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Quantum Mechanical Studies of the Structure-activity Relationship and Electronic Vibration of Some Dietary Flavonoids

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ABSTRACT

Eight dietary flavonoids were considered for their variation in activity as antioxidants. Semi-empirical models such as MNDO, AM1, RM1 and PM3; Density functional models at B3LYP energy level with 6-31G* and 6-31G** and moller-plesset perturbation model, MP2 at 6-31G* were used for full optimization of the structures. These methods were used to calculate the parameters such as lipophilicity, ovality, polarizability, vibrational frequency and ultraviolet absorptions which account theoretically for antioxidant potential of the flavonoids. The result of the vibrational frequency showed that MP2/6-31G* compare well with experimental values but could not determine the ultraviolet absorption bands. Myrcetin, of all the flavonoids under study, showed the highest antioxidant activity as well as antigen (stimulates an immune response in the body, especially the production of antibodies).

Key words: Lipophilicity, ovality, prostate-specific antigen, moller-plesset

INTRODUCTION

The application of computer codes to chemistry, involving approximation schemes such as Hartree-Fock, post-Hartree-Fock, density functional theory, semi-empirical methods (such as PM3) or force field methods have been widely studied. Molecular shape is the most frequently predicted property. Computers can also predict vibrational spectra and vibronic coupling but also acquire and Fourier transform Infra-red Data into frequency information. Computational chemistry and molecular modeling is a fast emerging area which is used for the modeling and simulation of small chemical and biological systems in order to understand and predict their behavior at the molecular level. It has a wide range of applications in various disciplines of engineering sciences, such as materials science, chemical engineering, biomedical engineering, etc. (Ramachandran *et al*., 2008). The most important natural pigments are carotenoids which are tetrapyrrole derivatives of naturally occurring phenolic compounds ubiquitously distributed in plant kingdom. Among these compounds, flavonoids constitute one of the most ubiquitous groups of all plant phenolics. So far, over 8,000 varieties of flavonoids have been identified (De Groot and Raven, 1998). The flavonoids are aromatic secondary plant metabolites which belong to the class of plant polyphenolics. Structurally they are heterocyclic π-electron systems built upon a C_6H_5(A)-C_3-C_6H_5(B) flavone skeleton in which oxygen is the heteroatom. A group of flavonoids is differentiated in several classes according to the degrees of oxidation and unsaturation of the heterocyclic C ring (Swain, 1976; Harborne and Williams, 2000; Cody *et al*., 1986). The antioxidant action of flavonoids is due to the combination of its chelating activity, via ortho-dihydroxy structures and its ability to sequester free

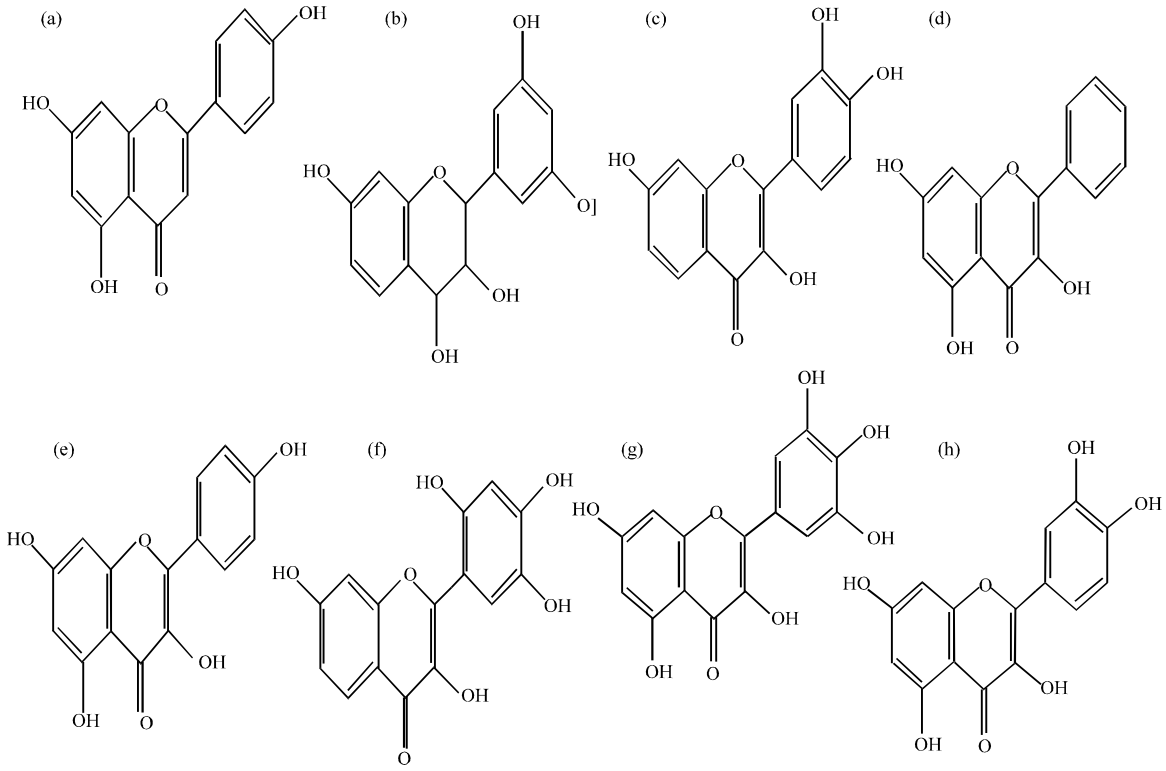

Fig. 1(a-h): Structures of the flavonoids under study, (a) Apigenin flavon), (b) Catchin flavon), (c) Fisetin flavonol), (d) Galagin flavonol), (e) Kaemferol flavonol), (f) Morin flavonol), (g) Myricetin flavonol) and (h) Quercetin flavonol)

radicals (Moridani *et al*., 2003). This occurs in three stages: formation of the superoxide ion and hydroxy radicals by Fenton's reaction and formation of lipid radicals and mechanisms that decrease lipid peroxidation (Rice-Evans *et al*., 1996).

Although, cells have mechanisms to protect themselves against toxic agents; some of these systems suffer a decline in their activities in some physiological and environmental conditions that lead to an increased production of Reactive Oxygen Species (ROS). Thus, dietary supplementation with nutrients that contain antioxidants may be important for additional protection against oxidative stress and prevention of diseases such as atherosclerosis, cancer, ischemia, inflammation and cardiovascular and neurological diseases (Lopez-Revuelta *et al*., 2006). The objective of this study is to theoretically investigate the structure-activity relationship, infrared and ultraviolet absorptions of some dietary flavonoids in the light of parameters such as lipophilicity, specific-prostrate antigen (PSA) and ovality.

MATERIALS AND METHODS

MMFFaq Molecular Mechanics Conformational Distribution was used to obtain the different conformers. These gave rise to different conformers for each of the eight dietary flavonoids studied with their corresponding energies. The most stable conformer (i.e., the conformer with the

lowest energy) obtained for each molecule (Fig. 1) was fully optimized. Gas phase optimization was carried out for all the molecules with SPARTAN'10 using all available semiempirical molecular orbital theory models (MNDO, AM1, RM1 and PM3), density functional theory model with Becke three Lee Yang Parr with 6-31G*, 6-31G** basis sets; and Moller-Plesset theory at 6-31G* level.

RESULTS AND DISCUSSION

Lipophilicity: Lipophilicity is a fundamental physicochemical property that plays a pivotal role in the absorption, distribution, metabolism and elimination of therapeutic drugs. Lipophilicity is expressed in several different ways, including terms such as log p, clogp, delta log p and log D. Often a parabolic relationship exists between measured lipophilicity and in vivo brain penetration of drugs, where those moderate in lipophilicity often exhibit highest uptake. Reduced brain extraction of more lipophilic compounds is associated with increased non-specific binding to plasma proteins. More lipophilic compounds can also be more vulnerable to P450 metabolism, leading to faster clearance (Waterhouse, 2003).

Mori *et al*. (1987) reported that the lipophilic compound 7,8-dihydroxyflavone exhibited weak activity against *S. aureus* and no activity against *P. vulgaris*. These results may be related to the high lipid content of the cell wall of *P. vulgaris* which may have trapped the 7,8-dihydroxyflavone. The cell wall of *S. aureus*, lacking a lipid layer, could be penetrated. The flavonoids exhibited a stronger effect on DNA synthesis in *P. vulgaris*, while exhibiting a stronger effect on RNA synthesis in *S. aureus* (Mori *et al*., 1987).

The lipophilicity, log p values above indicate that the order in which the flavonoids have affinity for lipid is apigenin = galagin>catechin>fisetin = kaempferol>morin = quercetin>myrcetin. Negative and large value of log p corresponds to lower affinity for lipids and increased reactivity against oxidants. The relationship between log p values and the flavonoids antioxidant effectiveness are in inverse proportional. That is, the lower the value of log p, the higher the antioxidant effectiveness and vice-versa as shown in Fig. 2.

This relationship between log p and antioxidant effectiveness is in agreement with the work of Xu and Lee (2001). Xu and Lee (2001) noted that the wide range of myricetin activity, both against Gram-positive and Gram-negative bacteria, was related to its inhibition of protein synthesis. They reported that only polyhydroxylated derivatives of flavonoids, except for flavone which contains no hydroxyl groups, were active against MRSA. The presence of at least one hydroxyl group in rings A or B at C-3, C-5 and C-7 was important for activity.

All the flavonols examined, except galagin which lacks hydroxyl substituent on its B ring, have higher reactivity than other flavonoids (catechin, a flavanol and apigenin, a flavone). Asides the contribution of the C-3, C-5 and C-7 hydroxyl substituent to reactivity, the presence of one or more

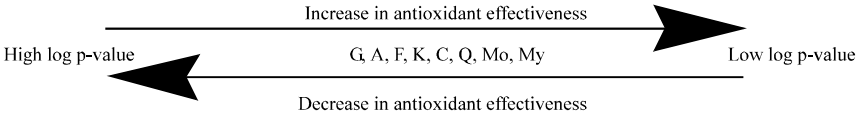

Fig. 2: Relationship between lipophilicity and antioxidant effectiveness of the studied flavonoids (A, G, C, F, K, Mo, Q and My represent apigenin, galagin, catechin, fisetin, kaempferol, morin, quercetin and myrcetin, respectively)

Table 1: Calculated hydrophobicity (log p) and haemoglobin delta (HBD) and haemoglobin alpha (HBA) counts

Structures	log p	HDB count	HBA count
Apigenin	-2.34	3	5
Catechin	-3.45	5	6
Fisetin	-3.46	4	6
Galagin	-2.38	3	5
Kaempferol	-3.46	4	6
Morin	-4.54	5	7
Myrcetin	-5.63	6	8
Quercetin	-4.54	5	7

Dimensionless unit

of this on the B rings, especially at C-3', C-4' and C-5', also contribute to high antioxidant activity. This is in line with the results of Mori *et al.* (1987). They observed a relationship between the structures of the flavonoids and their activity against *P. vulgaris* and *S. aureus*. Most of the activity was related to the presence of hydroxyl groups C-3', C-4' and C-5' in ring B and at C-3. Epigallocatechin and dihydrorobinetin exhibited weak activity indicating that the C_2-C_3 double bond was not crucial for antibacterial activity (Mori *et al.*, 1987). Schinazi reported that quercetin, myricetin and quercetagetin were shown to inhibit cellular DNA polymerase-**β** and DNA polymerase-I and that quercetin and queretagetin were strong inhibitors (Lin *et al.*, 1997).

Haemoglobin H_bA content: Haemoglobin subumit delta is a protein in humans encoded by HDB. Two **α**-chains plus two **β**-chains constitute H_bA which in adult life comprises about 97% of the total haemoglobin. As given in Table 1, a molecule with two HBA counts and two HBD counts can be said to have 1 H_bA. From the computed values for all the molecules, the order of increasing H_bA property of the flavonoids is apigenin = galagin<catechin = kaempferol = fisetin<quercetin = morin = myrcetin.

Prostate-specific antigen: Prostate-specific antigen, or PSA, is a protein produced by cells of the prostate gland. The blood level of PSA is often elevated in men with prostate cancer and a number of benign (not cancerous) conditions can cause a man's PSA level to rise. The most frequent benign prostate conditions that cause an elevation in PSA level are prostatitis (inflammation of the prostate) and benign prostatic hyperplasia (BPH) (enlargement of the prostate). The more a man's PSA level, the more likely it is that he has prostate cancer (Thompson *et al.*, 2004). Flavonoids are now also being evaluated in terms of prostate cancer prevention (Strom *et al.*, 1999). The full impact of these compounds, found in fruits, vegetables, tea and others on prostate disease development and treatment has yet to be determined. *In vitro* studies have demonstrated the partial estrogen/anti-estrogen activities of soy isoflavones and other flavonoids (Le Bail *et al.*, 1998; Zava *et al.*, 1997), as well as their antioxidant effects (Noroozi *et al.*, 1998; Ng *et al.*, 2000). In this study, the value of PSA is a measure of how much a flavonoid can inhibit the production of postrate cancer. High PSA value connotes high effectiveness of the flavonoids. That is, high antioxidant capacity of flavonoids corresponds to high calculated PSA value and great suppression of cancer growth. Hence, depending on the PSA value, (Table 2), the order of antioxidant potential of the studied flavonoids is galagin<apigenin<kaempferol<catechin<quercetin<morin<myrcetin.

Table 2: Calculated prostrate-specific antigen (PSA), ovality (dimensionless) and polarizability (in Bohr3)

Parameters	MNDO	AM1	RMI	PM3	B3LYP/ 6-31G*	B3LYP/ 6-31G**	MP2/ 6-31G*
Structure I							
PSA (Å2)	76.984	75.668	75.638	74.410	73.485	73.264	74.398
Ovality	1.400	1.380	1.370	1.380	1.370	1.370	1.370
Polarizability	60.170	60.010	59.760	59.910	60.840	59.490	59.430
Structur II							
PSA (Å2)	103.724	101.042	101.402	101.833	101.270	101.134	
Ovality	1.450	1.420	1.420	1.420	1.420	1.420	
Polarizability	61.520	61.210	61.080	61.200	61.980	60.510	
Structure III							
PSA (Å2)	98.260	94.723	95.911	96.711	92.156	92.043	92.985
Ovality	1.420	1.390	1.400	1.410	1.390	1.390	1.390
Polarizability	60.870	60.740	60.520	60.660	61.570	60.280	60.250
Structure IV							
PSA (Å2)	76.279	72.065	72.030	73.394	69.008	68.866	70.177
Ovality	1.400	1.360	1.370	1.380	1.350	1.350	1.360
Polarizability	60.240	60.060	59.800	59.960	60.880	59.580	59.530
Structure V							
PSA (Å2)	95.885	91.764	91.563	92.700	88.775	88.603	89.928
Ovality	1.420	1.380	1.390	1.390	1.380	1.370	1.380
Polarizability	60.830	60.880	60.400	60.560	61.470	60.180	60.140
Structure VI							
PSA (Å2)	117.037	112.120	108.992	109.961	107.073	106.882	108.192
Ovality	1.440	1.410	1.400	1.400	1.400	1.400	1.400
Polarizability	61.510	61.300	61.020	61.190	62.080	60.740	60.700
Structure VII							
PSA (Å2)	133.862	128.695	129.125	129.952	124.735	124.534	125.639
Ovality	1.450	1.420	1.420	1.430	1.400	1.400	1.410
Polarizability	62.010	61.840	61.550	61.720	62.610	61.320	61.290
Structure VIII							
PSA (Å2)	114.788	110.157	110.17	111.204	106.466	106.281	107.435
Ovality	1.430	1.400	1.40	1.410	1.390	1.390	1.390
Polarizability	61.440	61.280	61.00	61.160	62.040	60.770	60.730

Ovality: In computational chemistry, especially in QSAR studies, ovality refers to a measure of how the shape of a molecule approaches a sphere (at one extreme) or a cigar shape (at the other):

$$O=\frac{A}{4\pi\left(\frac{3V}{4\pi}\right)^{\frac{2}{3}}}$$

where, O is Ovality, A is Area and V is Volume (Henre and William, 2008).

High ovality value (Table 2) suggests a flavonoid molecular structure's proneness to deviation from its shape, thereby loosing activity as fast as possible.

Ultraviolet-visible spectroscopy: Ultraviolet-visible spectroscopy (UV = 200-400 nm, visible = 400-800 nm) corresponds to the excitations between the energy levels that correspond to the molecular orbitals of the systems. In particular, transitions involving π orbitals and lone pairs (n = nonbonding) are important a nd so UV-Visible. spectroscopy is most useful for identifying conjugated systems which tend to have stronger absorptions. The absorption of the electromagnetic radiation excites an electron to the LUMO and creates an excited state. The more highly conjugated the system, the smaller the HOMO-LUMO gap i.e., ΔE and therefore the lower the frequency and the longer the wavelength (Olajire, 2011). The ultraviolet spectra of the molecules under study calculated with DFT/B3LYP/6-31G* model chemistry are shown in Fig. 3a to h. As the HOMO-LUMO transition occurs in the ultraviolet region, near or out of the visible region, it can be predicted that these molecules will be colorless or slightly colored. All the dietary flavonoids studied except apigenin (a flavone) and catechin (a flavanol) are flavonols and they have strong absorptions close to the visible region and can be predicted to be more colored. Flavonol morin, for example, has the longest wavelength at 379.17 nm and its band encroach into the visible region than other flavonols as a result of the presence of more hydroxyl groups (auxochromes) on its B ring. It is therefore likely to be more colored than other flavonols. Catechin, a flavanol, lacks C_2-C_3 double bond, meaning that the hydroxyl groups at C_3 and C_4 has no contribution to the wavelength. Its absorption wavelength is therefore due to the A and B rings and their auxochromes (polyphenols).

Infrared spectroscopy: Characteristics infrared (IR) absorption bands such as C = O_{str}, C-H_{str}, C-O_{str}, C=$C_{str(aromatic)}$ among others were observed for the molecules. These give information on whether or not a molecule contains some functional groups. It has been shown that the structural features are very important for high antioxidant activity of flavonoids (Cody *et al*., 1986). The ability of flavonoids to scavenge radicals depends on their structures and the substituents of the heterocyclic ring A. It is also known that ortho subtituents in the B ring, especially those with electron donating capabilities enhance the free radical quenching. Among major determinants are also the presences of carbonyl group at C_4, a double bond between C_2 and C_3 conjugated with the C_4-oxo group (enabling higher electron delocalization) and C_3 hydroxyl group present in flavonols (Markovic *et al*., 2009).

Of all the model chemistry methods used for calculating the vibrational frequencies of the functional groups for all the molecules under study, MP2/6-31G* model chemistry gave the best prediction when compared with literature data. In fisetin molecule, for instance, C = O_{str} in the C ring according to Olajire, 2011, is 1710 cm^{-1}. The calculated value and the corresponding magnitude of variation from the literature value (1710cm^{-1}) is 2089 cm^{-1} (379) for semi-empirical MNDO basis set, 2026 cm^{-1} (316) for AM1, 1949 cm^{-1} (239) for RM1, 1935 cm^{-1} (225) for PM3, 1705 cm^{-1} (5) for DFT/B3LYP/6-31G*, 1703 cm^{-1} (7) for DFT/B3LYP/6-31G** and 1711 cm^{-1} (1) for MP2/B3LYP/6-31G*. MP2/B3LYP/6-31G* model chemistry with the lowest magnitude of variation from the literature data best predicts the IR absorption band. Catechin molecule lacks carbonyl group at C_4 and the vibrational frequencies observed from 1668-1709 cm^{-1} are due to the C = $C_{str(aromatic)}$ in its A and B rings. It is therefore worthy of note that the antioxidant capacity of flavanol catechin can be attributed to its possession of hydroxyl groups in the molecule. The

Table 3: Calculated infrared absorption bands of functional groups in apigenin molecule (cm^{-1})

Vibrations	Experimental	MP2/6-31G*	DFT/B3LYP/6-31G*	PM3
C-H_{def}(aromatic)	790-850	751-841	816-847	879, 900-98
C-O_{str}(lactone)	1200-1275	1340	1217	1053-1206
C-O_{str}(aromatic)	About 1230	1229-1325	1053-1126, 1207-1325	1248, 1554
C=C_{str}(aromatic)	1500, 1580, 1600	1498-1690	1511-1642	1476, 1554-1851
C=O_{str}(ketone)	1675, 1690	1674, 1714-1750	1655, 1680-1719	1908
C-H_{str}(aromatic)	3010-3040	3211-3274	3045-3073	3177-3250
O-H_{str}(bonded)	3100-3400	3313	3149	3683
O-H_{str}(free)	3600	3751	3749-3750	3751
Catechin molecule (cm^{-1})				
C-H_{def}(aromatic)	790-850	753-809	825-943	935-984
C-H_{def}(aliphatic)	Around 1400	1298, 1373-1465	1231, 1407-1447	1164
C-H_{str}(sp)	2800-2950	3029	2963-3033	2813-2845
C-O_{str}(aliphatic)	About 1100	1102, 1156	1099-1154	1311, 1332
C-O_{str}(lactone)	1200-1275	979, 1096	1082	1254-1268
C-O_{str}(aromatic)	About 1230	1311-1352	1341	Nil
C=C_{str}(aromatic)	1500, 1580, 1600	1485-1706	1506-1686	1425-1803
C-H_{str}(aromatic)	3010-3040	3214-3261	3178-3232	3047-3068
O-H_{str}(bonded)	3100-3400	3725-3727	3724-3727	Nil
O-H_{str}(free)	3600	3752-3757	3750-3753	3873-3887
Fisetin molecule (cm^{-1})				
C-H_{def}(aromatic)	790-850	771-1000	855, 860	798-993
C-O_{str}(lactone)	1200-1275	1134	1126, 1211-1256	1330-1362
C-O_{str}(aromatic)	About 1230	1310-1356	1299-1366	1391-1490
C=C_{str}(aromatic)	1500, 1580, 1600	1531-1696	1554-1652	1611-1870
C=O_{str}(ketone)	1675, 1690	1696-1715	1667-1705	1935
C-H_{str}(aromatic)	3010-3040	3216-3266	3180-3248	3040-3070
O-H_{str}(bonded)	3100-3400	3505-3766	3435	3865
O-H_{str}(free)	3600	3754	3708-3771	3883-3891
Galagin molecule (cm^{-1})				
C-H_{def}(aromatic)	790-850	749-956	816-951	947-1079
C-O_{str}(lactone)	1200-1275	1117	1118-1159	1211-1215, 1340
C-O_{str}(aromatic)	About 1230	1258-1326	1188-1340	1388-1405
C=C_{str}(aromatic)	1500, 1580, 1600	1478-1742	1498-1710	1608-1861
C=O_{str}(ketone)	1675, 1690	1685	1623, 1654	1890
C-H_{str}(aromatic)	3010-3040	3235-3275	3202-3250	3050-3069
O-H_{str}(bonded)	3100-3400	3396-3538	3297-3497	3696
O-H_{str}(free)	3600	3709-3765	3705-3774	3879-3891
Kaempferol molecule (cm^{-1})				
C-H_{def}(aromatic)	790-850	1138-1242	1156-1226	944-1206
C-O_{str}(lactone)	1200-1275	Nil	1280	1211, 1261
C-O_{str}(aromatic)	About 1230	1262, 1436	1305	1240
C=C_{str}(aromatic)	1500, 1580, 1600	1470-1648, 1700-1742	1479-1711	1520-1866
C=O_{str}(ketone)	1675, 1690	1653, 1686	1655	1891
C-H_{str}(aromatic)	3010-3040	3224-3277	3188-3267	3054-3080
O-H_{str}(bonded)	3100-3400	3396-3550	3303-3501	3696-3870
O-H_{str}(free)	3600	3751	3750	3879

Table 3: Continue

Vibrations	Experimental	MP2/6-31G*	DFT/B3LYP/ 6-31G*	PM3
Morin molecule (cm^{-1})				
C-H_{def}(aromatic)	790-850	1159-1228	844-1145	920-1071, 1147-1216
C-O_{str}(lactone)	1200-1275	1249	1258	1238, 1350-1362
C-O_{str}(aromatic)	About 1230	1317-1372	1302, 1362-1369	1256, 1372
C=C_{str}(aromatic)	1500, 1580, 1600	1507-1709	1520-1695	1501-1860
C=O_{str}(ketone)	1675, 1690	1712-1720	1709	1934
C-H_{str}(aromatic)	3010-3040	3229-3262	3201-3241	3041-3068
O-H_{str}(bonded)	3100-3400	3477-3562	3401-3505	3829-3856
O-H_{str}(free)	3600	3721-3764	3728-3770	3881-3894
Myricetin molecule (cm^{-1})				
C-H_{def}(aromatic)	790-850	790	793	945-1118
C-O_{str}(lactone)	1200-1275	1119-1153	1122-1144	1209
C-O_{str}(aromatic)	About 1230	1055, 1210	1273-1352	1218-1240
C=C_{str}(aromatic)	1500, 1580, 1600	1489-1599	1557-1709	1564-1864
C=O_{str}(ketone)	1675, 1690	1648-1685	1623-1654	1891
C-H_{str}(aromatic)	3010-3040	3235-3274	3203-3259	3054-3069
O-H_{str}(bonded)	3100-3400	3396-3536	3297-3496	3697
O-H_{str}(free)	3600	3712-3766	3716-3775	3870-3890
Quercetin molecule (cm^{-1})				
C-H_{def}(aromatic)	790-850	780-875	1037-1158	944-945, 1048-1212
C-O_{str}(lactone)	1200-1275	1116	1242	1342
C-O_{str}(aromatic)	About 1230	1206-1230	1195-1222	1231-1323
C=C_{str}(aromatic)	1500, 1580, 1600	1467-1580	1534-1638	1418-1863
C=O_{str}(ketone)	1675, 1690	1651	1654	1891
C-H_{str}(aromatic)	3010-3040	3209-3278	3176-3267	3053-3072
O-H_{str}(bonded)	3100-3400	3393-3549	3292-3507	3696-3870
O-H_{str}(free)	3600	3751	3747-3751	3879-3886

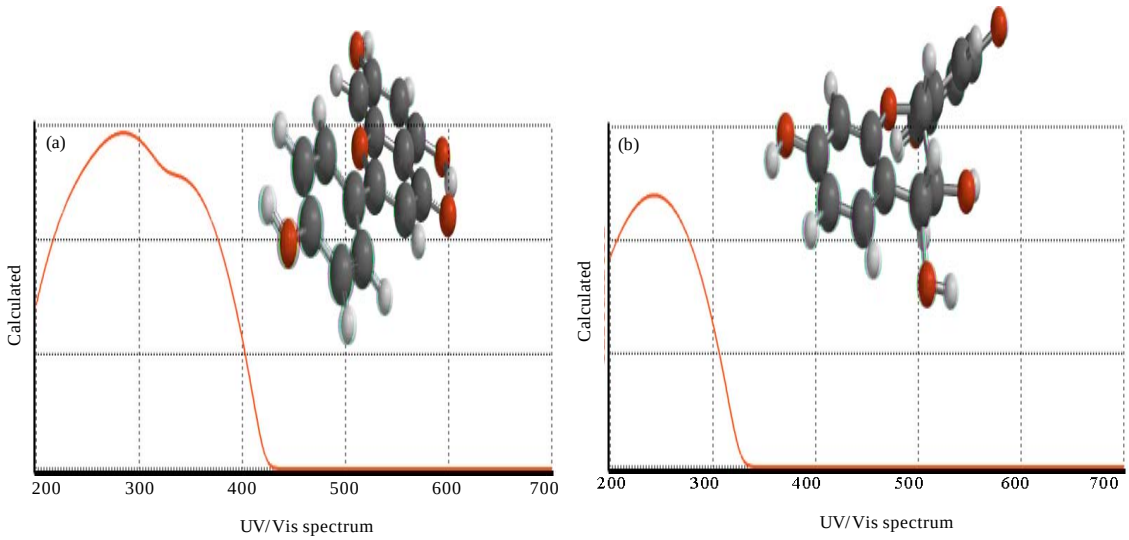

Fig. 3(a-h): Continue

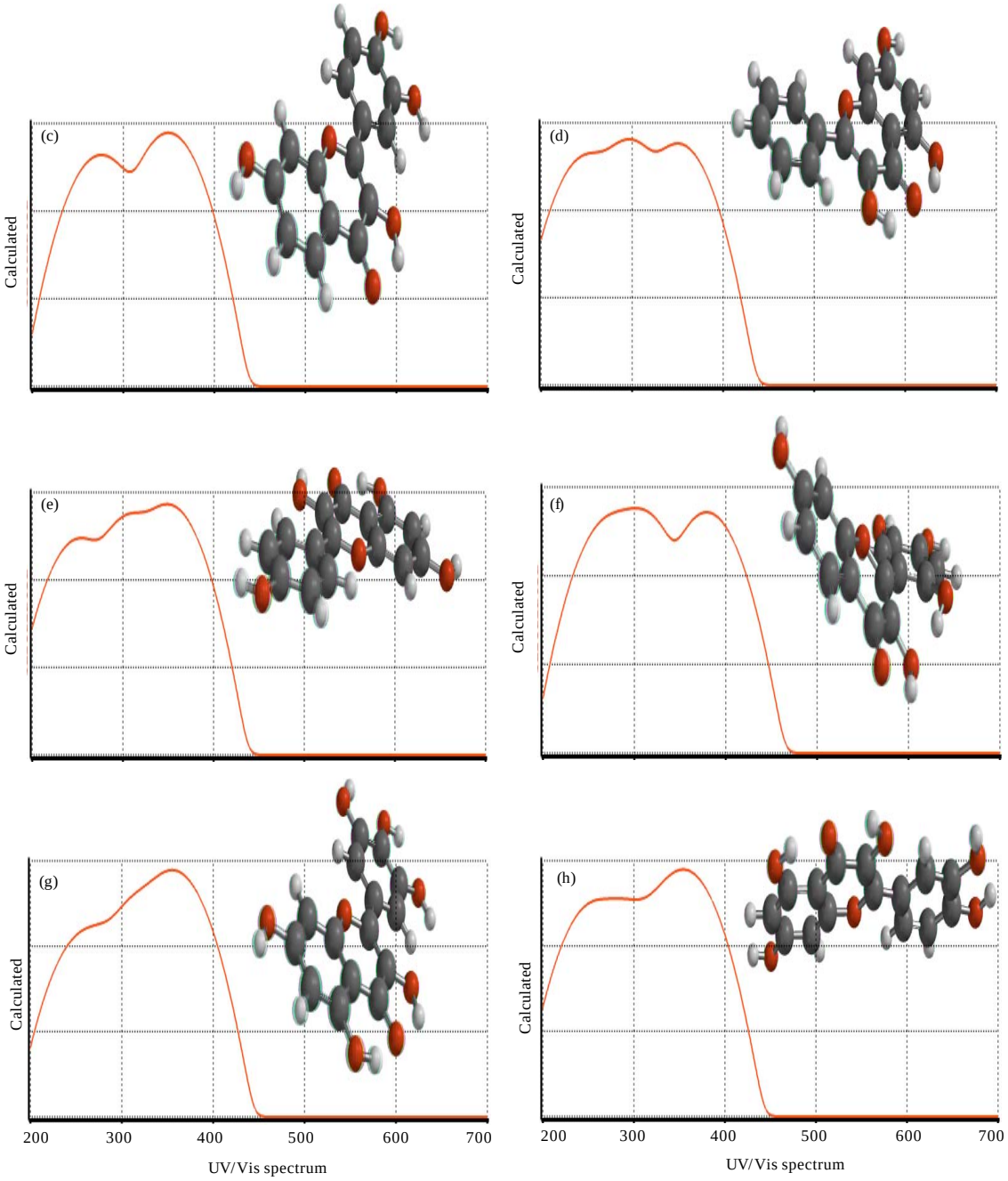

Fig. 3(a-h): (a) UV of apigenin calculated with DFT/B3LYP/6-31G* (b) Catechin calculated with DFT/B3LYP/6-31G*, (c) Fisetin (d) Galagin, (e) Kaempferol, (f) Morin, (g) Myrcetin and (h) Quercetin

infrared absorption bands of the functional groups in each of the molecules at three levels of calculations (MP2, DFT and PM3) are compared with corresponding experimental values shown in Table 3 Spectra showing the calculated IR absorption bands for the molecules under study are presented in Fig. 4 a to h.

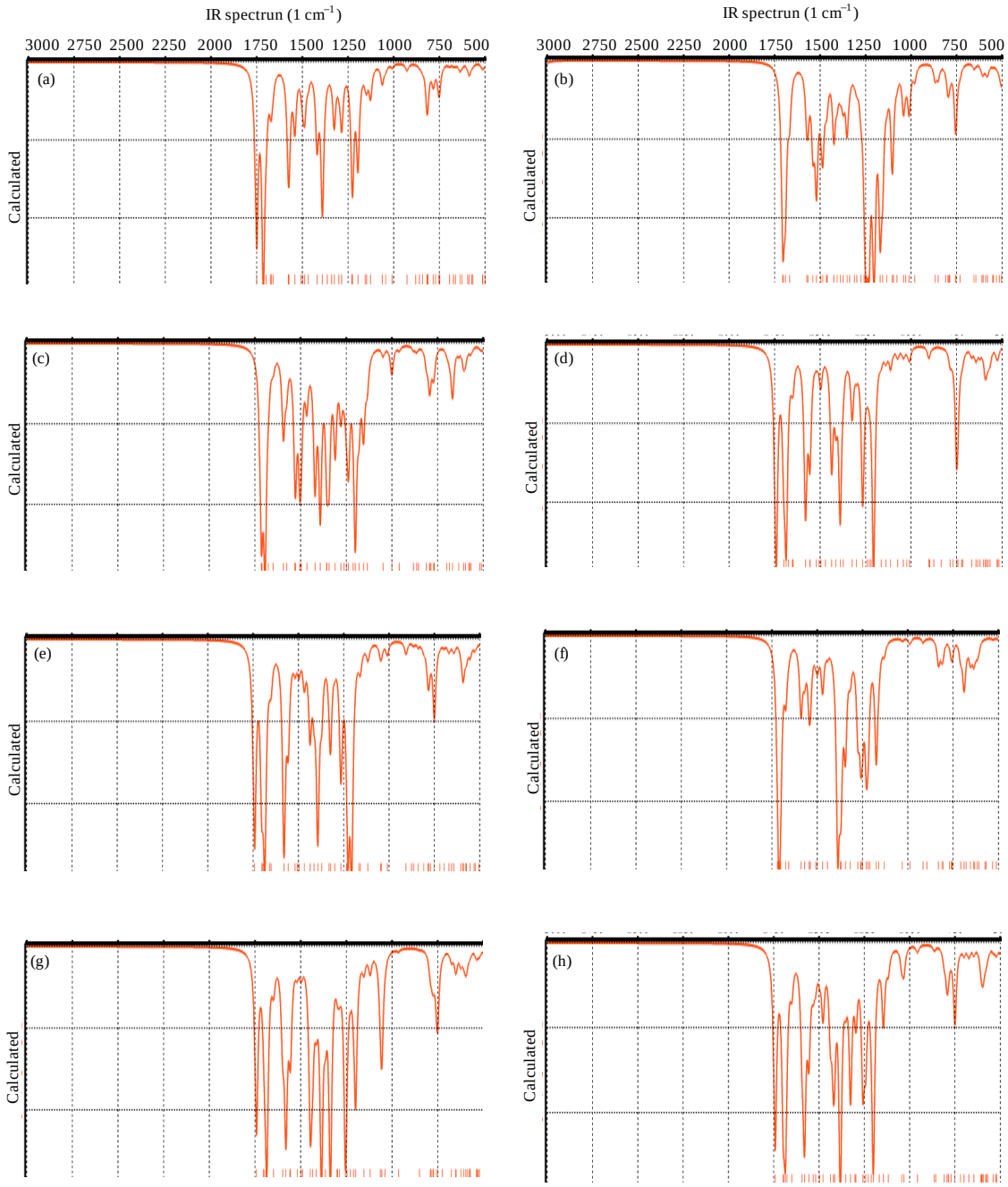

Fig. 4(a-h): (a) IR of the apigenin calculated with MP2/6-31G*, (b) IR catechin calculated with MP2/6-31G*, (c) Infrared spectra of the fisetin calculated with MP2/6-31G*, (d) Infrared spectra of the galagin calculated with MP2/6-31G*, (e) Infrared spectra of the kaempferol calculated with MP2/6-31G*, (f) Infrared spectra of the morin calculated with MP2/6-31G*, (g) Infrared spectra of the myrcetin calculated with MP2/6-31G* and (h) Infrared spectra of the quercetin calculated with MP2/6-31G*

CONCLUSION

The use of molecular modeling techniques via simulation of molecules has great impact on research and served as eye opener into the relevance of computational methods in scientific and non-scientific research. Antioxidant capacity of flavonoids can be attributed to their structures, as examined experimentally and also as treated theoretically in this study. Lipophilicity (logP), values showed that myrcetin has highest antioxidant effectiveness among all the studied flavonoids; which was also confirmed by the calculated PSA values. Applied theoretical approach confirms the importance of the B-ring and sheds light on the role of the C_3-OH group in reactivity, influencing antioxidant properties of the molecule which is dependent upon the presence of the C_2-C_3 double bond (Markovic *et al*., 2009). Infrared absorption spectra also indicated that this bond (C_2-C_3 double bond) is one of the determinants of how reactive a flavonoid will be; coupled with this is the information on their ultraviolet absorption which shows the contribution of the hydroxyl substituents on both A and B rings meaning that high number of hydroxyl substituent is in direct proportion to the effectiveness of flavonoids.

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