PA. Second step: After losing a proton, the molecule transforms into a phenoxide anion, which then releases an electron. This process is quantified using ETE.^[87–88] Table 1 shows the PA and ETE values for the investigated substances in the gas phase.

PA measures how well a molecule accepts protons after producing a radical. Hydroxychavicol (**2**) has a higher PA with value 15.594 eV than allyl-pyrocatechol (**1**) with value 15.049 eV, indicating that it is more stable after grabbing a proton. ETE refers to a molecule's ability to give away electrons. Allyl-pyrocatechol (**1**) has a greater ETE (2.213 eV) than hydroxychavicol (**2**) (2.022 eV), making it easier to donate electrons during oxidative circumstances.

3.4.4. Transition metal chelation (TMC)

$\Delta H_{\text{acidity}}$ is like a measure of how easily a molecule releases protons (H^+). This is important to know how well the compound can capture metal ions such as iron (Fe^{2+}). A low $\Delta H_{\text{acidity}}$ value causes the molecule to easily release protons and change into the negatively charged phenolate anion. This form is extremely significant because it can easily interact with and connect to transition metal ions, resulting in strong interactions.^[89–90] Compounds with low $\Delta H_{\text{acidity}}$ are more effective in binding metals and may exhibit greater antioxidant action through metal chelation processes. High $\Delta H_{\text{acidity}}$ makes it harder for the molecule to release protons, resulting in fewer negatively charged ions. As a result, its ability to collect and bind transition metal ions is diminished, making it less efficient at mitigating the oxidative stress caused by those metals. Based on Table 1, $\Delta H_{\text{acidity}}$ measures the energy needed to release protons. Hydroxychavicol (**2**) has a greater $\Delta H_{\text{acidity}}$ (15.529 eV) than allyl-pyrocatechol (**1**) (14.984 eV), making it more difficult to release protons. As a result, it is less likely to become negatively charged than allyl-pyrocatechol (**1**).

In summary, this study provided interesting or unexpected results. Although allyl-pyrocatechol (**1**) and hydroxychavicol (**2**) have the same core catechol structure, their antioxidant mechanisms are not identical based on the computational results in this study. The computational results show that allyl-pyrocatechol (**1**) is more dominant in the HAT and TMC mechanisms while hydroxychavicol (**2**) is more dominant in the SPLET mechanism. This factor is influenced by the better stabilization effect of phenoxyl radical on allyl-pyrocatechol (**1**) as well as the optimal *ortho*-OH structure for metal ion chelation. while hydroxychavicol is influenced by the electron induction effect of allyl which reduces the acidity of -OH, as well as the tendency to form phenolate before electron transfer.

3.5. Structure activity relationship based on distinct of position allyl group

Allyl-pyrocatechol (**1**) and hydroxychavicol (**2**) are phenolic group catechol compounds that both have antioxidant activity. This is highly dependent on the stability of the phenolate radical formed after releasing the hydrogen atom.^[91] Allyl-pyrocatechol (**1**) has two contiguous OH groups in the benzene system, so after losing one proton, the remaining electrons can be better delocalized through the resonance effect. Hydroxychavicol (**2**) also has two OH groups, but its allyl substituent structure slightly interferes with electron delocalization, so its radical stabilization is less effective than allyl-pyrocatechol (**1**).^[92] With better resonance, allyl-pyrocatechol (**1**) phenolate radicals are more stable, making it easier to donate hydrogen to capture free radicals in the HAT mechanism.

The allyl group ($-\text{CH}_2-\text{CH}=\text{CH}_2$) in the compound hydroxychavicol (**2**) has an induction effect (+I). This means it can push electrons to the benzene ring. The existence of this induction effect reduces the electronegativity of the benzene ring slightly, making hydroxychavicol (**2**) less effective in releasing protons and capturing free radicals. Meanwhile, allyl-pyrocatechol (**1**) has an allyl substituent that cannot provide a strong induction effect, so proton release is easier to occur.^[93]

Despite the allyl group's proximity to OH, allyl-pyrocatechol (**1**) is more prevalent in HAT and TMC because the phenoxyl radical resonance is more persistent following H release. TMC continues to be effective because this closeness does not prevent metal ion chelation. Because the induction effect is weaker and facilitates simpler proton release (greater PA), hydroxychavicol (**2**) is more prevalent in SPLET. Resonance stabilization improves with proton loss, favoring SPLET over HAT. The induction effect, radical stabilization, and steric interactions are all significantly impacted by the allyl group's location, which ultimately determines which antioxidant mechanism is more prevalent in each chemical.

In addition, the compounds allyl-pyrocatechol (**1**) and hydroxychavicol (**2**) are derived from a similar biosynthetic pathway, namely from phenylpropanoid metabolism in plants such as *P. betle*.^[94] In its biosynthesis, hydroxychavicol (**2**) is a precursor in the formation of allyl-pyrocatechol (**1**). This means that allyl-pyrocatechol (**1**) is the more oxidized form, which often correlates with increased antioxidant activity. More oxidized compounds tend to be more ready to donate electrons or hydrogen, which is important in antioxidant mechanisms.^[95]

In comparison with our previous research, in the in vitro test, allyl-pyrocatechol (**1**) has a lower IC_{50} in the DPPH test of 37.94 $\mu\text{g/mL}$ than hydroxychavicol (**2**) with an IC_{50} DPPH value of 44.25 $\mu\text{g/mL}$. The lower IC_{50} value indicates that allyl-pyrocatechol (**1**) is more effective in counteracting free radicals than hydroxychavicol (**2**). Overall, both experimental data and computational simulations show that allyl-pyrocatechol (**1**) has more potential as an antioxidant than hydroxychavicol (**2**).

Furthermore, our computational findings were confirmed or validated by previous experimental results from previous research that indicate allyl-pyrocatechol (**1**) exhibits higher antioxidant activity than

hydroxychavicol (**2**). These experimental studies supported our theoretical predictions and confirmed the relevance of our computational approach. Hence, our study provides an integrative analysis that combines quantum chemical computations and biological relevance to validate the antioxidant potential of the studied compounds.

4. Conclusion

This study provides computational insight into the antioxidant behavior of allyl-pyrocatechol (**1**) and hydroxychavicol (**2**) using the DFT method with the B3LYP functional and the 6–31 + G(2d,2p) basis set, highlighting for the first time the mechanistic differences-HAT, SET-PT, SPLET, and TMC-between these structurally related catechols. Allyl-pyrocatechol (**1**) demonstrates stronger hydrogen atom donation in HAT and greater potential for transition metal chelation, while hydroxychavicol (**2**) is more favorable in SPLET, with these differences attributed to the electronic influence of the allyl group on OH reactivity. As the present results are derived from gas-phase reactivity descriptors without explicit solvation, radical counterpart, or kinetic considerations, the reported energies should be interpreted as qualitative trends rather than precise quantitative values. Nevertheless, the findings align with experimental observations and provide a useful framework, while future studies incorporating solvation models, radical-specific pathways, and kinetic simulations are needed for a more comprehensive evaluation of antioxidant potential.

Declarations

CrediT authorship contribution statement

Sefren Geiner Tumilaar: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing - original draft, Writing – review and editing.

Declaration of competing interest

Author have no competing interests to declare.

Data availability statement

No data was used for the research described in the article.

Declaration of funding statement

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Figures

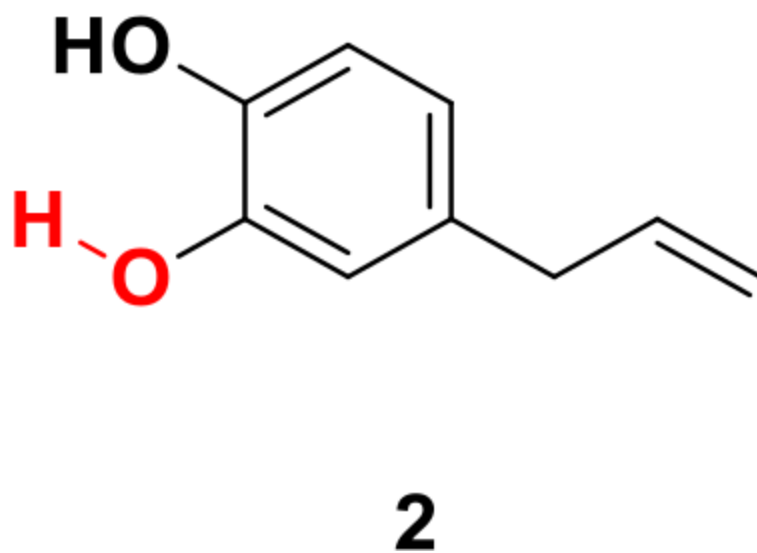
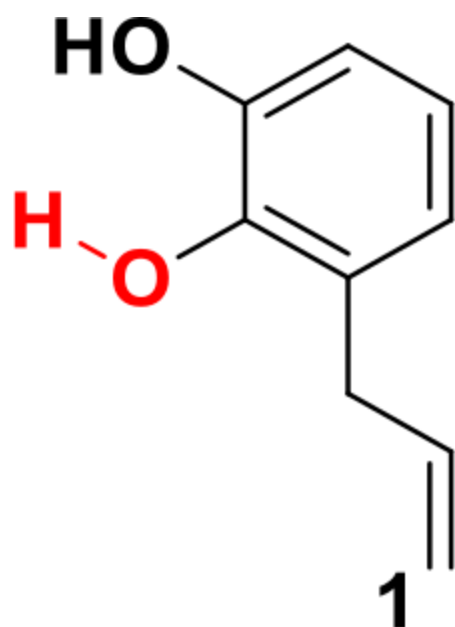
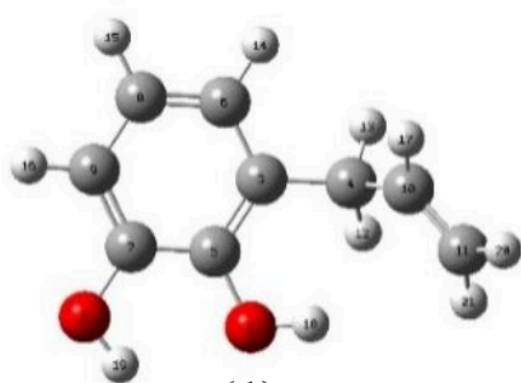
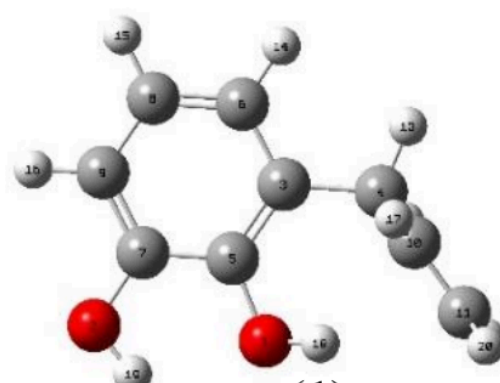


Figure 1

Chemical structure of allyl-pyrocatechol (1) and hydroxychavicol (2)



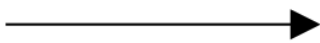
(1)
Before optimization



(1)
After optimization



(2)
Before optimization



(2)
After optimization

Figure 2

Schematic representation of the structure allyl-pyrocatechol (1) and hydroxychavicol (2):

Before and after optimization.

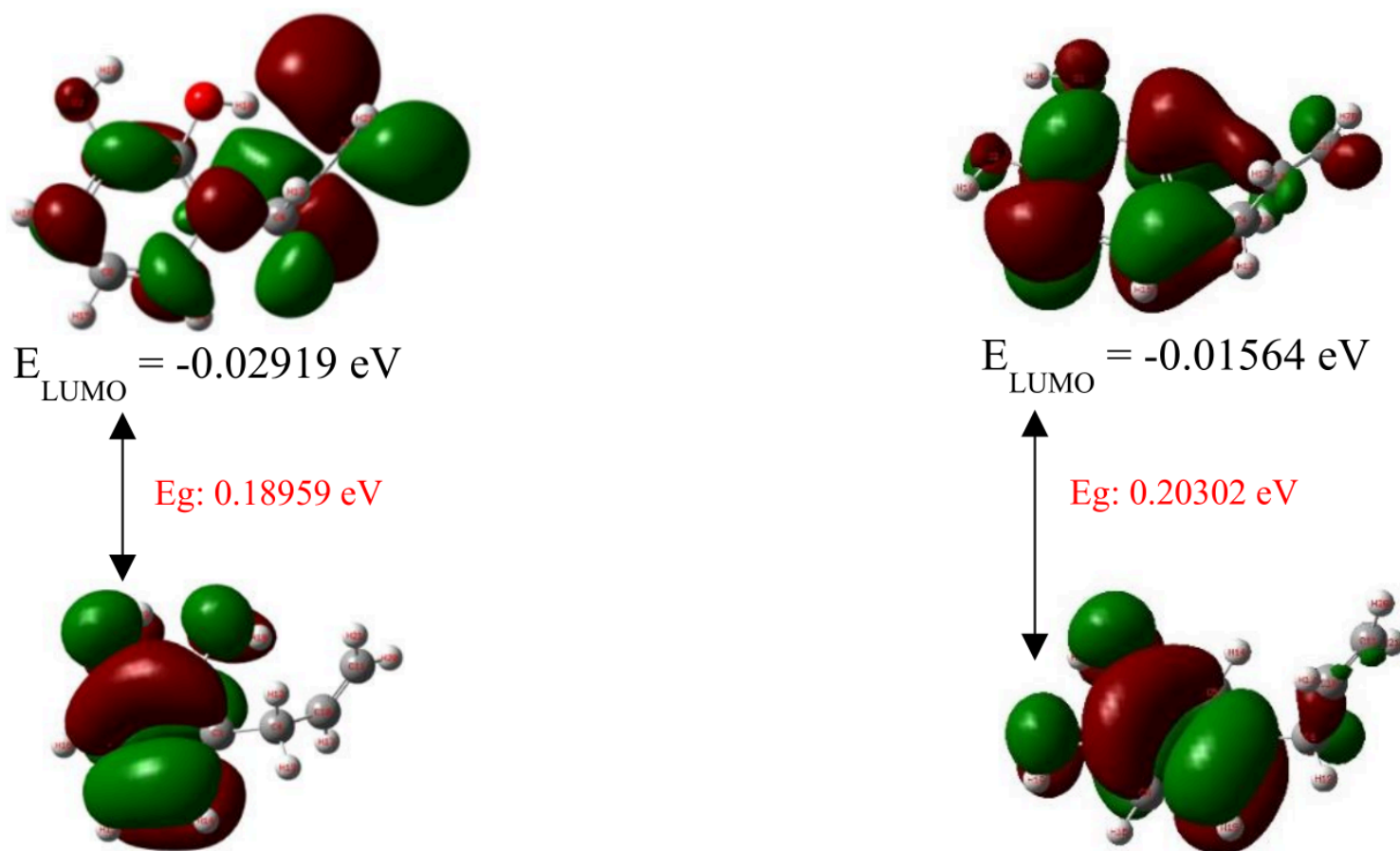


Figure 3

HOMO, LUMO, and Egap profiles of allyl-pyrocatechol (1) and hydroxychavicol (2) molecules

using the DFT method with the B3LYP functional and the 6-31+G(2d,2p) basis set.

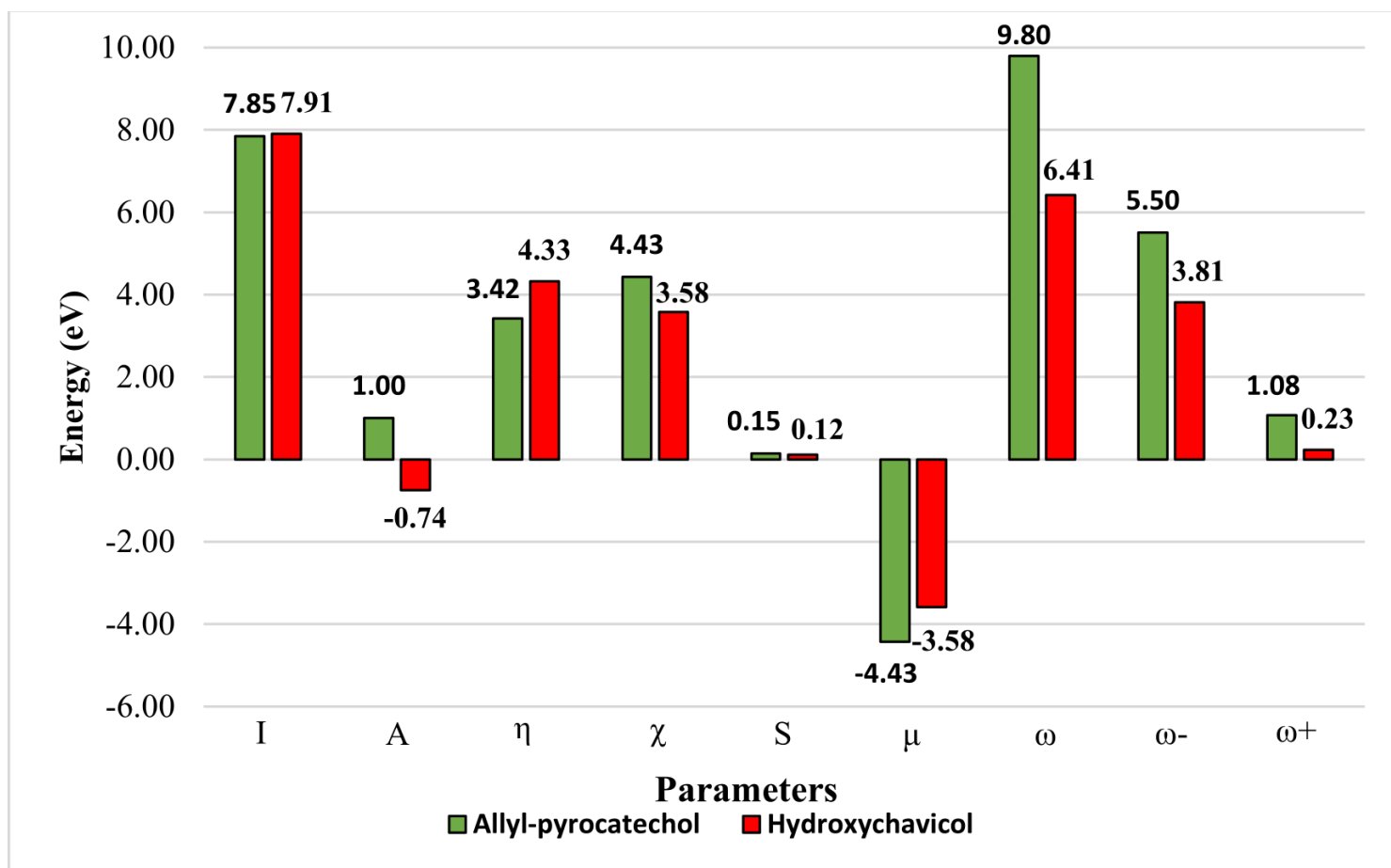


Figure 4

Global reactivity electronic descriptors of allyl-pyrocatechol (1) and hydroxychavicol (2) molecules using the DFT method with the B3LYP functional and the 6-31+G(2d,2p) basis set.