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DFT study of chemical reactivity of free radicals ABTS°$^{+}$ and DPPH° by Myricetin, Quercetin and Kaempferol

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ABSTRACT

Myricetin, quercetin and kaempferol are polyphenols belong to the group of flavonoids. They are known for their many biological activities and particularly their strong ability to trap free radicals that cause nuisance to living organisms. In order to rationalize and compare the antioxidant activities of these molecules, DFT study was conducted in the gas phase, at B3LYP / 6-311G (d, p) and M05-2X / 6-311G (d, p). approximation levels. Calculations carried out relate to electronic affinity EA, ionization energy IP, energy gap (HOMO-LUMO), hardness (η), softness (S), electronegativity (χ), electrophilic index (ω) and energy parameters. Results of various calculations compared to those of trolox, molecule identified in our previous work as reference for study antioxidant properties of bioactive molecules have shown that: The three molecules are good antioxidants and could be effective to fight the oxidative attacks of living organisms; The hydroxyl groups of catechol group and $C^2 = C^3$ double bond are determinant for the antioxidant activity of the three molecules; Myricetin is the most antioxidant among the three molecules followed by quercetin; The radical ABTS°$^{+}$ is more suitable for studying the antioxidant properties of molecules.

***Keywords*:** antioxidant activity, DFT, B3LYP, M05-2X

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1. INTRODUCTION

Flavonoids are organic molecules belonging to family of polyphenols which are polysubstituted aromatic molecules having role of secondary metabolites in plants. In organic compounds, flavonoids are one of the most important families; more than 9000 natural compounds are isolated, characterized and divided into different classes, the most important are: flavones, flavonols, flavanols, flavanones, dihydroflavanols, isoflavones, isoflavanones, chalcones, aurones and anthocyanins [1]. These compounds are known for their antioxidant character; they neutralize free radicals thus limiting certain oxidative damage responsible for certain diseases. They were meeting both in free form and in the form of glycosides. They are generally found in various organs of vascular plants: root, stem, wood, leaves, flowers and fruits [2].

Flavonoids are molecules recognized for their many biological activities. Several studies relating to their antiradicular activity have been reported in literature and show that, thanks to their low redox potential, they reduce free oxidizing radicals such as superoxides, peroxyl, alkoxyl and hydroxyl, by transfer of 'hydrogen.

Flavones and flavonols represent majority of flavonoids. Among the flavonols, we have quercetin derivatives, such as myricetin, fisetin and kaempferol and flavones include luteolin. Myricetin, quercetin, and kaempferol, which are flavonoids, with respective oxidation-reduction potentials of 0.310 V, 0.355 V, 0.433V, can reduce all radicals with redox potential greater than their [3].

Also, several works have been done to elucidate biological activities of myricetin, fisetin, kaempferol and luteolin. For example, from experimental point of view, numerous studies have shown that myricetin is qualified as the best flavonoid because of its multiple biological properties namely: antioxidants [4,5], anticarcinogen [6,7], anti-inflammatory [8,9], antibacterial [10], antiviral [11], and antidiabetic [12]. In the same vein, Deepak Kumar Semwal et *al.*; in 2016 [13] proved that myricetin is good antioxidant, it protects the body against lipid attacks and helps fight against Parkinson's and Alzheimer's diseases.

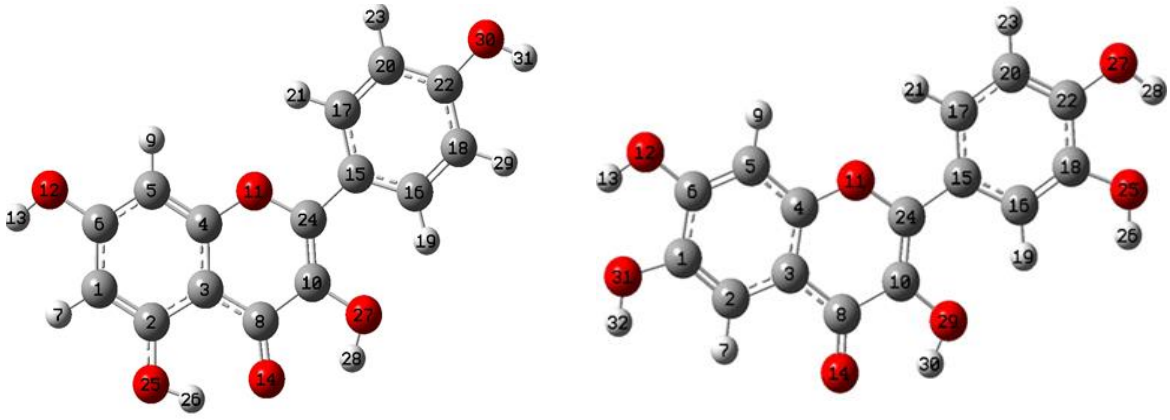
From theoretical point of view, results have also been published in literature on myricetin, fisetin, kaempferol and luteolin. Indeed, by calculations made with the approximations B3LYP / 3-21G* and B3LYP / 6-311 ++ G*, Pham Thanh Quan et *al.* ; in 2006 [14] showed a linear correlation between the spin density of the oxygen atom and the antioxidant activity of taxifolin, morin, luteolin, kaempferol and myricetin. and quercetin when they trap a radical. The work of these authors has also found that hydroxyl groups are the sites of manifestation of the antioxidant properties of each of these molecules. In 2010, Gonçalo C. et *al.* [15]; used six different semi-empirical methods to study the mechanisms of antioxidant properties in solution and gas phase of quercetin and myricetin. Their study revealed that there is not really much difference between molecular properties of these flavonols. However, they differ only in their mechanisms of manifestation of antioxidant properties especially when they are dissolved. They also showed that of the six methods, PM6 is better suited for studying the properties of these molecules. By B3LYP / 6-311G (d) method of DFT, Weirong Cai et *al.*; in 2014 [16] explored molecular properties and antioxidant activity of quercetin, hyperin and rutin. The calculation of the rupture dissociation enthalpy (BDE) and energy gap were compared with experimental results obtained by spectrophotometry. The results showed that these three molecules are very good scavengers of free radicals. They also proved that quercetin is the best antioxidant among the three.

The objective of the present work is to carry out comparative study of the antioxidant properties of myricetin, quercetin and kaempferol, by the methods of quantum chemistry. The reactivities of these molecules will be compared to that of trolox identified in our previous work as reference molecules for the study of the antioxidant properties of natural or synthetic bioactive molecules. To achieve this objective, various electronic, spectroscopic and energetic parameters have been calculated, and the results will make it possible to deduce an order of classification of the antioxidant powers of these molecules which will thus be compared to the order indicated experimentally and published in literature.

2. MATERIALS AND METHODOLOGY

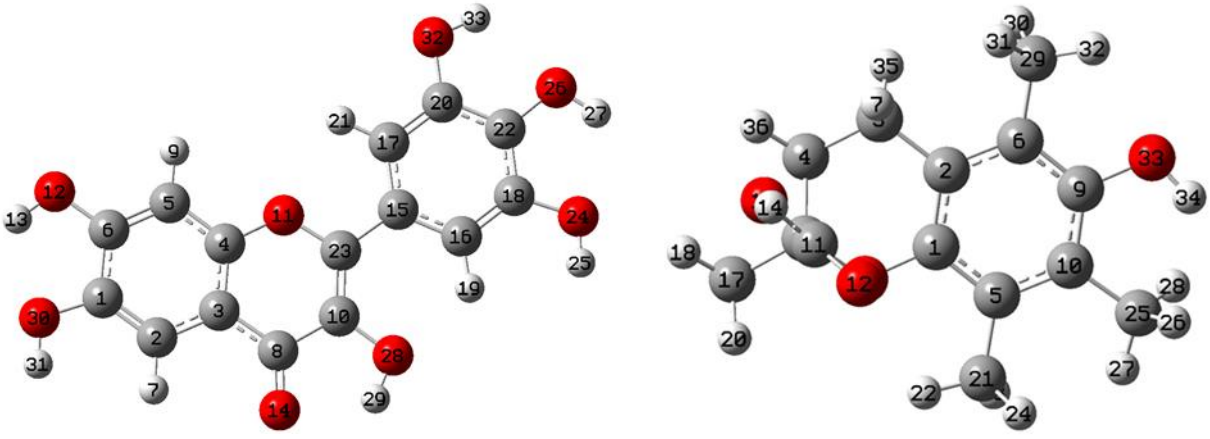
2. 1. Materials

The chemical systems in our study represent four molecules: myricetin, quercetin, kaempferol and trolox; two radicals ABTS$^{\circ +}$ and DPPH° (Figures 1, 2, and 3).



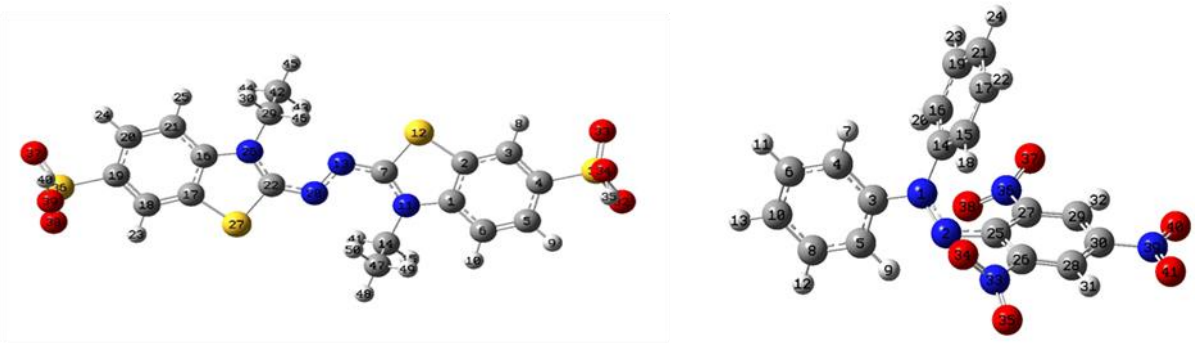
Kaempferol **Quercetin**

Figure 1. Representation of kaempferol and quercetin.



Myricetin **Trolox**

Figure 2. Representation of myricetin and trolox



Radical ABTS$^{\circ+}$ **Radical DPPH°**

Figure 3. Representation of radicals ABTS$^{\circ+}$ and DPPH°

2. 2. Methodologies

For each of the molecules (denoted ArOH), calculated electronic, energy and thermodynamic parameters were:

- electron affinity $AE = E_{ArOH^-} - E_{ArOH}$, [17] whose value indicate the ability of a molecule to accept electron or free radical;

- ionisation energy $IE = E_{ArOH^+} - E_{ArOH}$, [18],

- $Gap_{(HOMO-LUMO)} = AE - EI$, [19].

- hardness (η) which expresses the resistance of molecule to change its number of electrons or to the transfer of charge [20]. Harder the hardness, the less the molecule is reactive [21]: $\eta = \frac{(IP - EA)}{2}$

- Softness, defined as inverse of hardness [22]: $S = \frac{1}{2\eta}$

- electronegativity (χ), which measures the tendency of chemical species to attract electrons [23]: $\chi = \frac{(IP + EA)}{2}$

- electrophilic index (ω) representing the stabilization energy of molecule saturated by electrons from its surroundings [24]: $\omega = \frac{\chi^2}{2\eta}$

- energy parameters such as O-H bond dissociation energy (BDE). It is energy necessary for homolytic rupture of an O-H bond in a molecule:

$$BDE = \Delta H(ArO^{\circ}) + \Delta H(H^{\circ}) - \Delta H(ArOH \quad).$$

More lowly the energy is, more favorable is the homolytic rupture, and therefore more antioxidant is the molecule possessing the hydroxyl site.

• **Spectroscopic parameters** such as UV-visible spectra calculated by the TD-DFT method. Results of calculations will allow us to identify the molecule which is molecule likely to be quickly trapped by the radicals [25-28].

Calculations were performed by the DFT B3LYP and M05-2X functionalities in an atomic orbital base of Pople (6-311G (d, p) [29].

3. RESULTS AND DISCUSSIONS

3. 1. Study of the electronic properties of molecules

Electronic affinities (EA), ionization energy (IP), hardness (η), softness (S), electronegativity (χ), electrophile index (ω), energy gap (HOMO-LUMO), molecules were calculated (in eV) by the methods DFT // B3LYP // 6-311G (d, p) and DFT // M05-2X // 6-311G (d, p). The calculation results are shown in Table 1.

Table 1. Calculated values in electron volts (eV) of the electronic parameters of trolox, myricetin, quercetin and kaempferol at the approximation levels B3LYP / 6-311G (d, p) and M05-2X / 6311G (d, p).

Paramètres électroniques	**DFT**							
	B3LYP /6-311G (d, p)				**M05-2X/6 311G (d, p)**			
	M_1	M_2	M_3	M_4	M_1	M_2	M_3	M_4
Electronic affinities (EA)	1,52	-0.63	-0.65	-0.49	1,52	-0.46	-0.27	-0.60
ionization energy (PI)	7,05	6.94	6.20	7,56	6,91	6.78	6.72	6.94
GAP (HOMO-LUMO)	5,53	7.57	6.85	8.05	5,39	7.24	6.99	7.54
electronegativity (χ)	4,29	3.16	2.78	3.54	4,22	3.16	3.23	3.17
softness (S)	0,18	0.13	0.15	0.13	0,19	0.14	0.14	0.13
electrophile index (ω)	3,32	1.32	1.13	1.56	3,30	1.37	1.49	1.34
Hardness (η)	2,77	3.79	3.43	4.02	2,70	3.62	3.5	3.76

M1, M2, M3 and M4 names of Table 1, represent respectively trolox, myricetin, quercetin and kaempferol.

On the basis of the series of results in Table 1, the following observations can be made:

- With methods B3LYP / 6311G (d, p) and M05-2X / 6311G (d, p), the Gap values (HOMO-LUMO) were obtained in descending order: trolox-myricetin-quercetin-kaempferol.

These results have shown that trolox and myricetin are more antioxidant than quercetin and kaempferol. This are in agreement with those of literature [3-5,13].

- The results obtained by the methods of B3LYP / 6311G (d, p) and M05-2X / 6311G (d, p) of DFT have not been contradictory as regards the calculation of the softness (S). The highest values were obtained for trolox and myricetin, thus displaying them as the best antioxidants of the four molecules.

- With B3LYP / 6311G (d, p) method, the lowest values of electronegativity index (χ) were obtained for myricetin. This makes myricetin the most antioxidant of the four molecules. On the other hand, at the M05-2X / 6311G approximation levels (d, p) the lowest index value was obtained for quercetin.

- Calculations of electrophilic indices (ω) carried out by the method M05-2X / 6311G (d, p) revealed that trolox and myricetin are the most electrophilic and therefore the strongest antioxidants. By calculations B3LYP / 6311G (d, p), it is rather trolox and kaempferol that appear as the most antioxidant molecules.

- The hardness values (η) were ranked in the order η kaempferol> η quercetin> η myricetin> η trolox, for both methods of DFT. These results are in agreement with experimental data from the literature that trolox is more antioxidant than myricetin, which in turn is more antioxidant than quercetin and kaempferol [15,30].

Analysis of the results of calculations of the various electronic parameters electronic affinities (EA), ionization energy (IP), hardness (η), softness (S), electronegativity (χ), electrophilic index (ω), gap of energy (HOMO-LUMO) found that, overall, the methodM05-2X / 6311G (d, p) and B3LYP / 6311G (d, p) gave results concordant with the experimental data. In both methods, the results of DFT calculations have the same tendency: trolox is more antioxidant than myricetin, which is more antioxidant than quercetin, which is more antioxidant than kaempferol.

However, since some electronic parameters have given contradictory results with those of the literature, values of O-H homolysis cleavage enthalpies (BDE) of trolox, myricetin, quercetin and kaempferol will be calculated in order to derive more precise conclusions.

3. 2. Study of binding dissociation energies (BDE) of trolox, myricetin, quercetin and kaempferol

Table 2. Calculated values (in kcal / mol) of the BDE at the B3LYP / 6-311G (d, p) and M05-2X / 6-311G (d, p) levels for trolox, myricetin, quercetin and kaempferol

Molecules	**O-H Groups**	**B3LYP**	**M05-2X**
		6-311G (d, p)	**6-311G (d, p)**
Myricetin	$O\text{-}H^{1}$	82.83	101.66
	$O\text{-}H^{6}$	95.38	101.66
	$O\text{-}H^{10}$	89.11	95.38

	O-H ^{18}	82.83	89.11
	O-H^{20}	95.38	95.38
	O-H ^{22}	82.83	89.11
Quercetin	O-H^{1}	89.11	101.66
	O-H^{6}	95.38	101.66
	O-H^{10}	95.38	95.38
	O-H ^{18}	89.11	89.11
	O-H ^{22}	95.38	95.38
Kaempferol	O-H^{10}	100.40	89.11
	O-H^{2}	114.21	120.48
	O-H^{6}	102.91	101.66
	O-H ^{22}	98.52	95.38
Trolox	O-H^{3}	92,24	82.83

For the different O-H bonds found in trolox, quercetin, myricetin and kaempferol, the calculated values, at the B3LYP and M05-2X approximation levels, of the (BDE), are given in the following Table 2.

Results in Table 2 show that:

- By B3LYP / 6-311G (d, p) method, lowest O-H homolytic cleavage (BDE) dissociation enthalpy values are mainly obtained for the OH^{1}, OH^{18} and OH^{22} bonds of myricetin and OH^{1}, OH^{18} on the other hand for quercetin.
- For kaempferol it is rather the OH^{22} bond which gave lowest enthalpy value.
- These results indicate that the hydrogen atoms H^{1}, H^{18} and H^{22} can easily dissociate from these three molecules to release radicals capable of trapping free radicals.
- Thus, the OH^{1}, OH^{18} and OH^{22} sites appear to be the most important for the manifestation of the antioxidant activity of myricetin, quercetin and kaempferol. These results do not coincide exactly with those obtained in the literature because according to Seyoumet et *al.*; in 2006 [31], the hydroxyl groups of the catechol part (cycle B) and the one linked to the C3 carbon would be partly responsible for the antioxidant properties of these bioactive molecules
- Overall, by B3LYP / 6311G (d, p) method, BDE values given for myricetin are lower than those given by quercetin and kaempferol. The antioxidant activity of myricetin is therefore more important than that of the other two molecules.

- As regards M05-2X / 6311G (d, p) method, BDE has been obtained for the OH^{18} and OH^{22} bonds of myricetin, OH^{10} for quercetin and for kaempferol it is OH^{22} bond. These results indicate that OH^{18}, OH^{22} and OH^{10} sites appear to be the most important for the manifestation of antioxidant activity of myricetin, quercetin and kaempferol.
- For this method, there is not really any noticeable difference between the values of energies produced by the three molecules. However, the sites of manifestations of antioxidant properties obtained by it are in agreement with those experimental published in the literature.
- For trolox, the lowest values of the BDE were obtained with the method M05-2X / 6311G (d, p), the trolox therefore seems more antioxidant than the three molecules by this method.
- Better than B3LYP / 6311G (d, p) method, M05-2X / 6311G (d, p) gave the results close to those experimental; the hydroxyl groups of the catechol part (cycle B) and one linked to the C^3 carbon would be partly responsible for the antioxidant properties of these bioactive molecules.

3. 3. Study of the UV-visible spectra of the ABTS and DPPH radicals by myricetin, quercetin, kaempferol and trolox.

3. 3. 1. UV-visible spectra of myricetin, quercetin, kaempferol and ABTS°$^+$ radical at M05-2X / 6-311G (d, p).

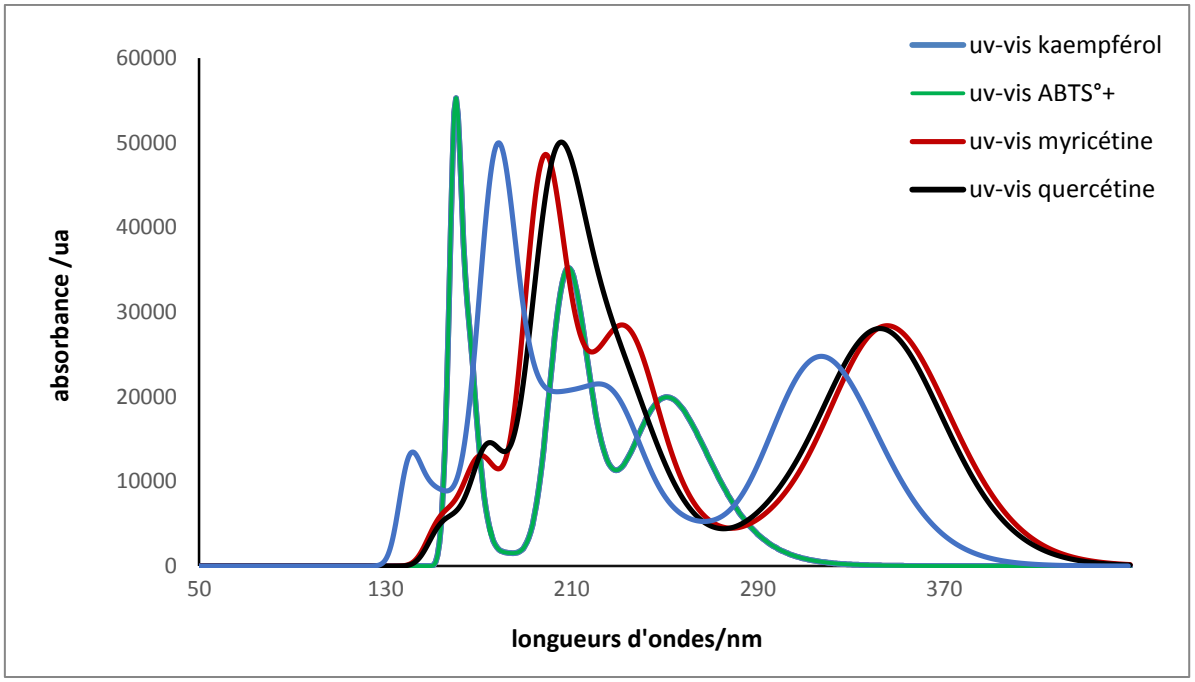


Figure 4. UV-visible spectra of myricetin, quercetin, kaempferol and ABTS°$^+$ radical at M05-2X / 6-311G (d, p).

From the analysis of the curves, it follows that:

UV-Visible absorption spectra of $ABTS^{+}$, myricetin, quercetin and kaempferol have globally had four peak absorption peaks, the largest absorptions of which are at 250 nm, 355 nm, 350 nm and 330 nm, respectively.

It can be seen that there is no overlap between the last peak of the $ABTS^{\circ+}$ radical and that of the three molecules. There will be no spectral interference between these peaks. This means that this radical can be easily trapped by myricetin, quercetin and kaempferol. However, the peaks at 355 nm and 350 nm for myricetin and quercetin being very far from that of $ABTS^{\circ+}$ radical relative to kaempferol, indicates that better than kaempferol, myricetin and quercetin can easily trap this radical. It follows that the antioxidant properties of myricetin and quercetin are much greater than that of kaempferol. Moreover, the interference observed between the peaks of myricetin and quercetin proves that there would be no great difference between the antioxidant powers of these two molecules.

3. 3. 2. UV-visible spectra of myricetin, quercetin, kaempferol and DDPH° radical at M05-2X / 6-311G level (d, p)

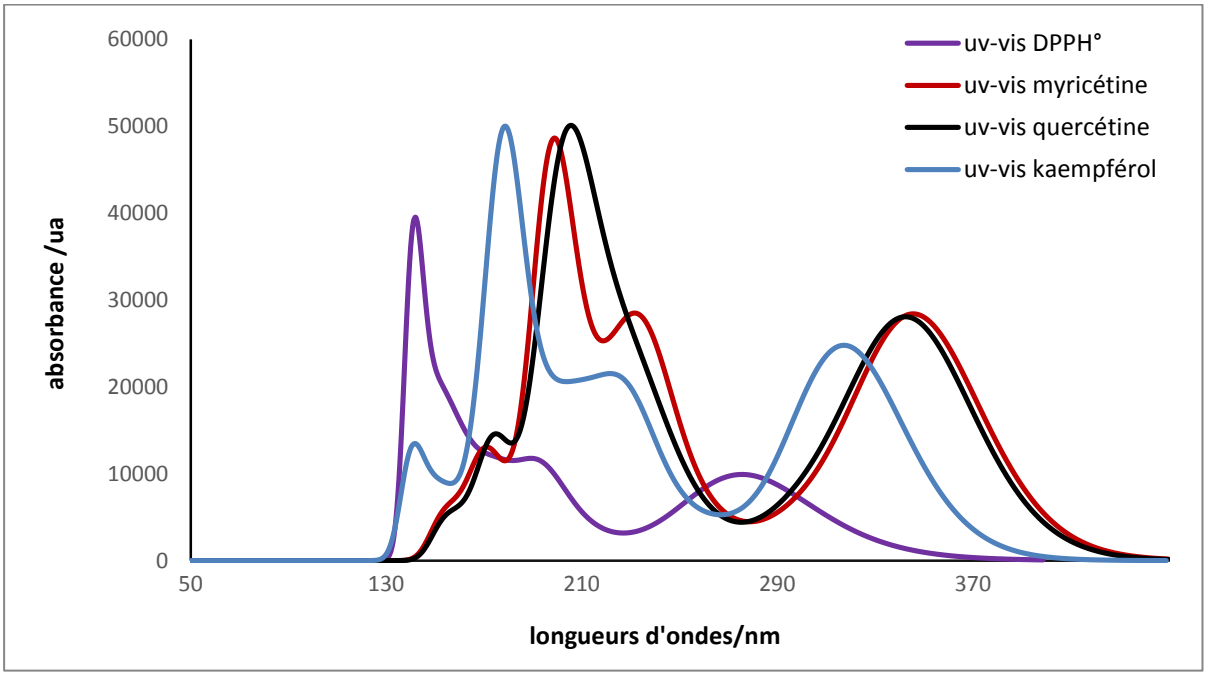


Figure 5. UV-visible spectra of myricetin, quercetin, kaempferol and DDPH° radical at M05-2X / 6-311G level (d, p)

UV-Visible absorption spectrum of the DPPH° radical exhibited the longest wavelength at 280 nm while the myricetin, quercetin and kaempferol showed overall three peak absorption peaks with the largest absorptions at 355 nm, 350 nm and 330 nm respectively. There will therefore be no spectral interference between these last absorption peaks. This means that this radical can be easily trapped by myricetin, quercetin and kaempferol.

The peak of the radical DPPH° being relatively close to those given by the myricetin, quercetin and kaempferol compared to the peak given by the radical $ABTS^{\circ+}$. It appears that DPPH° radical although able to trap these molecules seems less suitable for the study of their antioxidant properties.

These results confirm that $ABTS^{\circ+}$ radical is therefore much more suitable for studying antioxidant properties of myricetin, quercetin and kaempferol in particular and bioactive molecules in general.

4. CONCLUSIONS

Theoretical study of the chemical reactivities of three molecules (myricetin, quercetin and kaempferol) and trolox (used as a reference molecule in the experimental determination of antioxidant or antiradical activities of bioactive molecules) was carried out using B3LYP / 6-311G (d, p) methods .and M05-2X / 6-311G (d, p) of DFT. Comparison between calculated values of the various electronic and thermodynamic parameters made it possible to:

- release myricetin as the most antioxidant molecule of the three molecules and less antioxidant than trolox.
- note that the hydroxyl groups in the catechol (Cycle B) and C^3 carbon in the A ring would be responsible for the antioxidant properties of each of myricetin, quercetin and kaempferol

As far as the prediction of the antioxidant properties of the studied molecules is concerned, the theoretical results are in agreement with the experimental data, especially for the MO5-2X functional which gave the closest results of the experimental data.

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