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Full Length Research Paper

A semi-empirical study of flavone compounds with antioxidant efficiency

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In spite of the large quantity of experimental work, the electronic and structural aspects of flavones responsible for free radical scavenging ability are theoretically analyzed in this paper. Electronic parameters were calculated using the AM1 semi empirical level to calculate a set of molecular properties for flavone compounds. The electronic features found as being responsible for the antioxidant activity of the flavone compounds studied are reported. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) and dipole moment values are interpreted with Trolox equivalent antioxidant capacity (TEAC) value. The Mullikan charges of the optimized structures of flavones are interpreted. The 4th carbon and 4th carbon attached oxygen atomic charges of flavones closely resemble the experimental TEAC value. The results obtained can also bring improvements in the research, for better antioxidant flavone compounds. The present results provide a useful basis for the interpretation of the theoretical value with experimental antioxidant activity data.

Key words: Flavones, semi-empirical, free radical, AM1, highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO).

INTRODUCTION

Flavonoids are compounds with varied chemical structures and are commonly found in fruits, vegetables, nuts and seeds. These compounds are found at relatively high concentrations in the human diet and comprise several classes of molecules including flavonols, flavonones and flavones. A variety of properties have been found on several recent reports such as metal bind capacity and antioxidant activity (Pawlak et al., 2010; LaChman et al., 2010).

The highest binding energy clearly identifies the 3-hydroxyl-4-carbonyl group as the most probable chelation site for metal ion, followed by the 4-carbonyl-5-hydroxyl and 3'-4'-hydroxyl groups (Ren et al., 2008). Earlier published results indicate that the preferred site for metal chelation is the 3-hydroxyl and 4-carbonyl group. The attachment of the metal atom to the molecule breaks the double bond of the 4-carbonyl group and deprotonates the 3-hydroxyl group to form the two metal-O bonds (Dervan, 2001). The next site is the 4-carbonyl-5-hydroxyl group. After metal binding at 3-4, deprotonation of the 4-5 site cannot bind another metal because of steric repulsion (Ren et al., 2008). The published results suggests that there is a universal trend for metal- flavonoid complexation: The 3'- 4' site is the most favored site if present; otherwise 4-5 site also binds metal strongly. Only one of these two sites can bind a metal because of steric repulsion (Ren et al., 2008). The highest binding energy for the metal atom to a single quercetin molecule demonstrates that the 3-hydroxyl-4-carbonyl group is the optimal chelation site, followed by the 4-5 and 3'-4' sites.

The mechanism by means of which the flavonoids exert their antioxidant activity is not yet well known. The inhibition of the ROS can be done by avoiding its production through enzyme inhibition or chelation of trace elements (Fe, Cu, Zn) involved in its formation, or by means of the blockade of its activity once they have formed (Pietta, 2000; Miean and Mohamed, 2001; Burda and Oleszek, 2001); metal cations play an important role in biological process (Eswaramoorthy et al., 2004). However, the excess amount of metal cations will

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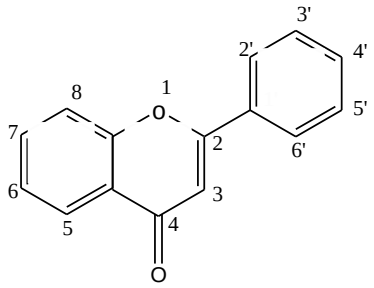
Table 1. Structural details of the flavones.

Flavone	Compound	-OH position	Other group	TEAC
	1	3', 4'	3-CH_2COOH	7.6
	2	7,3', 4	3-OCH_3	5.9
	3	3', 4'	3-OCH_3	4.40
	4	3', 4'	3-$O(CH_2)_2OH$	4.40
	5	7, 3', 4'	-	4.30
	6	3', 4'	7-$O(CH_2)_2OH$	4.30
	7	7, 3', 4'	3-$O(CH_2)_2OH$	3.40
	8	3', 4'	7-OCH_3	3.30
	9	5,6,7, 3', 4'	-	2.33
	10	5,6,7, 3'	-	2.16
	11	5,7,3',4'	-	2.10
	12	5, 7, 4'	-	1.45
	13	5,7	-	1.43
	14	5,6,7	-	1.22

generate oxygen free radicals in living organism through Fenton type reactions with production of hydroxyl radicals or Haber-Weiss cycle reactions with superoxide anions (Kehrer, 2000).

The purpose of the work described here is to examine the structure-antioxidant activity relationship of a group of structurally related flavone. The theoretical molecular properties of some flavone compounds, which were used as antioxidant are reported in the literature (Jang et al., 2003). We employed quantum chemical calculation (AM1, semiempirical method) to obtain properties that can describe the molecules. The elucidation of the mechanism of action of these flavone compounds with a good chemopreventive activity is investigated (Habib et al., 2011).

A set of 14 flavone compounds from the literature (Lien et al., 1999), 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 flavones with calculation based on semi-empirical theory. We optimize the structure of the various flavones 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 flavones. We find moderate agreement with the available experimental data.

METHODOLOGY

Quantum chemistry software

AM1 semi empirical calculations were performed using Arguslab 4.0. In all cases, full geometry optimization was carried out without any symmetry constraints. The geometries of the compounds studied in this work were initially optimized by using the quantum mechanical method QM and then by the AM1, semi-empirical chemical method. The calculations of the molecular properties used to describe the structural and electronic features of the compound under study were performed with the AM1 method and the program Arguslab 4.0. The atomic charges and the molecular electrostatic potential (MEP) maps were also obtained by the same program (Thompson, 2005).

RESULTS AND DISCUSSION

Table 1 shows the 14 flavone compounds studied in this work along with their TEAC values from literature (Southworth and Voelke, 2003), with very similar structures. The compounds are arranged in the decreasing order of TEAC. The geometry optimization of AM1 method was carried out without any symmetry constraints.

Table 2 shows the calculated energy values of flavone. The highest occupied and the lowest unoccupied molecular orbital energies (HOMO and LUMO, respectively), the frontier molecular orbital energy gap (LUMO-HOMO energy difference, Eg) with the calculated dipole moment values of the systems considered are also given in Table 2. The calculated energy parameters compared with the TEAC values and their correlation coefficients are also given in Table 2. The calculated energy parameters, enthalpy of formation, dipole moment, HOMO, LUMO and energy differences are plotted with TEAC values. It is hard to find correlation between the calculated energy parameters and the TEAC values of the compounds.

From the optimized structures, the calculated excess charges on the atoms on the 14 flavones are shown in Table 3. These atomic charges on 14 flavone compounds are plotted against TEAC values. The highest correlation coefficient exists for 4^{th} carbon and

Table 2. The energy parameters for the optimized structures of flavones.

Flavone	TEAC	ΔHf (kcal/mol)	HOMO (eV)	LUMO (eV)	Energy gap (eV)	Dipole moment (D)
1	7.6	-200.83	-0.33114	-0.03747	0.2936	3.4427
2	5.9	-158.8995	-0.3267	-0.03019	0.2965	0.7656
3	4.4	-114.3777	-0.3267	-0.03019	0.2965	1.9759
4	4.4	-167.98	-0.3340	-0.03533	0.2987	3.7557
5	4.3	-125.746	-0.3342	-0.02987	0.3043	2.05749
6	4.3	-170.2621	-0.3320	-0.02767	0.3044	3.2063
7	3.4	-212.521	-0.3307	-0.03534	0.2951	2.5412
8	3.3	-119.4513	-0.3327	-0.02907	0.3036	1.9164
9	2.33	-216.2709	-0.3297	-0.03645	0.2932	3.5234
10	2.16	-173.109	-0.3297	-0.03441	0.2952	2.6119
11	2.1	-172.9962	0.3351	-0.03195	0.3032	3.127
12	1.45	-129.8189	-0.3364	-0.03195	0.3045	2.3525
13	1.43	-85.1982	-0.3396	-0.0321	0.3075	2.8599
14	1.22	-128.4862	-0.3299	-0.03461	0.2953	2.7523
Correlation coefficient with TEAC		0.099	0.173	0.011	0.097	0.097

Table 3. Mullikan charges of the optimized structures of flavones.

Flavone	4 O	4 C	3 C	3'O	4'O	2 C	1 O	5H	1'C	5C	2C	2'C	5O
1	-0.3298	0.3502	-0.1271	-0.3	-0.32	0.1598	-0.1702	0.2323	-0.084	-0.1008	0.1598	-0.1434	-
2	-0.3289	0.3518	-0.0998	-2.99	-0.32	0.1313	-0.1689	0.2334	-0.0704	-0.0590	0.1313	-0.1447	-
3	-0.3244	0.3467	-0.1036	-0.30	-0.32	0.1337	-0.1706	0.2307	-0.0704	-0.1017	0.1337	-0.145	-
4	-0.3262	0.3497	-0.1106	-0.29	-0.32	0.1435	-0.1695	0.2321	-0.0752	-0.1005	0.1435	-0.1438	-
5	-0.3348	0.3561	-0.3577	-0.29	-0.32	0.1440	-0.1755	0.2332	-0.0755	-0.0607	0.144	-0.1419	-
6	-0.3362	0.3559	-0.3590	-0.29	-0.32	0.1441	-0.1774	0.232	-0.0743	-0.0680	0.1441	-0.1422	-
7	-0.3409	0.3545	-0.1070	-0.29	-0.32	0.141	-0.1681	0.2315	-0.0748	-0.0575	0.141	-0.1435	-
8	-0.3361	0.3563	-0.3589	-0.29	-0.32	0.1451	-0.1770	-	-0.0748	-0.0643	0.1451	-0.1419	-
9	-0.3742	0.3675	-0.3623	-0.29	-0.31	0.1567	-0.1723	-	-0.0795	0.1573	0.1567	-0.1405	-0.3317
10	-0.3753	0.3681	-0.3677	-	-0.29	0.1622	-0.1754	-	-0.1234	0.1574	0.1622	-0.1069	-0.3319
11	-0.375	0.3678	-0.3684	-0.29	-0.31	0.1522	-0.1749	-	-0.782	0.2345	0.1522	-0.1408	-0.3083
12	-0.3762	0.3684	-0.3638	-	-0.29	0.1576	-0.1781	-	-0.1219	0.2345	0.1576	-0.1074	-0.3085
13	-0.3748	0.3675	-0.3582	-	-	0.1489	-0.1768	-	-0.0.835	0.2347	0.1489	-0.1425	-0.3083
14	-0.3739	0.3672	-0.3622	-	-	0.1534	-0.1741	-	-0.0848	0.1576	0.1534	-0.1420	-0.3317

Table 3. Continued

Correlation coefficient with TEAC	0.716	0.717	0.488	0.45	0.28	0.133	0.318	0.658	0.197	0.6839	0.133	0.184	0.0013

4th keto group oxygen. The correlation coefficient thus evaluated are 0.717, 0.716, 0.684, 0.658, 0.488, 0.45 and 0.28 for 4th C, 4th O, 5th C, 5th H, 3rd C, 3' O and 4' O, respectively. The highest atomic charges are available in the 4th position oxygen atom. These theoretical values highly correlated with the metal binding properties of flavonoids as reported previously (Ren et al., 2008). The earlier result suggests that binding at the 3-4 site is stronger than at the 3'- 4' site. The complexation of iron with one Fe, Fe-quercetin binding strength at different sites has the order 3-4 > 4-5 >3'- 4', while for complexes containing two Fe atoms, the complex with one Fe bound at the 3-4 site and the second Fe at the 3'-4' site (Pawlak et al., 2010). Figure 1 shows the AM1 optimized structures of Flavones 1 and 2 and their Mullikan atomic charges of the molecule. Comparison of our results with the published data, the atomic charges are in the order of 4th C, 4th O, 5th C and 5th H. From these results, we conclude that the 4th position in the flavones have higher charges, hence chelation by metal occur in the 4th position keto group. The next chelation may occur at 3'O and 4'O. The HOMO energy maps of flavone (Figure 2) shows that most of the electron densities are in the B ring and C-2, C-3 double bonds only. However in the LUMO energy maps, the electrons are in between B and C rings and C-3 and C-4 bonds.

In addition, the maps of electron densities showed potential stabilization of the phenoxyl

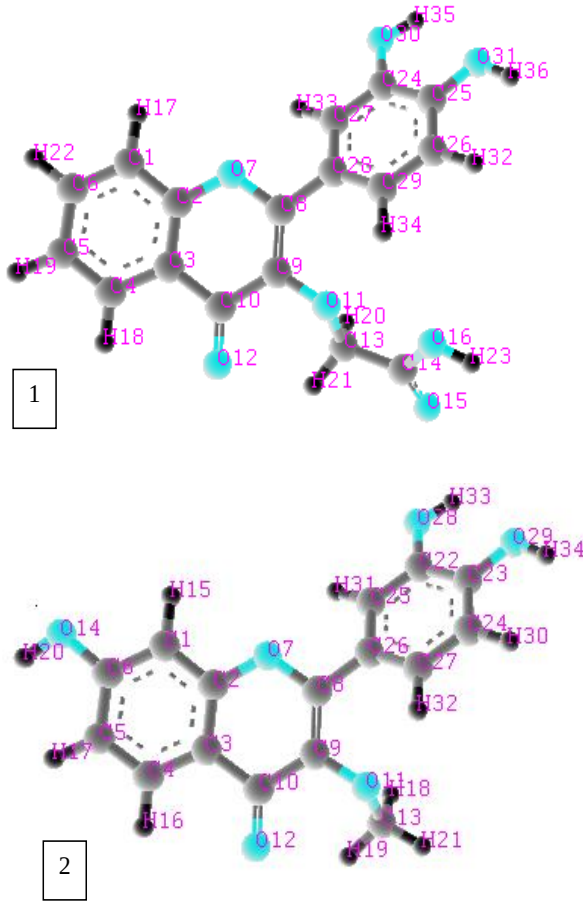


Figure 1. AM1 optimized structures of Flavone 1 and 2 and their Mullikan atomic charges are displaced for each atom in the molecule.

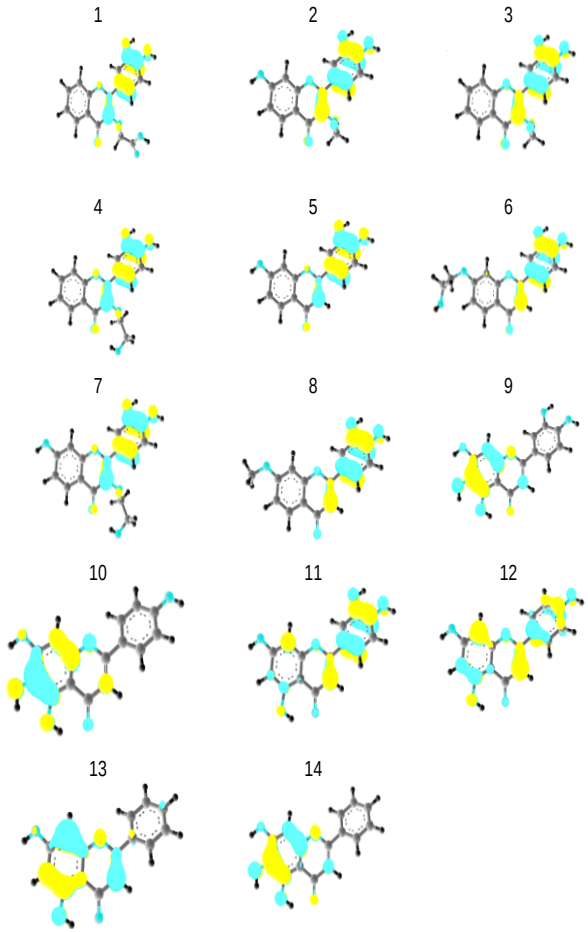


Figure 2. The highest occupied molecular orbital of flavones.

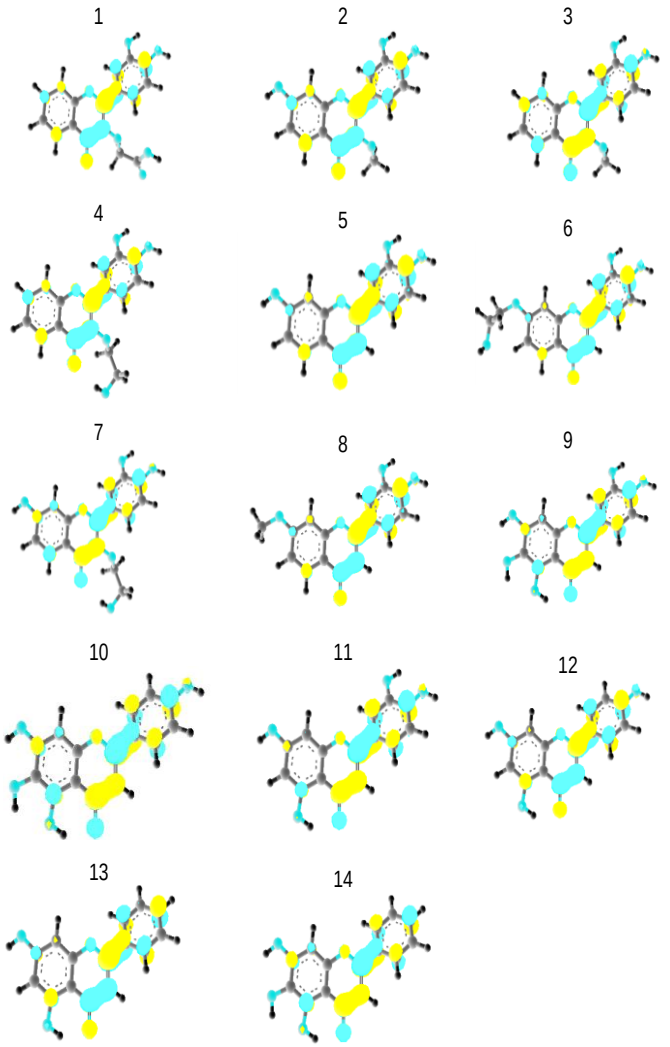


Figure 3. The Lowest unoccupied molecular orbital of flavones.

C-3 radical, formed by delocalization through ring B and C (Figure 3). From these energy maps, it is concluded that good antioxidant efficiency of flavone is ensured by the increased number of OH groups on the skeleton and attenuation of the formation of phenoxyl radicals derived from these groups. The most stable radicals originating in the course of antioxidative action may be attributed to OH groups at the position C3 on the ring C, hydroxyl groups at mutual ortho positions at C3', C4' or C4' and C5' on the ring B and the various positions on the ring A (Uivarosi et al., 2010).

The antioxidant efficiency of flavone also depends on the stability of the formed phenoxyl radical. The LUMO energy maps clearly show that there is higher electron density between ring B and C and between C-3 and C-4 and is clearly confirming the stability of radical between the rings.

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