

**Structure - Antioxidant Activity Relationship Study of Eugenol Derivatives Using semi-empirical Method**

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**Abstract:** In spite of the large quantity of experimental work, the electronic and structural aspects of Eugenol derivatives responsible for free radical scavenging ability are theoretically analyzed in this paper. Electronic parameters were calculated using the PM6 semi empirical level to calculate a set of molecular properties of Eugenol derivatives. The electronic features found as being responsible for the antioxidant activity of the Eugenol derivatives compounds studied, are the Mullikan net charge of oxygen atom (-OH), the energy of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), the energy gap ( $E_L-E_H$ ), ionization potential and dipole moment. These values are interpreted with Trolox equivalent antioxidant capacity (TEAC) value. The 7<sup>th</sup> O position in the eugenol compounds have higher charges, hence chelation by metal occur in the 7th position hydroxy group. The antioxidant activities increase with small the energy gap value ( $E_L-E_H$ ) and high the net charge. The results of the antioxidant activity are in the following order: diisoeugenol (4) > hydroxymethyl eugenol (3) > eugenol (1) > dihydroeugenol (2) as can be obtained from experimental data. On the basis of these results we are able to design a novel antioxidant with enhanced activity.

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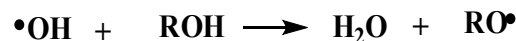
**Key words:** Eugenol, semi-empirical, Free radical, PM6, highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO).

**1. Introduction**

Eugenol is an allyl chain substituted guaiacol [1]. Eugenol is a member of the phenyl propanoids class of chemical compounds. It is a clear to pale yellow oily liquid extracted from certain essential oils especially from Holy basil (Tulsi) and bay leaf, clove oil, nutmeg, cinnamon etc. It is slightly soluble in water and soluble in organic solvents. It has a spicy, clove-like aroma [2].

Eugenol is used in perfumeries, flavorings, essential oils and in medicine as a local antiseptic and anesthetic [3]. It is a key ingredient in Indonesian kretek (clove) cigarettes. It was used in the production of isoeugenol for the manufacture of vanillin, though most vanillin is now produced from phenol or from lignin. When mixed with zinc oxide, eugenol forms a material which has restorative and prosthodontic applications in dentistry. Eugenol derivatives or methoxyphenol derivatives in wider classification are also used in perfumery and flavoring [4]. They are used in formulating insect attractants and UV absorbers, analgesics and biocides. Several other pharmacological effects, such as antitumor, hepatoprotective, anti-inflammatory (oral & topical), anti-ulcer, antimicrobial, antihyperlipidemic, and anti-viral activities, have also been attributed [5]. They are also used in manufacturing stabilizers and antioxidants for plastics and rubbers [6]. It is also used in mouse traps.

Compounds that have phenolic groups have long been known to exhibit antioxidant properties by quenching free radical species through loss of a hydrogen atom. During this process the antioxidant phenolic group is converted into a phenoxyl radical species which is more stable due to electron delocalization within adjacent benzene rings or dimerization. Thus phenoxyl radical is less harmful and does not react with many substrate molecules. The antioxidant property of the phenolic group is dependent on the ease with which it can lose electron to scavenge a radical.



(OH=hydroxyl radical, ROH = phenolic compound).

Several studies suggest that natural and synthetic antioxidants protect against ROS mediated cellular damage [7]. The synthetic antioxidants such as butylated hydroxytoluene (BHT), butylated hydroxy anisole (BHA) and propyl gallate (PG) are extensively used in food processing industries as preservatives [8]. The toxicity concerns of some of these synthetic antioxidants have therefore shifted the focus to the identification of naturally occurring antioxidants [9]. By and large the natural antioxidants have phenolic structure and these may occur in a variety of plants. Examples of common plant phenolic antioxidants include flavonoids, cinnamic acid derivatives, coumestrols, tocopherols and polyfunctional organic compounds [10].

Antioxidant properties of eugenol compounds can be explained by forming complexes with reduced metals. Potent inhibitory effect of isoeugenol on lipid peroxidation may be related to the decreased formation of perferryl ion or the iron-oxygen chelate complex as the initiating factor of lipid peroxidation by keeping iron at a reduced state. Inhibition of (low density lipoprotein) LDL oxidation by eugenol compounds is due to the suppression of free radical cascade of lipid peroxidation in LDL by reducing copper ion.

The antioxidative potency of phenolic compound depends on the chemical structure, in particular, electron delocalization on the aromatic nucleus [11]. However, the mechanism of their scavenging reaction *in vivo* is still obscure.

The purpose of the work described here is to examine the structure-antioxidant activity relationship of a group of structurally related of Eugenol derivatives. The theoretical molecular properties of some of Eugenol derivatives compounds, which were used as antioxidant are reported in the literature [12]. We employed quantum chemical calculation (PM6, semiempirical method) to obtain properties that can describe the molecules. The elucidation of the mechanism of action of these Eugenol compounds with a good chemopreventive activity is investigated [13].

Eugenol derivatives compounds from the literature [12], with very similar structures were tested by the same assay (trolox equivalent antioxidant capacity, TEAC). The variables responsible for free radical scavenging activity, metal chelation were investigated by correlation coefficient by linear regression.

In this work, we study the computational chemistry of few Eugerol derivatives with calculation based on semi-empirical theory. We optimize the structure of the various Eugerol derivatives using quantum mechanics and calculated their formation energies. From the semi-empirical methods, it is also possible to elucidate the various molecular properties. Mullikan atomic charges are calculated for all atoms in a molecule; these are compared with the antioxidant efficiency of Eugerol derivatives. We find moderate agreement with the available experimental data.

## 2. Method of calculations

Theoretical calculations were carried out by using PM6 semi-empirical methods in MOPAC2007 program, implemented on an Intel Pentium (R) 1.86 GB personal computer. Initial estimates for the geometries of all the structures were obtained by molecular mechanics program (ACD11) for Widows, followed by full optimization of all geometrical

variables (bond lengths, bond angles and dihedral angles), without any symmetry constraint, using PM6 semi-empirical methods in gas phase.

## 3. Results and Discussion

The chemical structures of the compounds under investigation are presented in figure 1. Table 1 shows TEAC values of the eugenol derivatives from literature [12], the calculated energy values of eugenol derivatives, the highest occupied and the lowest unoccupied molecular orbitals energies (HOMO and LUMO, respectively), the frontier molecular orbital energy gap (LUMO-HOMO energy difference,  $E_g$ ) with the calculated dipole moment values of the systems considered are also given in Table 1. The compounds are arranged in the decreasing order of TEAC. The calculated excess charges on the atoms of the optimized structures of the Eugenol compounds are shown in Table 2.

The highest atomic charges are available in the 7th position oxygen atom of compounds, table 2. These theoretical values highly correlated with the metal binding properties of eugerol compounds as reported previously [14]. Figure 1 shows the structures number of eugerol compounds and their Mullikan atomic charges shown in table 2. Comparison of our results with the published data, the atomic charges are in the order of 7th O, 8th O, 10th C and 12th C. From these results, we conclude that the 7<sup>th</sup> O position in the eugerol compounds have higher charges, hence chelation by metal occur in the 7th position hydroxy group (OH).

The scavenging activity of phenolic antioxidant is determined by the O-H bond dissociation energy (BDE) [15], and the O-H BDE is mainly governed by the stability of the phenoxyl free radical generated after H-abstraction for the antioxidant. Generally, the factors enhancing the stability of the free radical will increase the antioxidant activity.

The polar effect, including inductive and resonance stabilization, is responsible for the stability of parent molecule (SPM), and the spin delocalization of the unpaired electron determines the stability of phenoxyl radical (SPR) [16]. The radical resonance structure of eugerol is stabilized by resonance effect, which is converted into a phenoxyl radical species, which is more stable due to electron delocalization within adjacent benzene rings, there are four resonance structures in the case of eugerol (**1**) figure 2.

Both the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are the main orbitals taking part in the chemical reaction.

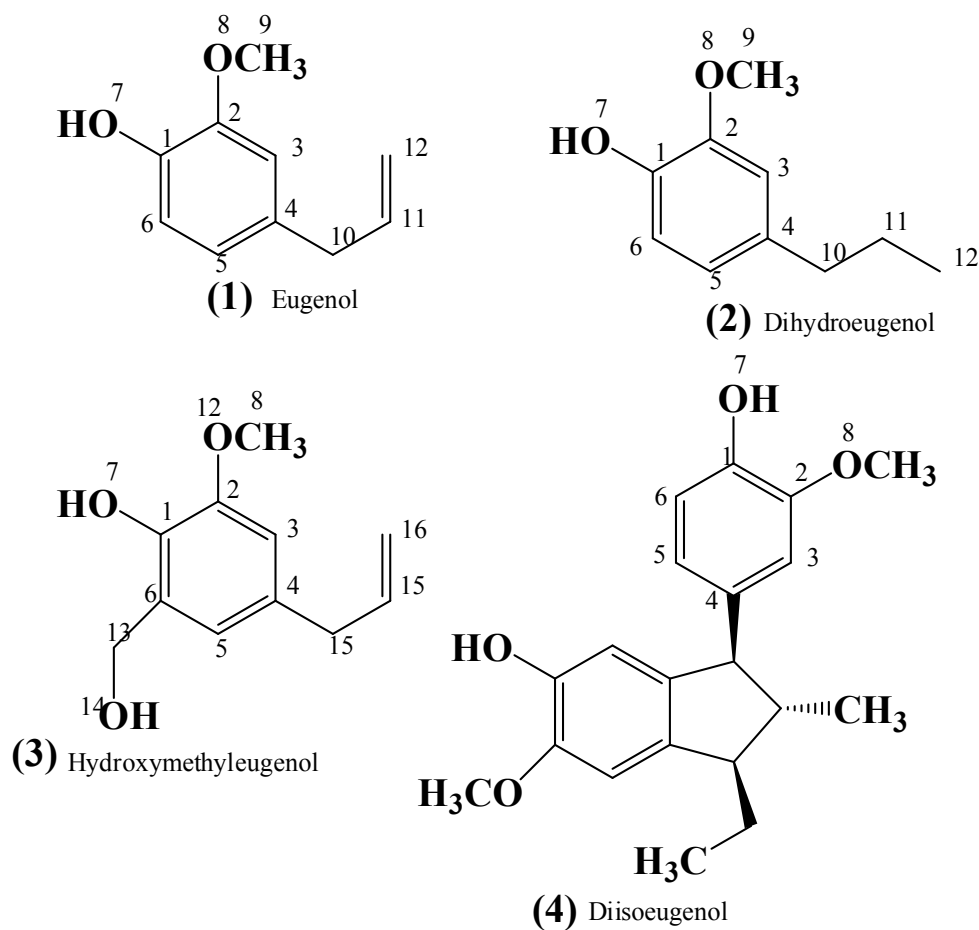


Figure 1. The structure of Eugenol and its derivatives

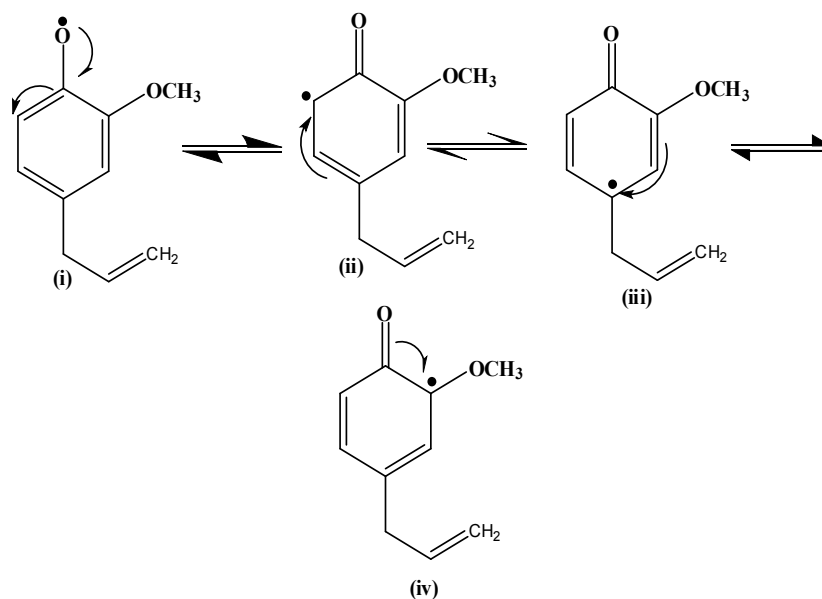


Figure 2. The Resonance structures of Eugenol (4-allyl-2-methoxyphenol), radical

The HOMO energy which characterizes the ability of electron-giving is appropriate to represent the free radical scavenging efficiency of phenolic compounds because the process to inhibit auto-oxidation may include the electron-transfer besides the abstraction of the H-atom [17]. Considering the disposition of HOMO and LUMO orbitals, the OH group of 1-position is easily attacked by either the electrophilic or nucleophilic agents, such as radicals, metal ions and O<sub>2</sub>. The most active compound toward antioxidant is diisoeugenol (TEAC is 2.61), table 1, which has high HOMO energy (-8.215 ev), lower ionization Potential (8.214 ev), and high dipolemoment (2.023 D).

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According to the data in table 1, there is a good correlation in LUMO- HOMO energy gap by these methods in gas phase, it can be seen that diisoeugenol (**1**) is best antioxidant and has smallest LUMO-HOMO gap i.e (8.302 eV), but the dihydroeugenol (**2**), which is least antioxidant and has highest LUMO- HOMO gap i.e (8.534 eV). Thus as can be seen from table 1 for our methods of calculations, the antioxidant activity increases as the E<sub>L</sub>-E<sub>H</sub> values decrease, which indicates the stability of formed phenol oxide radicals, i.e the order of the antioxidant activity as follows: **4** > **3** > **1** > **2** as can be obtained from experimental data [12]. This indicates that the best correlations between experimental and calculated antioxidant activity obtained by using Pm6 method, in gas phase for eugenol derivatives, correlations are in the same order.

**Table 1. The energy parameters for the optimized structures of Eugenol derivatives**

Eugenol	TEAC*	ΔHf (kcal/mol)	E <sub>HOMO</sub> (eV)	E <sub>LUMO</sub> (eV)	E <sub>L</sub> -E <sub>H</sub> (eV)	Ionization Potential (eV)	Dipole Moment (D)
<b>1</b>	1.68 ± 0.05	-46.0241	-8.396	0.143	8.539	8.396	1.365
<b>2</b>	1.59 ± 0.02	-75.3610	-8.373	0.210	8.583	8.372	1.560
<b>3</b>	1.8 ± 0.1	-95.3095	-8.646	-0.200	8.446	8.645	1.171
<b>4</b>	2.61 ± 0.09	-139.4349	-8.215	0.087	8.302	8.214	2.023

\*TEAC values for the eugenol derivatives are taken from reference [12]

**Table 2. Mullikan charges of the optimized structures of Eugenol compounds**

Eugenol (1)			Dihydroeugenol (2)			Hydroxymethyleugenol (3)			Diisoeugenol (4)		
No.	type	charge	No.	type	charge	No.	type	charge	No.	type	charge
<b>1</b>	C	-0.3329	1	C	-0.2929	1	C	-0.2829	1	C	-0.0160
<b>2</b>	C	0.0980	2	C	0.1113	2	C	0.1004	2	C	0.0080
<b>3</b>	C	0.2343	3	C	0.2447	3	C	0.2460	3	C	-0.2565
<b>4</b>	C	-0.2052	4	C	-0.2180	4	C	-0.2161	4	C	-0.2448
<b>5</b>	C	0.1672	5	C	0.1007	5	C	0.0937	5	C	0.1247
<b>6</b>	C	-0.2414	6	C	-0.2060	6	C	-0.1286	6	C	0.2106
<b>7</b>	O	-0.4429	7	O	-0.4846	7	O	-0.3558	7	O	-0.4849
<b>8</b>	O	-0.3324	8	O	-0.3617	8	C	-0.1767	8	O	-0.3632
<b>9</b>	C	-0.1945	9	C	-0.1765	12	O	-0.4788	14	C	-0.2805
<b>10</b>	C	-0.3283	10	C	-0.3085	13	C	0.0124	17	C	-0.2217
<b>11</b>	C	-0.0492	11	C	-0.1987	14	O	-0.5370	19	O	-0.4830
<b>12</b>	C	-0.3924	12	C	-0.4656	15	C	-0.3272	20	O	-0.3617
						16	C	-0.0525	23	C	-0.4622
						17	C	-0.3859	24	C	-0.4981

It was noted that dihydroeugenol **2** less active scavenger than eugenol **1**, because compound **1** has allyl substituent in para position to hydroxyl group, while the introduction of another hydroxyl group like a hydroxymethyl moiety (CH<sub>2</sub>OH) in compound **3** enhanced antioxidant capacity. It is known that

polymeric or dimeric phenols (comp. **4**) have a higher antioxidant (antiradical) activity than monophenols (comp. **1**, **2** & **3**). These results suggest that bulky substituents are necessary at the neighboring position of the hydroxyl group in eugenol.

#### 4. Conclusion

Through PM6 semi-empirical quantum chemical calculations, a correlation between parameters related to structure of some eugenol derivatives and their ability as anti-oxidant activity could be established.

The relative stability of the radical forms depends on specific positions, as phenoxyl radical, and contributes to the resonance effect. The anti-oxidant activity of eugenol derivatives obtained experimentally increase with the increased in  $E_{\text{HOMO}}$ , and decreased in the energy of the gap ( $\Delta E$ ), disoeugenol have higher antioxidant activities than that of the monomers, because it had the highest HOMO energy and low ( $\Delta E$ ) values, and it was most capable of free radical scavenger. Comparison of theoretical and experimental data exhibit good correlation confirming the reliability of the method employed here. The results lead to the conclusion that eugenol derivatives could be used as a model for the design of more active compounds with higher antioxidant potency.

#### Supplementary Information

Supplementary information (output results of quantum chemical calculations) is available free of charge, on correspondence to the author on request.

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