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Theoretical investigations on the antioxidant potential of a non-phenolic compound thymoquinone: a DFT

Approach

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Abstract

Thymoquinone (TQ) is a natural compound occurred in black cumin (*Nigella sativa* L.), which possesses potent antioxidant activity without having any phenolic hydroxyl group believed to be responsible for antioxidant activity of a molecule. In the present study, computational calculation based on Density Functional Theory (DFT) have been executed to assess systematically the worth of antioxidant behavior of this compound. Geometrical characteristics, HOMO-LUMO and MEP surface have been studied. Thermochemical parameters correlated to the leading antioxidant mechanisms such as HAT, SETPT and SPLET have been studied in gas and water media. In addition, the changes of thermochemical parameters such as ΔG and ΔH have been computed for HA from TQ to hydroxyl radical in gas and water phases to investigate its free radical scavenging potency. The low and comparable values of BDE, PDE, IP, PA and ETE suggest the antioxidant activity. The ΔG and ΔH also convey apposite thermodynamic evidence in favor of antiradical capability of TQ. The attack of the free radical takes place preferentially at 3CH position of the molecule.

Keywords: thymoquinone, DFT, antioxidant, free radical, theoretical investigation

Introduction

Free radicals form in biological reactions in living cells [1], but some external factors such as radiation, pollutants, physical stress, pesticides, several treatments etc. also cause its formation [2]. The highly reactive free radicals can initiate chain reactions interacting with proteins, lipids and DNA, and thereby damage the tissues [3]. Foods containing antioxidant compounds play a crucial role to check the human illnesses caused by the detrimental effects of free radicals [4]. Polyphenols, phenolic acids and flavonoids either synthetic or natural can guard biomolecules against unexpected oxidative damage triggered by the free radicals. Thus, they inhibit the oxidative mechanisms that lead to degenerative diseases [5][6].

Thymoquinone (TQ) is an active component of black cumin (*Nigella sativa* L.) essential oil possessing antineoplastic, anti-inflammatory, neuro- and hepato-protective properties. These properties are attributed to the antioxidant potential of TQ, which seems to be unlikely due to its structure [7]. It has a number of pharmacological properties, among them antioxidant activity is the most important one [8]. It is a common belief that, only the compounds having phenolic OH groups are responsible for antioxidant activity and/or free radical scavenging power [9][10][11][12]. Recently it has been proved that, compound without phenolic OH group can pose antioxidant or antiradical capability. Baschieri et al explained the antioxidant activity of three common non-phenolic terpenoids [13]. Several investigations have

also exposed that some CH bonds contribute to the antioxidant characteristics of natural products [14][15]. Antioxidant potential of TQ is well recognized in various literature [16][17][18][19], although it also does not contain any phenolic OH group.

In computational method, the antioxidant activity of a compound can be thermodynamically evaluated by some physicochemical descriptors such as bond dissociation enthalpy (BDE), proton dissociation enthalpy (PDE), proton affinity (PA), ionization potential (IP), electron transfer enthalpy (ETE), hardness, softness and electronegativity. Recently, computational techniques, especially DFT method, have been commendably applied to determine these thermodynamic parameters of antioxidant molecules [3][20].

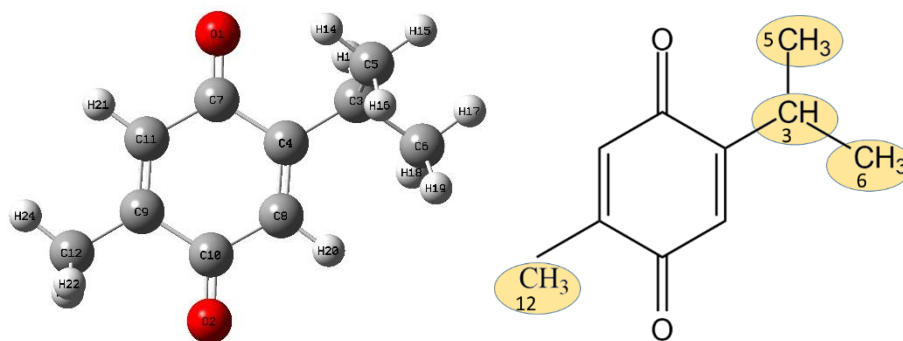
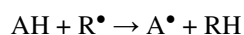


Figure 1. Optimized (left) and schematic structures of TQ and possible groups considered for antioxidant action (right)

However, so far we have studied, no or less computational study on the antioxidant power of TQ molecule (Figure 1) has been reported till date. The objective of this article is to apply the computational methods to evaluate the antioxidant ability of TQ in connection to its non-phenolic structure. In addition, the stability of the formed radicals from the entitled compound has been explained to govern the comparative radical scavenging ability of the groups undertaken in this study.

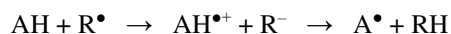
In the modern computational platform, antioxidant ability of a compound can be successfully determined by monitoring some specific chemical reaction mechanisms. Among them, hydrogen atom transfer (HAT) is familiar one and defined as follows:



Which relates to the bond dissociation enthalpy (BDE) of the corresponding (A-H) bond that presents direct relation to experimental determination of antioxidant activity [21].

$$\text{BDE} = H(\text{A}^\bullet) + H(\text{H}^\bullet) - H(\text{AH})$$

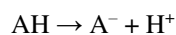
Another important mechanism is the single electron transfer-proton transfer mechanism (SETPT) in which the IP of the molecule and PDE from $\text{AH}^{\bullet+}$ are accounted [3].



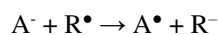
$$\text{IP} = H(\text{AH}^{\bullet+}) + H(\text{e}) - H(\text{AH})$$

$$\text{PDE} = H(\text{A}^\bullet) + H(\text{H}^+) - H(\text{AH}^{\bullet+})$$

The third pathway is sequential proton loss electron transfer (SPLET) mechanism to investigate the antioxidant potential of a molecule [22]. SPLET is given by:



$$\text{PA} = H(\text{A}^-) + H(\text{H}^+) - H(\text{AH})$$



$$\text{ETE} = H(\text{A}^\bullet) + H(\text{e}) - H(\text{A}^-)$$

The reactivity and stability of a molecule are considered as significant factors to determine the antioxidant potency which depend upon the difference (ΔE) between lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) [23]. Large ΔE indicates low reactivity and high stability of the compound. The chemical reactivity also rest on the synergistic effects of different parameters. The E_{HOMO} energy of a molecule show the electron donating ability whereas E_{LUMO} characterizes electrons accepting ability. Ionization potential (IP) and electron affinity (EA) are also roughly accompanying with E_{HOMO} and E_{LUMO} according to Janak's Theorem [24].

$$IP = -E_{\text{HOMO}}$$

$$EA = -E_{\text{LUMO}}$$

Hardness (η) is defined as resisting power towards the polarization of electron cloud of a chemical species [25].

$$\text{Hardness, } \eta = \frac{IP - EA}{2}$$

$$\text{or Hardness, } \eta = \frac{E_{LUMO} - E_{HOMO}}{2}$$

Softness is just reciprocal of the hardness [26].

$$\text{Softness, } \sigma = \frac{1}{\eta}$$

Electronegativity (χ) can be described as the ability of an atom to have more attraction to covalently bonded shared electrons toward itself. It is computed as follows:

$$\text{Electronegativity, } \chi = \frac{-(E_{HOMO} + E_{LUMO})}{2}$$

Thus, antioxidant power of a compound can be estimated by taking account all the possible physicochemical characteristics such as geometrical, thermochemical and orbital.

Computational details

All calculations were accomplished in Gaussian 9 software tool [15]. The structures of TQ, its ions and radicals were optimized using the functional B3LYP [27] and basis set 6-311+G(d,p) in gas phase and water medium. This methodology has demonstrated good agreement between theoretical and experimental outcomes [28][29]. All the optimized structures were accepted through vibrational frequency analysis (no imaginary frequency was found for optimized structure). The thermochemical parameters (BDE, IP, PDE, PA, ETE) associated with antioxidant mechanisms have been calculated for the TQ molecule as follows [30][31]. Here in the equations, TQ has been written as (TQ-H) for better understanding.

$$\text{BDE} = H(\text{TQ}^\bullet) + H(\text{H}^\bullet) - H(\text{TQ-H})$$

$$\text{IP} = H(\text{TQ-H}^{\bullet+}) + H(\text{e}) - H(\text{TQ-H})$$

$$\text{PDE} = H(\text{TQ}^\bullet) + H(\text{H}^+) - H(\text{TQ-H}^{\bullet+})$$

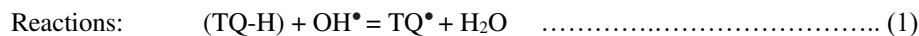
$$\text{PA} = H(\text{TQ}^-) + H(\text{H}^+) - H(\text{TQ-H})$$

$$\text{ETE} = H(\text{TQ}^\bullet) + H(\text{e}) - H(\text{TQ}^-)$$

where $H(TQ^\bullet)$ and $H(H^\bullet)$ are the enthalpies of TQ^\bullet radical and H atom respectively, $H(TQ-H)$ and $H(e)$ are the enthalpies of neutral TQ molecule and electron respectively, $H(TQ-H^{\bullet+})$ is the enthalpy of radical cation, $H(H^+)$ is the enthalpy of proton, and $H(TQ^-)$ is the enthalpy of anion formed after elimination of a proton.

In order to calculate the reaction enthalpies, it needs the enthalpies of hydrogen atom, proton and electron. The gas phase values were taken from previous calculations [32] [33]. Enthalpies of proton and electron in water were taken from reference [34], and that of hydrogen atom from reference [35].

Changes of Gibbs free energy (ΔG) and enthalpy (ΔH) of the hydroxyl radical scavenging reaction by TQ were calculated according to the simple equations of thermochemistry as follows.



Gibbs free energy changes for the reactions

$$\Delta G = \{G(TQ^\bullet) + G(H_2O)\} - \{G(TQ-H) + G(OH^\bullet)\}$$

$$\Delta G = \{G(TQ-H)^{\bullet+} + G(OH^-)\} - \{G(TQ-H) + G(OH^\bullet)\} \text{ respectively,}$$

and similarly enthalpy changes for the above reactions

$$\Delta H = \{H(TQ^\bullet) + H(H_2O)\} - \{H(TQ-H) + H(OH^\bullet)\}$$

$$\Delta H = \{H(TQ-H)^{\bullet+} + H(OH^-)\} - \{H(TQ-H) + H(OH^\bullet)\} \text{ respectively.}$$

Where, $G(X)$ and $H(X)$ are the free energy and enthalpy respectively obtained from the optimized geometry of the associated species X calculated at the same level of theory.

Spin density analysis

Spin density distribution is an important quantum property in the estimation of free radical scavenging power of a compound. The stability of a free radical largely depends upon the electron spin density distribution over the radical. Higher delocalization of spin density in the radical reflects its easier formation as well as higher stability [36].

Results and Discussions

Geometry optimization and conformational analysis

To know the antioxidant behavior of a compound, it is highly recommended to examine its geometrical conformation. For this reason, the geometrical structures of TQ, its radicals, cation, and anions were optimized in the gas and water at B3LYP/6-311+G(d,p) condition using DFT. Some characteristic such as bond length, bond angle and torsion angle of the entitled compound have been tabulated in Table 1. The optimized structure with atom numbering and the schematic projection of TQ are shown in Figure 1. Very little or no change in the geometrical parameters was observed for optimized TQ molecule in gas phase and water media. Energy changes along the optimization process are depicted in the figure (S-Figure 1). Optimized structure of TQ in aqueous phase contains 5.39 kcal/mole less energy than that in gas phase.

Table 1. Geometrical parameters of TQ molecule optimized at the level of B3LYP/6-311+G (d, p) in gas phase and water

	Bond length (Å)		Bond angle (degree)			Dihedral angle (degree)			
	Bond	Gas	Water	Angle	Gas	Water	Dihedral angle	Gas	Water
Thymoquinone (TQ)	O1-C7	1.222	1.225	O1-C7-C4	121.117	121.044	O1-C7-C4-C3	3.219	3.574
	O2-C10	1.222	1.226	O1-C10-C9	120.724	120.671	O2-C10-C9-C12	-0.015	0.118
	C3-C4	1.512	1.512	C9-C12-H23	110.543	110.576	C8-C4-C3-C5	-102.589	-101.428
	C9-C12	1.497	1.496	H24-C12-H23	109.153	108.987	C7-C4-C3-C5	76.885	77.960
	C3-C5	1.546	1.546	C4-C3-H13	106.172	106.320	C10-C9-C12-H22	58.506	58.950
	C3-C6	1.533	1.533	C4-C3-C5	110.079	110.005	C11-C9-C12-H24	-0.324	-0.170
	C12-H23	1.094	1.094	C4-C3-C6	113.760	113.778	H13-C3-C6-H17	56.499	56.414
	C3-H13	1.095	1.095	C5-C3-C6	110.944	110.866	H13-C3-C5-H14	58.247	59.403
	C5-H15	1.093	1.093	C5-C3-H13	106.850	107.098	C6-C3-C5-H15	56.938	57.676
	C6-H19	1.094	1.094	H18-C6-H19	108.151	108.256	C5-C3-C6-H17	-60.700	-60.896

After withdrawal of proton from 3CH bond, permanent carbon-carbon double (C=C) bond formed between C3 and C4 with delocalization of π -electrons around C4-C8-C10 of the ring (S-Figure 3) and in case of 3CH-radical,

delocalization of electrons is distributed over C3-C4-C8-C10 areas both in gas and water phase (S-Figure 2). One important change observed after removal of proton and hydrogen atom from 3CH group is that, the 5CH₃ and 6CH₃ groups came to the same plane of the ring that means the whole structure became planer (S-Figure 2 and S-Figure 3). Due to the subtraction of proton from 12CH₃, carbon-carbon double bond observed between C12 and C9 with delocalization of electrons around C9-C11-C7 of the ring in both phases studied and similar changes were found for 12CH₃ radical. These delocalization of electrons recommends in favor of antioxidant potential of the studied molecule [31]. But such significant changes were not observed for the elimination of proton and hydrogen atom from 5CH₃ and 6CH₃ groups of TQ.

Bond dissociation enthalpy and spin density: HAT mechanism

Bond dissociation enthalpy (BDE) plays a vital role in the evaluation of antioxidant potential of a compound as it describes the hydrogen atom donating ability and formation of a stable radical. The lower the BDE, the higher the hydrogen atom donating tendency as well as the higher free radical scavenging power [37]. The BDEs for concerned (C-H) bonds of TQ were calculated in gas and aqueous phases at B3LYP/6-311+G(d,p) level in DFT and presented in Table 2. From the calculated values of BDE for the possible functional groups of TQ, it has been found that, 3CH, 12CH₃, 5CH₃, and 6CH₃ possess BDEs of 77.40, 83.68, 100.25, 100.19 kcal/mole in gas phase and 75.80, 83.07, 100.15, and 100.26 kcal/mole in water medium respectively. The values of BDE of the groups in the water medium has been decreased slightly which shows very good agreement with a previous study [3]. The values of BDE of group 12CH₃ and 3CH are less than or close to the literature values computed for other compounds such as ascorbic acid, gallic acid [3], myricetin [38] and myricetin 3,4-di-O- α -Lrhamnopyranoside [39]. The comparable values of BDE of HAT reaction calculated for TQ suggest its antioxidant potential through free radical scavenging mechanism.

Table 2. BDE for different C-H bonds of TQ calculated at B3LYP/6-311+G(d,p) level

Group of TQ	BDE (kcal/mole)		ΔE for radical		ΔE for anion	
	Gas phase	Water	Gas phase	Water	Gas phase	Water
3CH	77.40	75.80	389.55	387.95	340.87	293.92
12CH ₃	83.68	83.07	395.84	395.22	341.63	296.30
5CH ₃	100.25	100.15	412.40	412.30	356.40	306.98

6CH ₃	100.19	100.26	412.34	412.41	380.25	338.24
Ascorbic acid 3-OH	81.80	77.6				
Gallic acid 3-OH	87.40	85.3				
4-OH	79.10	79.2				

The values of ascorbic acid and Gallic acid were taken from the reference [3].

In order to elucidate the changes in BDEs, the distributions of spin density of the corresponding TQ• radicals were figured out in the gas phase and water phase, and presented in Figure 3. It is a reasonably trustworthy quantity to explain the stability of the free radical. Radical with higher delocalization of spin density is more stable [40]. As displayed in Figure 2, after deduction of a hydrogen atom from the functional groups studied here, 3CH and 12CH₃ groups had the most delocalized spin density in the corresponding radical which are in good concordance with their sequence of BDE values.

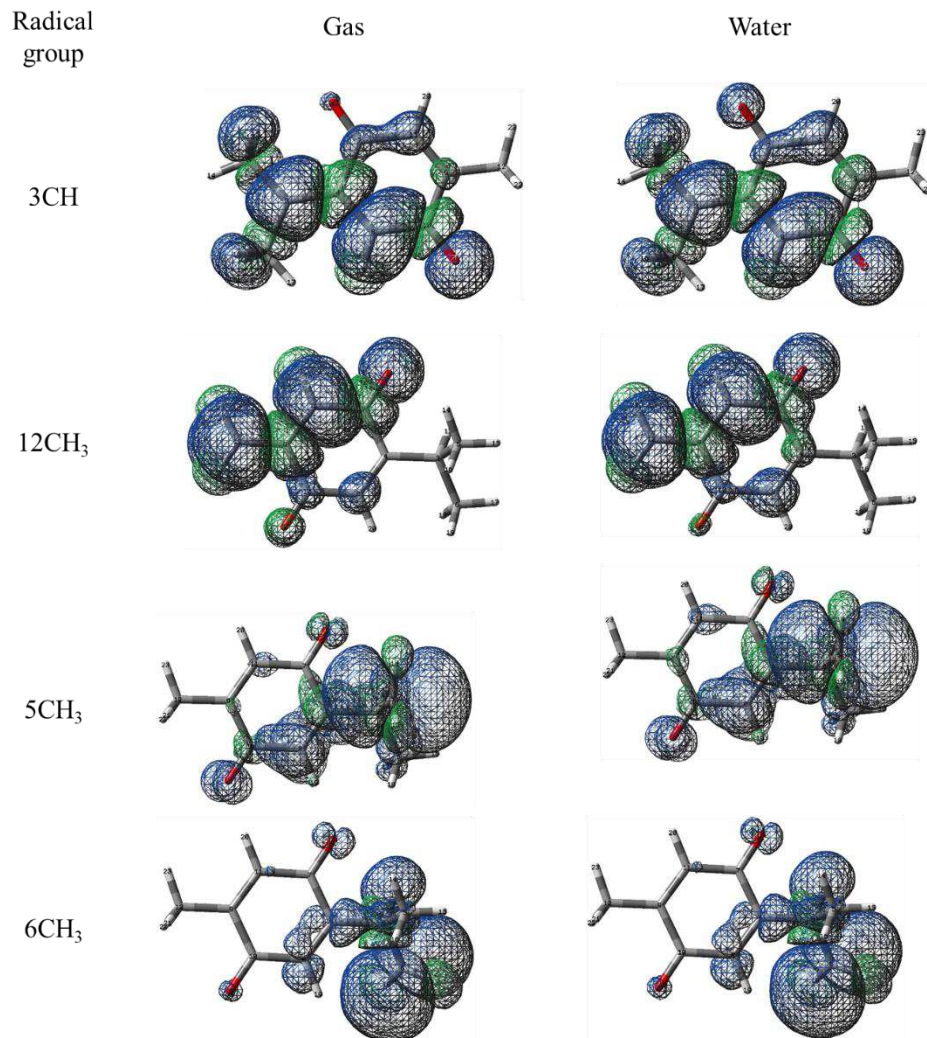


Figure 2. Spin density distribution of the radicals formed after elimination of hydrogen atom from the functional groups concerned.

The spin density for 3CH and 12CH₃ radicals are more distributed whereas those for 5CH₃ and 6CH₃ are more localized around the concerned groups. This can also reflect the evidence for the more free radical scavenging strength of the TQ molecule with respect to 3CH and 12CH₃ groups. This tendency is almost similar for all the radicals in both gas and water media. As can be concluded from the above discussions that, the 3CH and 12CH₃ groups mainly contribute to the antioxidant activity of TQ, while the other groups play little role *via* HAT mechanism.

Ionization potential and proton dissociation enthalpy: SETPT mechanism

SETPT mechanism comprises two stages: donating electron to a free radical R• and subsequently transfer a proton to the anion. In order to justify the possibility of these reactions, it requires to determine ionization potential (IP) for the former step and proton dissociation enthalpy (PDE) for the later one. SETPT mechanism combines IP and PDE to define the antioxidant activity of a compound. The lower IP and PDE values represent higher antioxidant tendency through SETPT scheme [31]. The Table 3 represents the IP of TQ molecule and PDEs of its different CH bonds. The PDE value is lowest (193.04 and 220.88 kcal/mole in gas and water respectively) for CH bond of 3CH group and highest, 215.88 kcal/mole of 5CH₃ in gas, and 245.34 kcal/mole of 6CH₃ in water. The PDE value of CH bond of group 3CH is less than that of literature value of other substances demanding antioxidant capacity [41], [42]. The lower value of PDE of 3CH bond may be due to the two electron donating methyl groups attached to the carbon atom. But here the IP values of TQ have been found to be a bit higher in comparison to literature [3]. It can be explained that, it is slightly difficult for TQ do donate electron. The electron-donating ability is related to an extended electronic delocalization over the entire molecule. A molecule having a high degree of π -delocalization is more active [43]. From the above discussion it can be said that, TQ is less likely to pose SETPT formalism of antioxidant behavior.

Table 3. PDE and ETE values of TQ calculated at B3LYP/6-311+G(d,p) level of theory

TQ group	PDE (kcal/mole)		IP (kcal/mole)	
	Gas phase	Water	Gas phase	Water
3CH	193.04	220.88	198.73	169.28
12CH ₃	199.32	228.15		
5CH ₃	215.88	245.23		
6CH ₃	215.83	245.34		
Ascorbic acid			191.82	
3-OH	202.92			
Gallic acid			189.20	
3-OH	212.60			
4-OH	204.30			

The values of ascorbic acid and Gallic acid were taken from the reference [3].

Proton affinity and electron transfer enthalpy: SPLET mechanism

The third mechanism of the antioxidant activity (SPLET) is characterized by the proton affinity (PA) value which corresponds to the enthalpy of proton dissociation from the neutral molecule, and the electron transfer enthalpy (ETE) value that corresponds to the enthalpy of transfer of an electron from the antioxidant anion to the free radical. The lower PA and ETE values is characteristic of higher antioxidant activity through the SPLET mechanism [31]. The calculated PA and ETE values for TQ in the gas phase and water are given in Table 4. The PA values for the studied CH bond of TQ are comparable to the literature value [3]. PA values of TQ are lower in water than in gas phase which is in good consistent with previous literature [31]. The PA values are in the range of 342-381 kcal/mole in gas phase and 295-339 kcal/mole in water. The minimum (342.35 kcal/mole) PA has been found for CH bond of 3CH group and maximum (381.73 kcal/mole) of 6CH₃ group in gas phase. The lower value of PA for 3CH can be due to the electron pushing character of two methyl groups attached herewith. The ETE values of various CH bonds of TQ are lower in gas than in water which is also in agreement with literature [43]. The ETEs are in the range of 32-56 kcal/mole in gas whereas in the range of 74-106 kcal/mole in water. This also shows very good agreement with literature of similar study [31]. These values are less than or close to the corresponding values of another similar research [40] [43]. Lowest PA values were observed for 3CH group both in gas and water, and lowest ETE values were computed for 6CH₃ group both in gas and water. These data clearly reveal the capability of TQ as a potential antioxidant molecule.

Table 4. PA and ETE values of TQ in gas phase and water calculated at B3LYP/6-311+G(d,p)

Group of TQ	PA (kcal/mole)		ETE (kcal/mole)	
	Gas phase	Water	Gas phase	Water
3CH	342.35	295.40	49.42	94.77
12CH ₃	343.12	297.79	54.94	99.65
5CH ₃	357.88	308.46	56.74	106.06
6CH ₃	381.73	339.72	32.84	74.90
Ascorbic acid				
3-OH	328.98		65.76	
Gallic acid				
3-OH	329.00		72.90	

The values of ascorbic acid and Gallic acid were taken from the reference [3].

Frontier molecular orbitals (HOMO – LUMO)

Frontier molecular orbitals (FMO) or HOMO and LUMO denote the highest occupied molecular orbital and the lowest unoccupied molecular orbital respectively. FMOs are important parameters to predict the antioxidant activity of a compound [44]. The E_{HOMO} represents the ability of electron donation, because it is energetically easiest to take away electron from this orbital, whereas E_{LUMO} shows the capability to accept electron [45]. Molecules with lower E_{HOMO} are more stable and less expected to give electrons and the shape of HOMO determines the sites for free radical attack [38]. The calculated FMO of TQ molecule in gas and water phases are represented in Figure 3. FMO with traditional π -like molecular orbital appearance and distribution approximately over the entire molecule suggests antioxidant power of the molecule [31]. As shown in Figure 3, HOMO and LUMO orbitals are distributed on an average over the entire TQ structure with little above the 5CH₃ and 6CH₃ groups, which directs their less involvement in antioxidant reactions. HOMO orbital is well distributed over 3CH and 12CH₃ groups, suggesting the probable contribution to antioxidant activity. The HOMO-1 orbital is mostly contributed to the π orbitals of double bonds and oxygen atoms. Theoretically, E_{HOMO} is an effective indicator for free radical scavenging power [46]. LUMO orbital is mainly distributed over the ring with the two oxygen atoms. Small energy gap between LUMO and HOMO infers the softness whereas large gap indicates the hardness of the molecule. Soft molecule is more reactive than hard one and it can donate electron more easily to the receiver. [47]. The global reactivity descriptors derived from E_{HOMO} and E_{LUMO} are calculated and presented in Table 5. The comfort of electron donation depends on the electronegativity. The values of hardness, softness, IP, EA and electronegativity of TQ calculated in this study are very close to those computed for other molecules claimed as potential antioxidant [3].

Table 5. HUMO-LUMO energy and global reactivity descriptor values of TQ

Property	Symbol and formula	Value, eV	
		Gas phase	Water
LUMO energy (eV)	E_{LUMO}	-3.575	-3.646

HOMO energy (eV)	E_{HOMO}	-7.447	-7.564
Energy gap (eV)	$E_g = E_{\text{LUMO}} - E_{\text{HOMO}}$	3.872	3.918
Ionization potential	$IP = -E_{\text{HOMO}}$	7.448	7.565
Electron affinity	$EA = -E_{\text{LUMO}}$	3.575	3.646
Global hardness	$\eta = (E_{\text{LUMO}} - E_{\text{HOMO}})/2$	1.936	1.959
Softness	$\sigma = 1/\eta$	0.516	0.510
Chemical potential	$\mu = (E_{\text{LUMO}} + E_{\text{HOMO}})/2$	-5.511	-5.605
Electrophilicity	$\psi = \mu^2/2\eta$	7.845	8.019
Electronegativity	$\chi = -\mu$	5.511	5.605

Molecular electrostatic potential

Molecular electrostatic potential (MEP) is another supportive aspect for investigating and forecasting antioxidant capacity of a compound. The electron-deficient (positive) sites are the most likely sites for free radical attack [31]. It can be seen from the Figure 4 that, most electron-rich (negative) surfaces are positioned over the oxygen atoms whereas the electron-deficient (positive) surfaces are located around the hydrogen atoms of the ring and the side chains in both gas phase and water. These upshots could be useful in prediction of the positions for free radical attack of TQ molecule. However the antioxidant reaction is an intricate and multifarious process and could be subjective to numerous aspects [48].

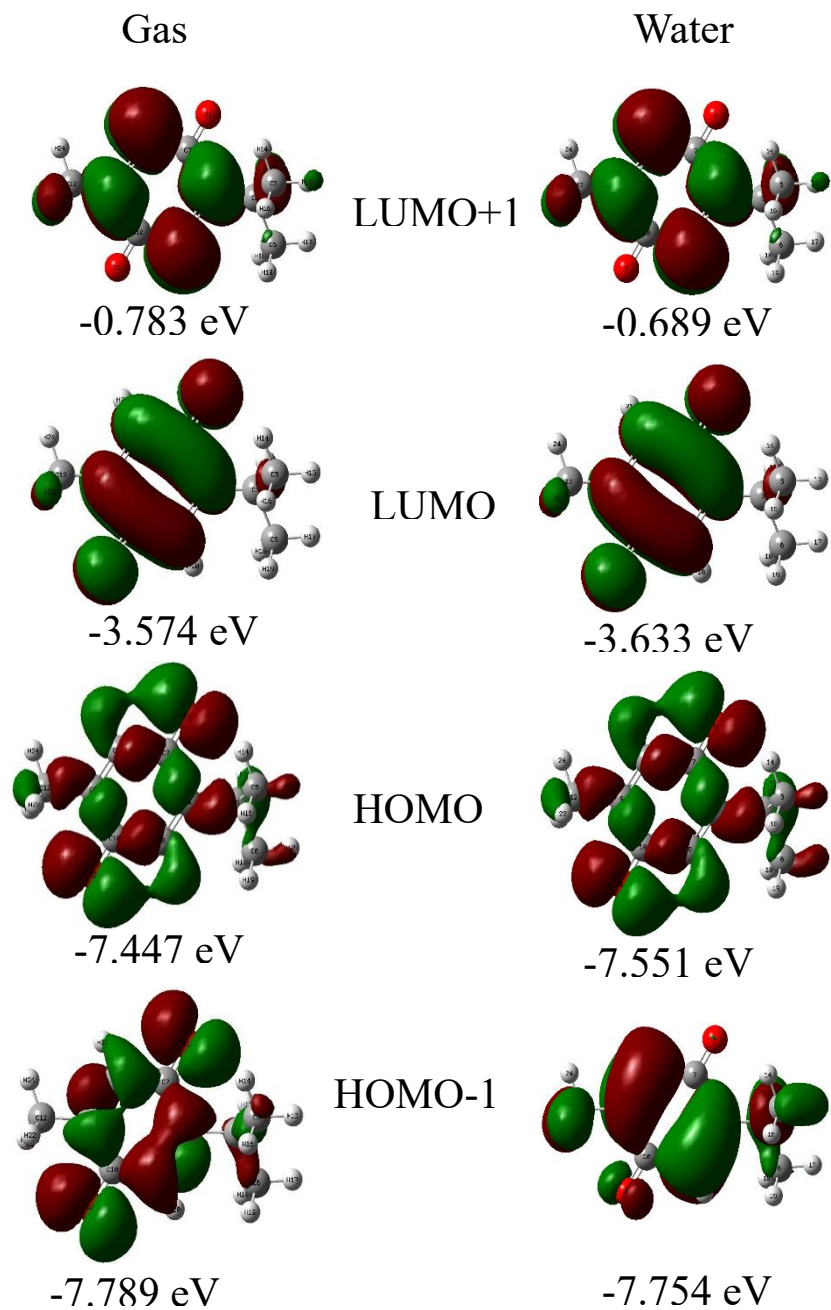


Figure 3. LUMO+1, LUMO, HOMO and HOMO-1 frontier orbitals of TQ calculated in the gas and water phases at B3LYP/6-311+G (d,p) level of theory

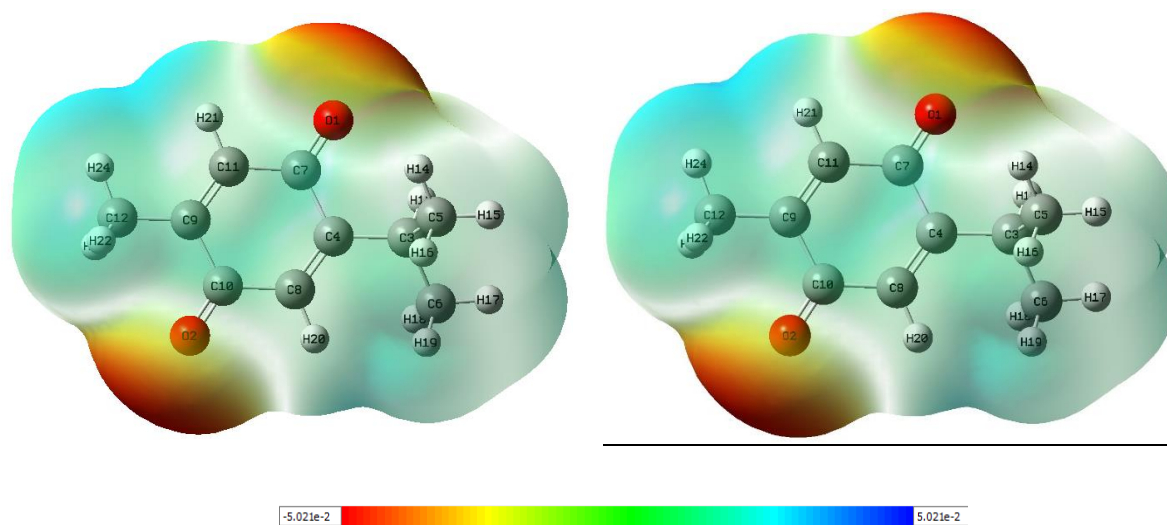


Figure 4. Molecular electrostatic potential (MEP) surface of TQ molecule in gas (left) and water (right) calculated at B3LYP/6-311+G(d,p) level of theory

Thermodynamically favored mechanism

In order to investigate the antioxidant activity and mechanism of TQ, Gibbs free energy and enthalpy changes of the hydrogen abstraction (HA) from TQ to OH^\bullet radical have been computed from the theoretical data of optimized geometry of the concerned reactants and products as per the simple principle of thermochemistry. The calculated ΔG and ΔH values for various CH groups of TQ against OH^\bullet radical are shown in table 6. It is very interesting to report that, all the ΔG and ΔH calculated here are negative for the HA reaction which is in favor of antioxidant power of TQ through HAT mechanism. The lowest ΔG and ΔH were observed for 3CH group in all cases studied here which is in good consistent with other thermochemical parameters such as BDE, PDE and PA discussed in the earlier sections. In addition to this, from the table 6 it can easily be seen that, the order of ΔG and ΔH values for the studied four CH groups of TQ molecule are around similar as BDE, PDE and PA in both gas and water media. The values of ΔG and ΔH for the OH^\bullet radical scavenging reaction ($\text{TQ} + \text{OH}^\bullet = \text{TQ}^\bullet + \text{H}_2\text{O}$) are within the range of -17.50 to -40.61 and -15.95 to -38.74 kcal/mole respectively in gas and -19.14 to -43.54 kcal/mole and -15.88 to -40.34 kcal/mole respectively in water. The ΔG of HA from 3CH group and 12 CH_3 groups of TQ to OH^\bullet radical are -40.61 and -32.29 in gas, and -43.54 and -35.39 kcal/mole in water respectively which are significantly lower than the literature value. Similarly the calculated ΔH values of HA reaction of TQ are remarkably less than the literature values abovementioned. The negative and less values of ΔG and ΔH for OH^\bullet radical scavenging reaction thermodynamically

provide apposite support toward the antioxidant potentiality of TQ as free radical scavenger via HAT. On the other hand, the values of ΔG and ΔH for electron transfer reaction $((\text{TQ-H}) + \text{OH}^\bullet = (\text{TQ-H})^{+\bullet} + \text{OH}^-)$ from TQ to OH^\bullet radical to form OH^- ion are positive in both media which deliver less potency of TQ to this mechanism of action.

Table 6. Changes of Gibbs free energies (ΔG kcal/mole) and enthalpies (ΔH kcal/mole) related to the reactions of TQ toward HO^\bullet radical calculated in the gas phase and water at B3LYP/6-311+G(d,p) level of theory

Radical species	ΔG , kcal/mole		ΔH , kcal/mole		ΔG , kcal/mole		ΔH , kcal/mole	
	(for hydrogen abstraction to OH^\bullet)				(for electron transfer to OH^\bullet)			
	Gas	Water	Gas	Water	Gas	Water	Gas	Water
3CH	-40.61	-43.54	-38.74	-40.34				
12CH ₃	-32.92	-35.39	-32.46	-33.07				
5CH ₃	-17.29	-19.14	-15.89	-15.99	156.73	157.29	47.76	48.42
6CH ₃	-17.50	-19.18	-15.95	-15.88				
References	-24.2 [49]	-31.7 [49]	-22.0 [49]	-29.4 [49]				
	-9.37 [31]	-11.26 [31]						

Conclusion

Antioxidant activity of TQ, a non-phenolic molecule has been successfully evaluated in gas and water phases using DFT calculation. The observed information revealed that, the studied compound can pose as stronger antioxidant as other available ones. In both gas and water, 3CH and 12CH₃ positions are thermodynamically more feasible to scavenge free radical in comparison to 5CH₃ and 6CH₃ groups studied here. In this regard, HAT mechanism is preferable than SETPT and SPLET pathways. Obtained results clearly exhibit free radical scavenging potential of TQ molecule without possessing any phenolic group in its structure, which paves the way for other such compounds to be searched for their antioxidant power.

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Conflicts of interest/Competing interests

No conflicts of interest/competing interests.

Availability of data and material

All the data are provided in the manuscript and supplementary file.

Code availability

Not applicable

Authors' contributions

Jewel Hossen: Conceptualization; Data curation; Formal analysis; Methodology; Visualization; Writing - original draft; Editing; M. Abbas Ali: Editing and reviewing; Sultanur Reza: reviewing.

Ethics approval

The articles has not been submitted to elsewhere.

Consent to participate

All the authors actively participated in this work.

Consent for publication

If this manuscript is accepted for publication in this journal, we would not withdraw it.

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Figures

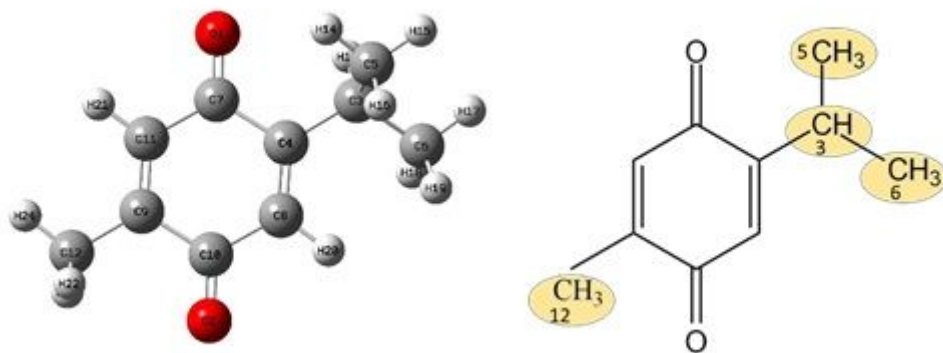


Figure 1

Optimized (left) and schematic structures of TQ and possible groups considered for antioxidant action (right)

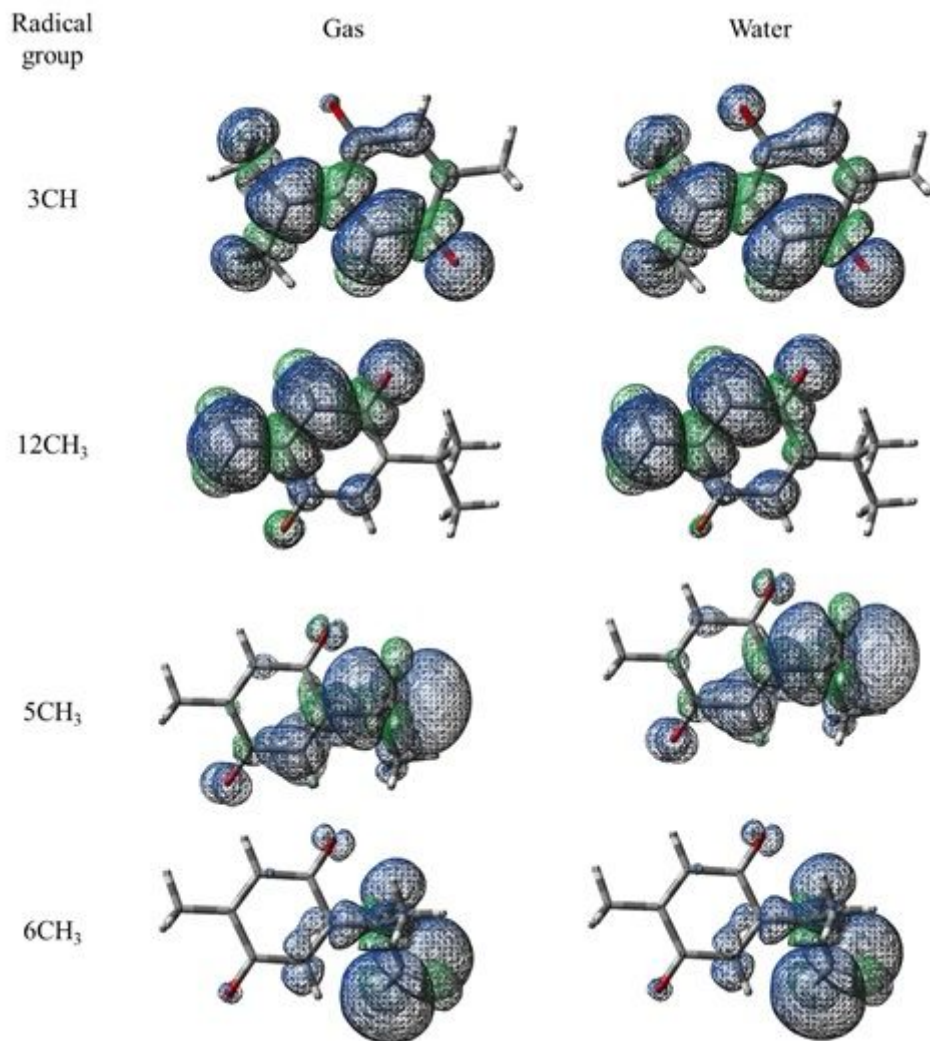


Figure 2

Spin density distribution of the radicals formed after elimination of hydrogen atom from the functional groups concerned.

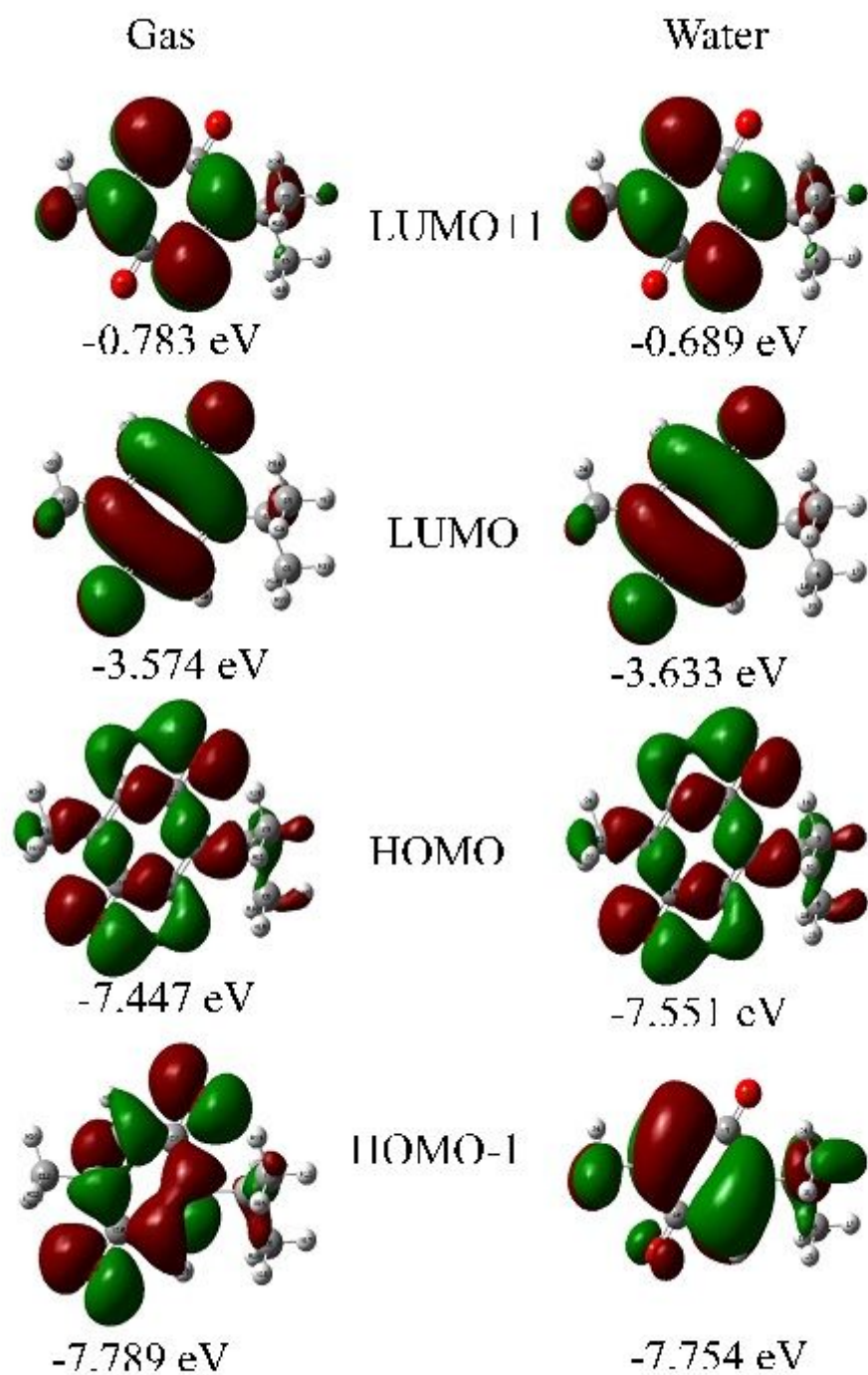


Figure 3

LUMO+1, LUMO, HOMO and HOMO-1 frontier orbitals of TQ calculated in the gas and water phases at B3LYP/6-311+G (d,p) level of theory

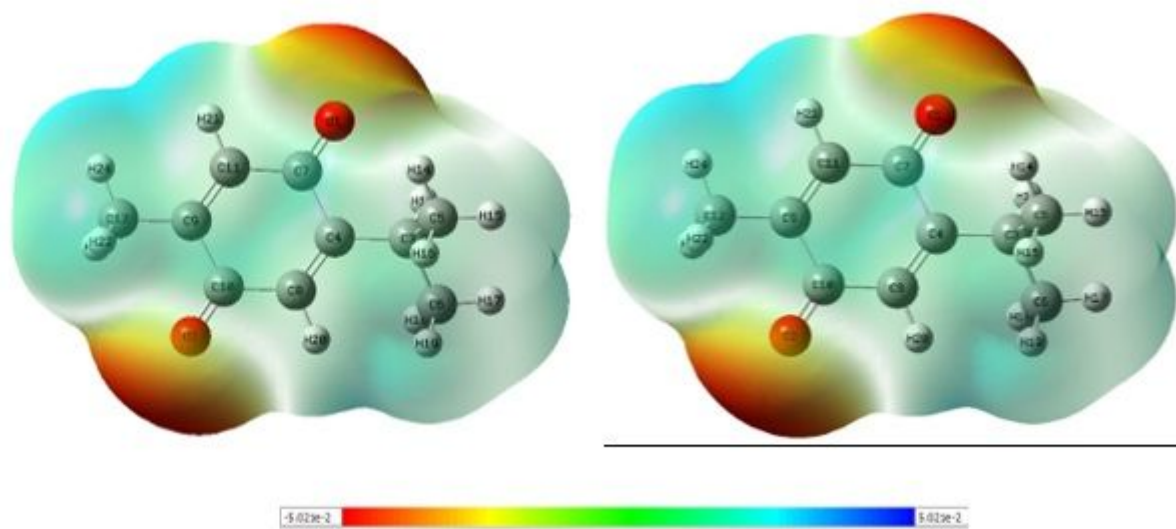


Figure 4

Molecular electrostatic potential (MEP) surface of TQ molecule in gas (left) and water (right) calculated at B3LYP/6-311+G(d,p) level of theory

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