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Short Communication

DFT-Based Investigation of a Natural Flavonoid as a Potential Oxidative Stress Regulator

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Abstract

Oxidative stress is a major contributing factor in the pathogenesis of various chronic diseases, particularly cardiovascular disorders. Natural flavonoid compounds have gained attention due to their ability to modulate oxidative stress pathways. In this study, we present a computational analysis of a flavonoid-derived molecule, 3'-hydroxy-5,7-dimethoxy-4-O-2'-cycloflavan, using Density Functional Theory (DFT). The molecular geometry was optimized using the B3LYP/6-31G(d) basis set via Gaussian 09 software. Key electronic properties such as HOMO-LUMO gap, dipole moment, and molecular electrostatic potential (ESP) were evaluated to assess the antioxidant potential of the molecule.

Key Words: DFT; flavonoid; oxidative stress; antioxidant activity; HOMO-LUMO

1. Introduction

Oxidative stress [1], resulting from an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses, plays a central role in the onset and progression of chronic diseases such as cardiovascular [2], neurodegenerative [3], and inflammatory [4] disorders. Flavonoids, a diverse group of plant-derived polyphenolic compounds, have demonstrated strong antioxidant properties through free radical scavenging, metal chelation, and modulation of enzymatic pathways [5].

3'-Hydroxy-5,7-dimethoxy-4-O-2'-cycloflavan is a naturally derived flavonoid-like compound that possesses multiple functional groups conducive to electron donation and delocalization. This study employs a quantum chemical approach to investigate the electronic and structural properties of this molecule and evaluate its theoretical potential as an oxidative stress regulator.

2. Computational Analysis Methodology

The molecular structure of the compound in its lowest energy configuration was simulated using the Gaussian 09W software suite [6]. To accurately capture the intricate interplay between molecular forces and electronic distributions, Density Functional Theory (DFT) techniques were applied. The extensive computational results were then thoroughly examined and graphically represented with the aid of Gaussian View 5 visualization software [7], enabling an in-depth insight into the molecule's behavior.

All calculations employed the B3LYP hybrid functional, which integrates Becke's exchange functional with the LYP correlation component [8]. This approach was complemented by the adoption of the 6-311++G(d,p) basis set [9], recognized for its robustness in modeling electronic properties and reaction energetics of molecular systems. The use of this basis set provided a detailed perspective on molecular interactions, thereby improving the reliability of the findings.

3. Results and Discussion

3.1. Electronic Properties

Quantum chemical computational techniques such as Density Functional Theory (DFT) allow for precise calculation of molecular orbitals. In this research, the E_{HOMO} and E_{LUMO} energy levels of the flavan-containing molecule were determined using the DFT approach. These values were then used to calculate important electronic parameters including the energy gap (ΔE), electron affinity (A), ionization potential (I), electronegativity (χ), chemical softness (S), and chemical hardness (η) based on electron density-derived formulas. The summarized results are presented in Table 1.

Table 1. Molecular orbital energy calculations of the flavan-based molecule.

Parameter	**B3LYP /6-311++G(d,p)**
E_{HOMO} (eV)	-5.85
E_{LUMO} (eV)	-0.57
$\Delta E = E_{LUMO} - E_{HOMO}$ (eV)	5.28
Ionization Potential, I (eV)	5.85
Electron Affinity, A (eV)	0.57
Electronegativity, χ (eV)	3.21
Chemical Hardness, η (eV)	2.64
Chemical Softness, S (eV^{-1})	0.09
Total Energy, E_{TOTAL} (a.u)	-0.25

The concepts of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are essential in evaluating a molecule's reactivity, stability, and electronic behavior. In the present study, the energy values of E_{HOMO} and E_{LUMO} were calculated for the flavonoid-derived compound using DFT at the B3LYP/6-31G(d) level. A detailed visualization of the HOMO and LUMO orbitals is provided in Figure 1, highlighting electron-dense and electron-deficient regions within the molecular framework. These regions are particularly relevant for understanding the compound's potential interaction with reactive oxygen species (ROS), which is central to its proposed role as an oxidative stress regulator. The HOMO-LUMO gap also contributes valuable insight into the compound's overall chemical stability and biological applicability, laying the groundwork for future pharmacological evaluations

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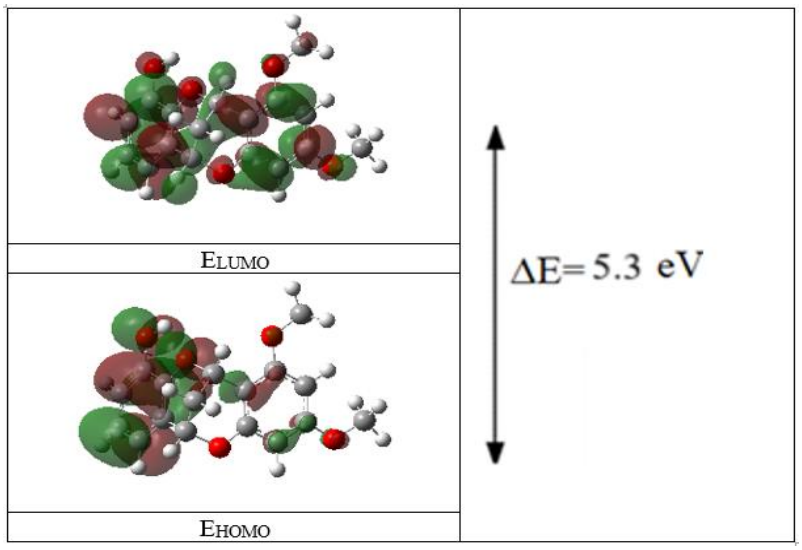

Figure 1: Three-dimensional visualization of HOMO and LUMO orbitals in the flavan-based molecule

3.2. Molecular Electrostatic Potential Surfaces (MEPS)

Molecular electrostatic potential (MEP) analysis is an essential tool for evaluating a molecule's reactivity, intermolecular interactions, and possible biological activity. In this study, the three-dimensional electrostatic potential surface of the optimized structure of the flavonoid-derived compound was generated using the B3LYP/6-31G(d) level of theory. The resulting MEP map is presented in Figure 2.

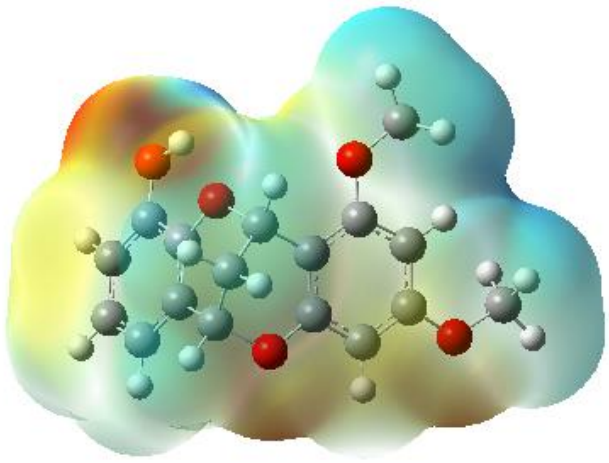

Figure 2: Molecular electrostatic potential (MEP) surface map

The MEP surface reveals a heterogeneous electron density distribution across the molecule. Electron-rich (negatively charged) regions are represented in red, while electron-deficient (positively charged) regions appear in blue. Upon examination of the map, areas of high electron density were observed primarily around the hydroxyl (–OH) and methoxy (–OCH_3) substituents, indicating potential sites for hydrogen bonding or radical scavenging. In contrast, lower electron density regions were localized around the hydrophobic carbon framework, especially near C–H bonds.

These findings support the molecule's predicted antioxidant potential. The presence of electron-rich sites suggests possible reactivity toward reactive oxygen species (ROS), aligning with the compound's proposed function as an oxidative stress regulator. MEP analysis thus provides critical insight into the physicochemical behavior of the molecule and its likely interactions in biological environments, particularly in the context of redox balance and cellular protection.

4. Conclusion

In this study, the flavonoid-derived compound 3'-hydroxy-5,7-dimethoxy-4-O-2'-cycloflavan was investigated using Density Functional Theory (DFT) at the B3LYP/6-31G(d) level to evaluate its structural, electronic, and potential biological properties. Geometry optimization confirmed a stable conformation, while calculated HOMO-LUMO energies, dipole moment, and molecular electrostatic potential (MEP) surfaces revealed favorable electronic characteristics associated with antioxidant activity.

The observed electron-rich regions around the hydroxyl and methoxy groups, as demonstrated by the MEP analysis, suggest strong potential for free radical scavenging and hydrogen bonding, both of which are key in mitigating oxidative damage. The moderate HOMO–LUMO energy gap indicates a balance between chemical reactivity and molecular stability, further supporting the compound's potential as an oxidative stress modulator.

These findings support the hypothesis that the investigated compound may serve as a promising candidate for pharmacological applications, particularly in managing oxidative stress-related conditions such as cardiovascular diseases. Theoretical results presented here form a foundational basis for future experimental validation and drug development studies targeting oxidative damage pathways.

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