



Theoretical assessment of antioxidant property of polypropenoid and its derivatives

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Abstract

Derivatives of parent molecules possess similar structural activity which makes them to be the topic of equal interest. In the present work, a naturally occurring acid eugenol and its co derivatives allyl-2-methoxy-4-nitrophenol and 5-Allyl-3-nitrobenzene-1,2-diol are theoretically investigated for their antioxidant role using density functional theory (DFT). Becke's exchange correlation functional B3LYP and Minnesota functional M062X along with the basis set 6-311++G(d,p) are used to investigate the structural property through geometry optimization, frontier molecular orbital analysis, electrostatic potential analysis, and molecular descriptive parameters. Electron donating capability of the molecules is analyzed using frontier molecular orbital analysis and molecular descriptors. Molecular surface potential analysis facilitated to locate highest and lowest potential regions in these molecules. Hydrogen atom abstraction property (radical scavenging property) of the molecules is studied with the help of hydrogen atom transfer mechanism.

Keywords Eugenol derivatives · Density functional theory · Antioxidant activity

Introduction

Phenolic compounds obtained from natural sources find major applicability in the field of medicine. Either naturally

extracted or reverse engineered in laboratory, some of the derivatives are also obtained along with the parent molecule and such derivatives also possess health-promoting abilities similar to that of their parent. Hence, equal amount of research interest is also been shed towards the derivative molecules. In such a way, a polypropenoid named eugenol (4-allyl-2-methoxyphenol) physically derived from pepper, bay leaves, cinnamon, nutmeg, camphor, and some natural oils has gained momentum for further investigations. It is a feeble acid and soluble in organic solvents. The oil originating from clove flower buds has the compositions of eugenol (60–90%), eugenyl acetate, caryophyllene, and other substances. Similarly, 82–88% of eugenol is present in clove leaves, small quantities of eugenyl acetate, and other negligible ingredients [1, 2]. The oil derived from the twigs of cloves consists of 90–95% of eugenol. Eugenol also can be produced synthetically by the allylation of guaiacol with allylchlorid [3, 4]. Eugenol is used as constituent to add fragrance in soaps and cosmetics, skin care products, flavoring substance for food, dental, and pharmaceutical products. Eugenol enhances or stimulates the absorption of medications applied on human body parts. It is a potential weapon to safeguard food products from the attack of microorganisms such as *Listeria monocytogenes* and *Lactobacillus* during storage. It also acts as insect killer,

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antifungal agent, and useful for many skin related disorders in human beings [5].

Since eugenol is found to be related to ROS-independent mechanisms and possess lesser cytotoxicity, the present research work focuses on eugenol along with its synthesized derivatives 4-Allyl-2-methoxy-4-nitrophenol(ED1) and 5-Allyl-3-nitrobenzene-1,2-diol (ED2) for their antioxidative property through theoretical modeling. The synthesis routes of the eugenol derivatives ED1 and ED2 are been clearly given by Hidalgo et. al [6].

Computational methodology

In this work, the antioxidative capability of eugenol derivatives has been carried out with the help of density functional theory. Density functional theory (DFT) is an extensively used tool for quantum chemical calculations which is a promising tool for the analysis of radical scavenging potential of flavonoids and other compounds [7]. All the calculations are carried out by B3LYP and M062X level of theories with basis set 6-311++G(d,p) in gas and solvent phases (ethanol and water) with the help of Gaussian 16 package at room temperature. The optimized structures are found to be in a ground state with the absence of negative frequency, and the conformers of ED1 and ED2 are characterized with intramolecular hydrogen bond of length 1.70 Å and 1.72 Å. Molecular energy-based properties such as global reactive parameters and electrostatic potential energy (ESP) surface analysis have been done to exhibit the structural activity of the derivative compounds. Antioxidant capacity of the derivatives is calculated using thermodynamically favored HAT (hydrogen atom transfer atom) mechanism followed by SPLET (sequential proton loss electron transfer) mechanism and SET-PT (sequential electron transfer and proton transfer) mechanism (Fig. 1) [8].

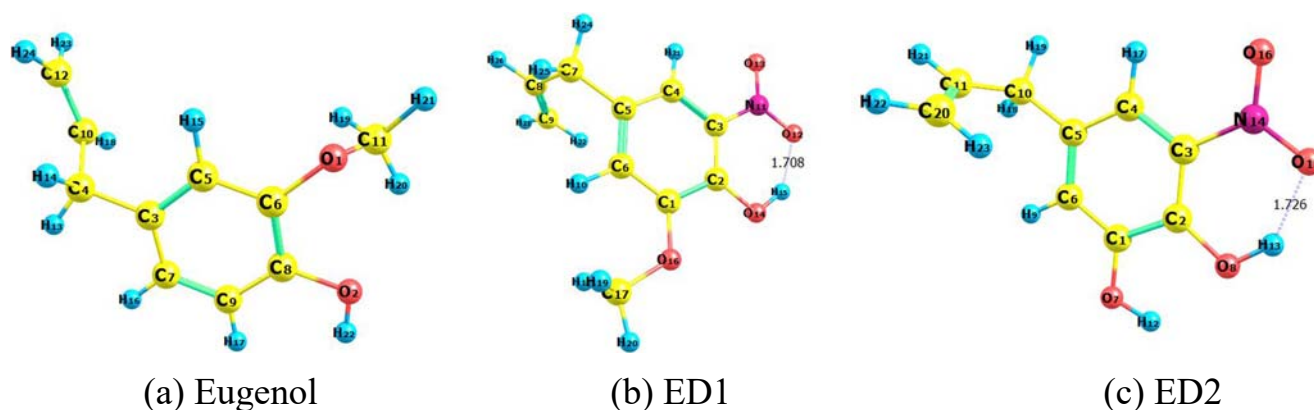


Fig. 1 Optimized geometries of (a) Eugenol, (b) ED1, and (c) ED2

Results and discussions

Global reactive parameters or molecular descriptors

The antioxidant capability of eugenol can be explored by computing the descriptors χ , IP, EA, η , S, and ω . The electron-contributing capability is exhibited by ionization potential (IP), aversion for transport of charge is characterized by hardness (η), whereas ω signifies propensity of charges in a system. In DFT, ω is negative of chemical potential [9]. The sharing of electrons between donor and acceptor is revealed by the computation of electrophilicity index (χ) [10]. In the light of the above, the magnitudes resulting from total orbital method for the compounds under study are depicted in Table 1.

Table 1 shows that eugenol possesses minimum ionization energy when compared with its derivatives ED1 and ED2, so electron removal is easier in eugenol. The difference in magnitude of the IP values is found to be 1.3 and 1.7 eV between eugenol and its derivatives. Electron affinity varies by the order of 1.4 eV between three molecules. Regarding hardness and softness values, eugenol facilitates more flexibility than its derivatives ED1 and ED2, respectively. Binding energy decomposition is quite low to eugenol than its derivatives. From the above discussions, it is evident that eugenol possesses superior structural activity than ED1 and ED2. Whereas between ED1 and ED2, energy differences are in decimals and they no longer have much influence over structural activity. Hence, both are said to possess similar structural activity. While comparing the level of theories, B3LYP seems to give much favorable results than M062X and are in line with experimental findings.

Frontier molecular orbital analysis

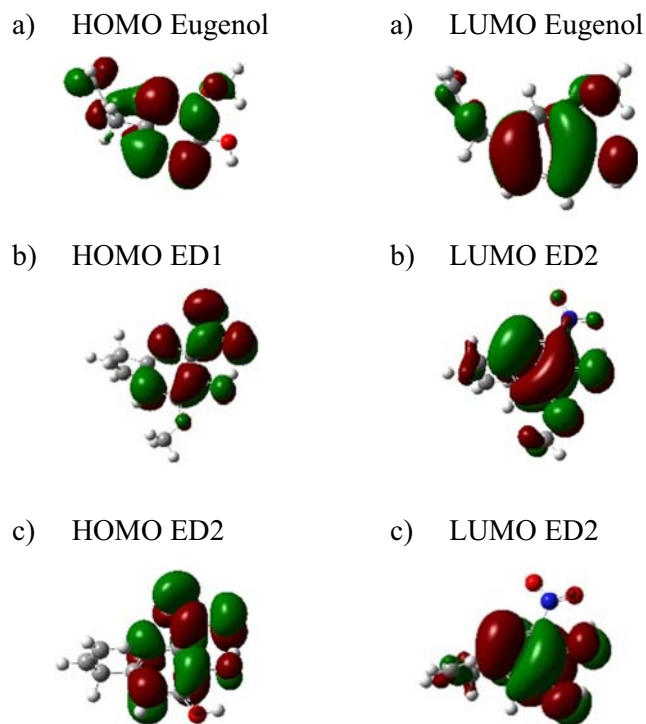
Frontier orbitals provide an insight on organic reactions based on how orbitals interact to control the outcome of reactions.

Table 1 Molecular descriptive parameters of eugenol, ED1, and ED2

Descriptors	Eugenol (eV)		ED1 (eV)		ED2 (eV)	
	B3LYP	M062X	B3LYP	M062X	B3LYP	M062X
IP	5.97	7.35	6.30	7.79	6.73	8.03
EA	0.26	0.69	2.72	1.76	3.20	1.95
η	2.85	3.31	1.79	3.01	1.76	3.04
S	0.17	0.15	0.27	0.16	0.28	0.16
ω	3.11	4.02	4.51	4.78	4.96	4.99
χ	1.69	2.4	5.68	3.78	6.99	4.10

Here, they are been used to understand the characteristics nucleophilic and electrophilic components by visualizing the occupied and unoccupied molecular orbitals [11].

From the visuals of Fig. 2 for all the three molecules, it is identical that highest occupied molecular regions are found to be confined over phenyl ring and hydroxyl units attached to it. They are observed with bonding type of orbitals around them depicting the electronic population there. This allows them to act as active charge donors (σ to σ^* transition), i.e., hydroxyl units are the active electron donors here or otherwise known as electrophilic sites. While lowest unoccupied molecular orbitals (LUMO) are found with antibonding orbitals showing poor electronic movement in particular regions, this is due to increased electronegativity nearer to oxygen attached sites (NO_2 in C3 and OCH_3 in C7) in both ED1 and ED2. These regions act as sites of nucleophilic attack (π to π^* transition);

**Fig. 2** HOMO and LUMO of (a) eugenol, (b) ED1, and (c) ED2

therefore, they proceed as electron acceptors instead of electron donors. Based on the occupied orbital density and energy gap between HOMO and LUMO, it is found that molecules eugenol and ED2 act as better electron donor possessing better antioxidant activity.

Molecular electrostatic potential analysis

The electrostatic potential of a molecule is a potential tool in assessing the molecules' reactivity towards positively or negatively charged reactants (e.g., radicals) from the optimized geometry [12]. For eugenol, ED1, and ED2, the highest electrostatic potential regions are witnessed nearer to hydroxyl units present in 5C and 4C positions, respectively, leading to active electron donation. Lower electrostatic potential regions are been witnessed over the oxygen atoms attached to the nitrogen at 3C position for ED1 and ED2. Whereas remaining portion of the molecules lacks lesser charge movement thereby displays mid electrostatic nature indicating their stable nature. From the above observation, it can be concluded that the molecules act as electron donors and all the observations are in line with FMO results (Fig. 3).

Antioxidant mechanisms

Generally, antioxidant property of a molecule can be evaluated by analyzing its ability to scavenge invading radicals. Radical scavenging nature is assessed using several

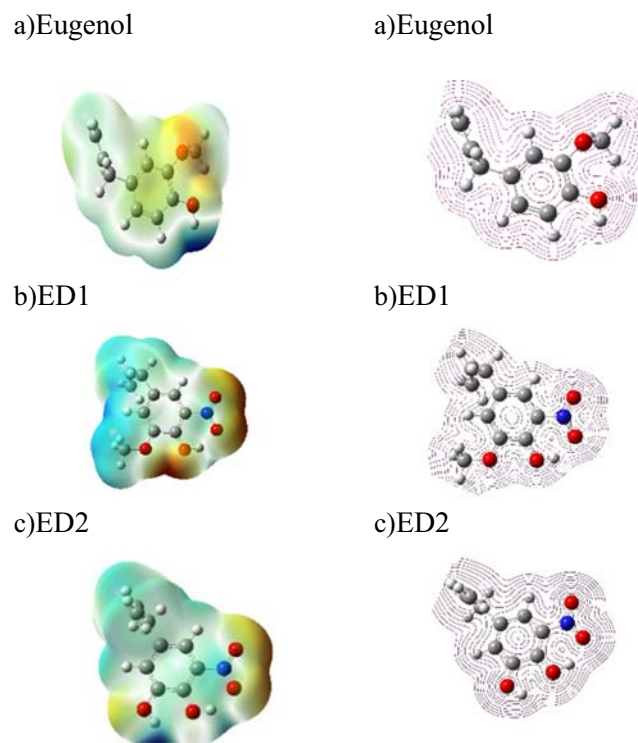
**Fig. 3** Molecular electrostatic potential analysis of (a) eugenol, (b) ED1, and (c) ED2

Table 2 Thermodynamic properties of eugenol, ED1, and ED2

OH Sites	Eugenol(kcal/mol)		ED1(kcal/mol)		ED2(kcal/mol)	
	B3LYP	M062X	B3LYP	M062X	B3LYP	M062X
Gas phase						
4 OH	****	****	****	****	84.92	87.32
5 OH	74.56	77.35	86.0	87.5	85.36	87.60
Aqueous phase						
4 OH	****	****	****	****	88.64	89.1
5 OH	78.21	81.44	90.23	91.21	89.13	90.5
Ethanol phase						
4 OH	****	****	****	****	88.92	89.32
5 OH	78.46	81.35	90.15	91.3	89.41	90.7

thermodynamic properties (Table 2) like bond dissociation enthalpy (BDE), proton affinity (PA), electron affinity(EA), and ionization potential(IP) values obtained from mechanisms such as hydrogen atom transfer(HAT), single electron transfer followed by proton transfer (SET-PT), and a proton loss followed by electron transfer (SPLET).

HAT mechanism

The oxidative reaction can be destroyed by releasing of H-atom by the antioxidant to t free radical through the process of O–H bond cleavage which is subsequently computed by HAT mechanism. The stability of hydroxyl group after releasing the H-atom is calculated by bond dissociation enthalpy (BDE) [13].

The dissociation enthalpy of the O–H group or bond dissociation enthalpy (BDE) is a useful parameter to analyze the structure activity of antioxidants [14]. It is observed from the Table 2 that the difference in BDE values for eugenol, ED1, and ED2 is 11 to 10 kcal/mol in gas phase, and in solvent phases, the difference of about 12 kcal/mol has been observed. These observations clearly makes the sense that eugenol favors easier dissociation since it possesses lesser dissociation values in the studied environments when compared with its derivatives. This is due to which the hydroxyl unit (5 OH) of eugenol does not affect any electrostatic interaction with its neighbors making electron donation easier there. For ED1, different perspectives are noticed due to the presence of methoxy unit in the 5C position making charge localization to be higher in its region; in addition, the formation of intramolecular hydrogen bonding with lone pair oxygen atom present in 6C (NO₂) position also plays a vital role which makes bond dissociation too complicated in 4 OH position. Hence, these factors reduce the capability of 4 OH to scavenge the radical species. On other hand, the BDE values of 5 OH ED2 comparatively seem to be nearer to that of eugenol; 4 OH exhibits lesser dissociation value when compared with its

neighbor 5 OH which forms intra molecular hydrogen bonding with oxygen atom attached to nitrogen in 6C position. Regarding correlation, functional B3LYP delivers favorable results than M062X.

SET-PT mechanism

This mechanism is used to compute the energy required to liberate an electron which in turn induces proton transport [15]. ET then PT (EP) or PT then ET (PE) is a chronological pathway which take place through analogous channels. This mechanism is best explained with the help of ionization potential (IP) and proton dissociation enthalpy (PDE). From Table 3, it is noted that IP values (8–10 k.cal/mol) are with the difference of 1 eV between gas and polar phases. PDE values are found to be within the magnitudes of 400 kcal/mol thereby depicting that second step is almost not possible to occur.

A sequential mechanism is the one in which electron and proton transport occurs at two different steps and hence the name sequential proton loss electron transfer. It is characterized by proton affinity (PA) and electron transfer enthalpy (ETE) values [16]. SPLET mechanism depicted in Table 4 exhibits similar characteristics as that of SET-PT where electron transfer (around 43, 75, and 65 kcal/mol) seems to be favorable but proton dissociation requires more amount of energy (350–400 kcal/mol) which still makes this mechanism a crucial one to occur.

Conclusion

Antioxidant property of the polypropenoid eugenol along with the derivatives ED1 and ED2 is theoretically investigated using DFT. The optimized geometries for the three molecules

Table 3 Proton affinity of eugenol, ED1, and ED2

OH Sites	Eugenol (kcal/mol)		ED1 (kcal/mol)		ED2 (kcal/mol)	
	B3LYP	M062X	B3LYP	M062X	B3LYP	M062X
Proton affinity (kcal/mol)						
Gas phase						
4 OH	****	****	****	****	493	497
5 OH	347	349	493	496	496	499
Aqueous phase						
4 OH	****	****	****	****	494	498
5 OH	348	351	494	497	497	500
Ethanol phase						
4 OH	****	****	****	****	492	495
5 OH	344	346	492	494	494	497

Table 4 Electron transfer of eugenol, ED1, and ED2

Electron transfer enthalpy (kcal/mol)						
OH Sites	Eugenol (kcal/mol)		ED1 (kcal/mol)		ED2 (kcal/mol)	
	B3LYP	M062X	B3LYP	M062X	B3LYP	M062X
Gas phase						
4 OH	****	****	****	****	65.76	67.11
5 OH	43.53	45.21	74.10	76.57		
Aqueous phase						
4 OH	****	****	****	****	66.85	69.3
5 OH	44.84	47	75	77.91		
Ethanol phase						
4 OH	****	****	****	****		
5 OH	42.87	44	76	79.11	64.92	67.15

are obtained using two level of theories B3LYP and M062X with the basis sets 6-311++G(d,p). Absence of negative frequencies reveals that all the optimized geometries exist in the ground state only. Optimized structure of the molecules has been utilized in various analyses to validate their antioxidative capacity, and the findings are listed below.

Molecular descriptive parameter gives lowest ionization potential value for eugenol when compared with its derivatives ED1 and ED2. Similarly, affinity towards electrons, molecular flexibility, and decomposition of bond dissociation is in favor of eugenol. ED1 and ED2 with minor variations in magnitudes prefer to act as molecules with similar structural activity.

FMO analysis displays HOMO occupancy over phenyl ring and its hydroxyl units with bonding type of orbitals making sense that those regions are rich in electronic movement hence favors easier electron donation. LUMO is concentrated over electronegative atoms. Based on the energy gap value, the activity of the molecules is ordered as eugenol>ED2>ED1.

Antioxidant potential for the three molecules has been examined by analyzing their ability to scavenge the free radicals. HAT is found to be the dominant mechanism which facilitates radical scavenging activity and is witnessed through the presence of lowest BDE values when compared with SET-PT and SPLET mechanisms. In HAT, the gas phase BDE values are found to be lower than aqueous and ethanol phases.

The chief factor that acts as structural activity director here is $-NO_2$ region which is responsible for suppression of activity in both ED1 and ED2. Eugenol which lags $-NO_2$ in its para position facilitates easier charge movement inside the structure thereby facilitating better antioxidant activity. The findings made in this theoretical investigation are also in line with that of experimental results.

Based on the above discussions, it is evident that the polyphenolic eugenol and its derivatives ED1 and ED2 act as potent antioxidants of the order of eugenol>ED2>ED1.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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