Experimental and Computational Studies on the Electrochemical Behavior of Carvacrol and Menthol

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ABSTRACT: *In this study, the effects of solvent on the electrode potentials of menthol and carvacrol species were investigated experimentally and computationally and their antioxidant properties were compared in different solvents by calculating the half-wave potential $E_{1/2}$ of species, Vand Dissociative Energy (BDE), Ionization Energy (IE), and Electron Affinity (EA). Electrochemical behavior of menthol and carvacrol species in four solvents (MeOH, EtOH, DMSO, and Heptane) were studied using cyclovoltametric technique in a glass electrode as a working electrode and the calculations for obtaining the electrode potential were performed using DFT functional including B3LYP with 6-311+G(d,p)basis set and PCM and IEFPCM models for calculation of solvent energy. Finally, the results were compared and confirmed by experimental methods. Where in the compound carvacrol represent more properties antioxidant than menthol due to lower values $E_{1/2}$ in gas and solution phases. Also, the lower BDE in the gas phase is 80.19 kcal/mol compared with menthol (98.91 kcal/mol). Moreover, compound carvacrol has the IE value of 1.12 eV smaller than menthol and has the EA value of 0.35 eV higher than menthol. Calculations show that the model had no effect on computational results. Also, according to the results, the antioxidant properties of carvacrol in non-polar solvents were higher due to the smaller amount of $E_{1/2}$.*

KEYWORDS: *Menthol; Carvacrol; Solvent effect; Antioxidant activity; Electrode potentials.*

INTRODUCTION

Herbs and spices have been used as preservatives and medicine because of the high antioxidant activity in certain spices and their beneficial effects on human health [1-4]. Including these Herbs can be mentioned menthol and carvacrol. Menthol acts as a strong antioxidant and it has an important role in various sectors of the economy, for example, the pharmaceutical industry, perfumery, cosmetics, and food. Several biological functions are associated with species by popular medicine, used for the treatment of burns, headache, colic, fever, reports of antifungal activity, antiemetic, carminative, insecticide, repellent, and antibacterial [5, 6]. Carvacrol is in thyme oil, coconut oil, and wild coconut. There is between 5 to 75 percent of carvacrol in thyme, while bitter species contain

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1 to 45 percent [7]. Several studies have shown that carvacrol has an anti-fungal, anti-inflammatory, ant nociceptive, anti-inflammatory, antibiotic, antiviral, cardioprotective, antidiabetics and antioxidant properties [8-10].

Antioxidants are compounds that inhibit or eliminate the actions of released radicals and protect the cells from the harmful effects of these compounds, thus combating the aging process and the spread of various diseases. These substances can prevent the formation of free radicals in the body and, if formed, reduce their effect on the body [11]. Radicals have one or more unequal oxygen, so they are extremely unstable. These radicals are looking for a combination to absorb or lose electrons. Consequently they damage cells, proteins and DNA. In fact, antioxidants are compounds that are used to prevent or slow down the damage caused by oxidation reactions in the body and act as neutralizing free radicals and thus prevent the damage caused by this compounds in the body [12].

The antioxidant activity of a compound is related to the electrochemical parameters, in particular its oxidation potential, which provides the amount of energy needed to donate an electron. In fact, when the oxidation potential of a compound is high, it will easily emit an electron and its antioxidant activity will be higher [13]. Electrochemistry is a central technique for cyclic voltammetry, where the current through an electrochemical cell is measured as the cell potential. The accurate prediction of redox potentials using appropriate computational approaches can help us understand redox mechanisms of geochemical reactions and aid us in designing and optimizing redox-sensitive remediation techniques. As theoretical methods are used to predict other properties of molecules [14,15]. Redox action of an antioxidant at an electrode is related to its action in chemical redox reaction with a radical that can easily be performed by applying cyclic voltammetry [16-19]. Electrochemical organic transformations are often used as an efficient way to perform complicated organic syntheses. Various aspects involved in the electrochemical synthesis of organic compounds, for example, mechanism of redox processes, kinetics of electrode reactions, homogeneous or heterogeneous electron transfers, coupled electron transfer processes, have been reviewed [20-22].

Although the literature review shows various biological activities of these compounds, to the best of our knowledges, their antioxidant potential has not been evaluated by both experimental and theoretical approaches yet. Thus, the goal of study is to predict the free radical scavenging activity of two compounds carvacrol and menthol *via* two widely accepted mechanisms: Hydrogen Atom Transfer (HAT) mechanism and Single Electron Transfer (SET) and reduction potential ($E_{1/2}$) of them. The intrinsic parameters of the studied compounds including Bond Dissociation Enthalpies (BDE), Ionization Potential (IP) and Electron Affinity (EA) were calculated by Density Functional Theory (DFT) approach at the B3LYP/6-311+G(d,p) level of theory in the gas and solution phases. We hope that the methods described in this work serve as a helpful tool to choose appropriate computational methods for redox-potential predictions in areas of chemistry, biology, and mineralogy of carvacrol and menthol coumpounds. However, our main intention is, after having evaluated computational approaches for the prediction of reduction potentials, to develop and apply a reliable computational approach.

EXPERIMENTAL SECTION

Species were dissolved in 0.1 M NaOH and solvents mixture with ratio 50%. The stock solutions were stored in darkness at 277 K to avoid decomposition. Solutions were purged with purified nitrogen and the temperature was kept at 298 ± 0.1 K.Cyclic voltammetry, controlled-potential coulometry and preparative electrolysis were performed using an Autolab model PGSTAT 20 potentiostat/galvanostat. The used working electrode in the voltammetry experiment was a glassy carbon disc (1.8 mm diameter) and platinum wire was used as counter electrode. The used working electrode incontrolled-potential coulometry and macroscale electrolysis was an assembly of four carbon rods (6mm diameterand 4 cm length) and a large platinum gauze constitute thecounter electrode. The working electrode potentials were measured versus Ag/AgCl.

COMPUTATIONAL DETAIL

Computational program

Structural of menthol and carvacrol molecules in four solvent MeOH, Ethanol, DMSO and Heptane were optimized by Density Functional Theory (DFT), using the B3LYP, and 6-311+G(d,p) basis set in the Gaussian 09 computational program [23].

Several solvation models for the dielectric fluid approach are available in the literature and incorporated in some quantum-mechanical programs, such as PCM (polarizable continuum model) [24], CPCM (conductor-like polarizable continuum model) [25–27], IEF-PCM (integral equation formalism-polarizable continuum model) [28,29], SMD (solvation model density) [30], COSMO (conductor like screening model) [25], COSMO-RS (conductor like screening model for real solvents) [31,32], and PB (Poisson-Boltzmann) finite element model [33–35]. Among these solvation methods, CPCM solvation has been one of the most widely used solvation method to study solvation effects. At the present research solvation effects, molecular structure, solvation energies, sum of electronic and thermal free energies were carried out using models of Polarized Continuum Model (PCM) containing CPCM and IEFPCM calculations.

Calculation method

At the present study, the gas-phase contribution to the Gibbs energy, ΔG°(gas) and solvation energy, ΔΔG°(solv) were determined from DFT/ 6-311+G (d,p) level of theory. The gas-phase Gibbs free energy changes (ΔG°(gas)) of reaction 1 was calculated using Eq.1.

Reaction 1: $A + e \overset{H^+}{\rightarrow} AH$

$$\Delta G^{\circ}_{gas} = G^{\circ}_{gas}(AH) - G^{\circ}_{gas}A \quad (1)$$

$\Delta\Delta G^{\circ}_{solv}$is calculated according Eq. 2.

$$\Delta\Delta G^{\circ}_{solv} = G^{\circ}(AH_{(solv)} - AH_{(g)}) - G^{\circ}(A_{(solv)} - A_{(g)}) \quad (2)$$

A common practice to calculate Gibbs free-energy changes of a reaction (ΔG°total) is by summing ΔG°gas and ΔΔG°solv using the thermodynamic cycle of Scheme 1 and Eq. 3.

$$\Delta G^{\circ}_{tot} = \Delta G^{\circ}_{gas} + \Delta\Delta G^{\circ}_{solv} \quad (3)$$

Finaly, Eº is calculated according Eq. 4.

$$\Delta G^{\circ} = nf(E^{\circ} - E^{\circ}_{ref}) \quad (4)$$

Where ΔG° is total free energy for reaction 1, E° is the calculated potential and F is the faraday constant (F=96500 $Cmol^{-1}$). However, cycle scheme 1 effectively uses calculated values of ΔG_g and ΔG_S, and effectively uses empirical (accurate) values. Thus, this calculation method is simple, and in this cycle, the key ingredients for the calculation of a redox potential are the gas-phase Gibbs free energy of reaction and the free energies of solvation of the reagents, that is, of the reactants and products. An added advantage of this approach is that *E*SHE is no longer needed, thereby eliminating a source of uncertainty. However, since the method relies on systematic error cancellation, it is expected to work best when the reference molecule is structurally similar to ref. The major limitation of this approach is that a structurally similar reference with accurately known *E*° may not always be available.

HAT/SET mechanism

The HAT and SET mechanisms, which are the most widely accepted antioxidant actions, were evaluated [36,37].

Hydrogen Atom Transfer (HAT) mechanism

H-atom donating ability of the compounds increases in the descending order of BDE value.

Single Electron Transfer (SET) mechanism

Single electron transfer consists in an important mechanism of antioxidant [38]. In a modern concept, a good antioxidant *via* SET mechanism is not only a good electron donor, characterized by Ionization Potential (IP), but also a good electron acceptor from free racial, represented by electron affinity (EA) property. The lower the IE value is, the easier electron donation is, while the higher the EA is, the easier electron acceptation is.

+ Hydrogen atom transfer (HAT):

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

+ Single electron transfer (SET):

$$AH \rightarrow AH^{+\bullet} + e^{-} \text{ (IE)}$$

$$A\text{–}H + e^{-} \rightarrow AH^{-\bullet} \text{ (EA)}$$

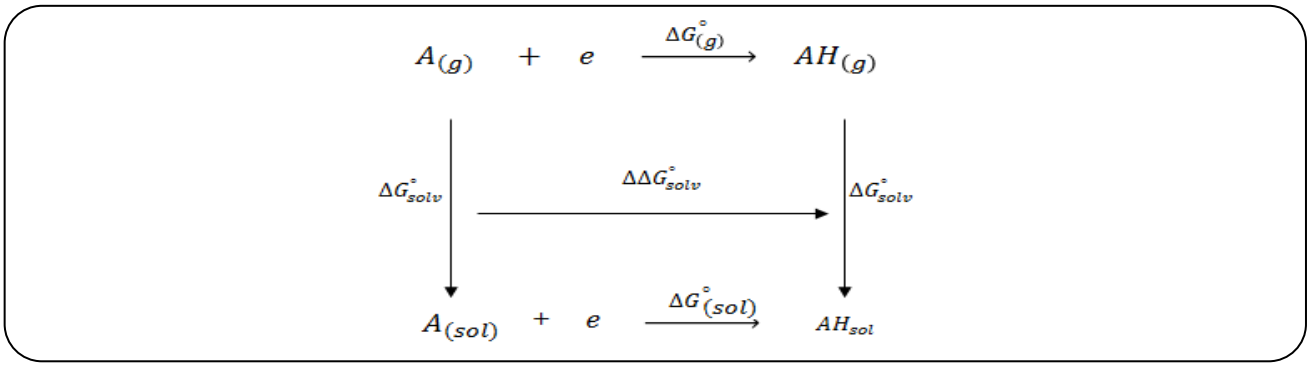
Three intrinsic properties including BDE, adiabatic IE and EA which characterize for the above mechanisms were calculated in the gas phase as follows [38,39].

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

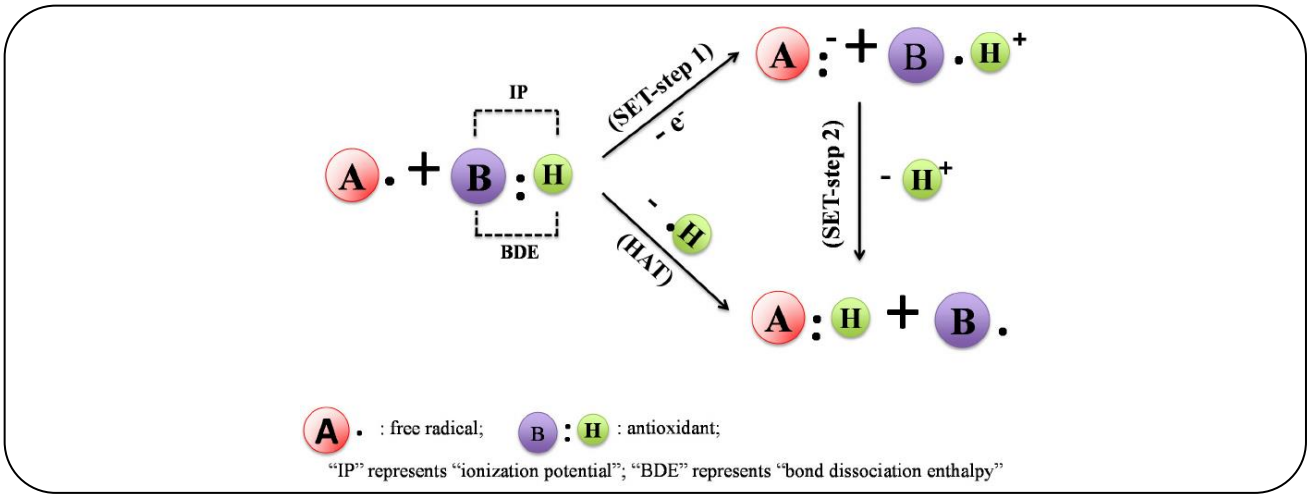
$$IE = H(AH^{+\bullet}) + H(e^{-}) - H(A\text{–}H)$$

$$EA = H(AH^{-\bullet}) + H(e) - H(A\text{–}H)$$

Where H is the sum of electronic and thermal enthalpies of the studied species at 298.15K and 1 atm which can be found from the output data files (Scheme 2).



Scheme 1: The thermodynamic cycle of Gibbs energy in the gas phase solution for menthol and carvacrol.



Scheme 2: Mechanisms of antioxidant reacting with free radical

RESULTS AND DISCUSSION

The electrochemical behavior of menthol and carvacrol species was studied using cyclic voltammetry method in a glass carbon electrode considered as a work electrode in such studies [40-45] (Figs. 1 and 2).

Investigation of the oxidation potentials of both the menthol and carvacrol compounds show that carvacrol oxidation is easier than menthol in different solvents. This means that carvacrol can remove electrons more easily. As a result, it has higher antioxidant strength. The Effect of solvent was done on the oxidation reaction of the compounds studied in DMSO, methanol, ethanol and heptane solvents by constant holding of all other parameters (electrolyte type and concentration, dissolution concentration and scanning voltage).

Studies show that for menthol there is no voltammetry response in ethanol, which means that the chemical oxidation of this compound in this solvent requires of a potential higher than the maximum potential of the device relative to the Ag/AgCl electrode [46, 47].

On the other hand, for two studied compounds in the other solvents, an anodic peak was observed, with no definite or unknown cathode peak in the reverse-scan phase, indicating that oxidation in the carbon electrode is an irreversible process [48]. This observation is in agreement with other relevant studies concerning some of the currently investigated drugs [49].

The half-wave $E_{1/2}$ potential for the species studied in each solvent is listed in Table 1. In carvacrol, oxidation process is more easily accomplished by reducing solvent polarity. But in menthol, the reduction of solvent polarity does not have a significant effect on the oxidation potential. In these two combinations, the sensitivity of the oxidation potential relative to solvent is not similar. As shown by E_{ap} the difference in oxidation of carvacrol with the replacement of non-polar solvent of heptane

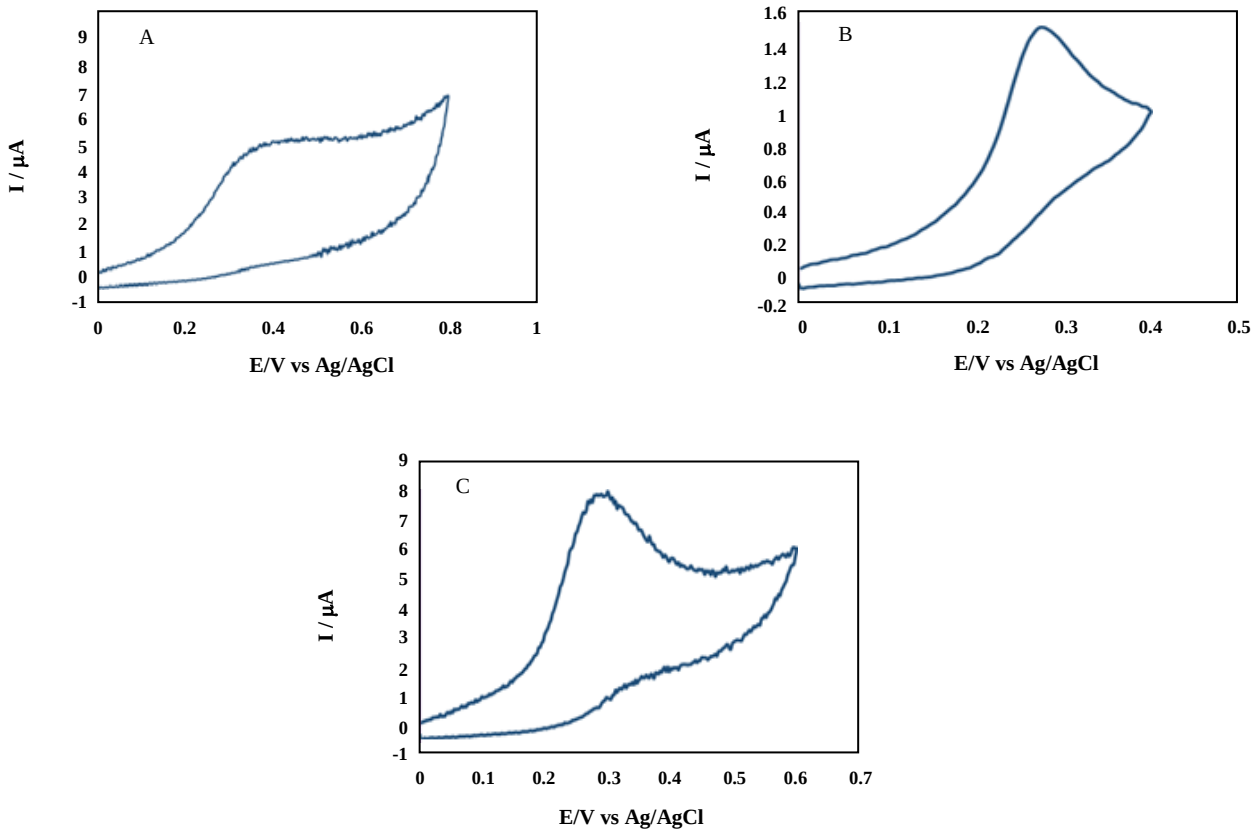


Fig. 1: Cyclic voltammogram of 1.0 mM of menthol in (A): methanol (B): DMSO (C): Heptane solvents at a glassy carbon electrode. Scan rate; 100 mV/s.

is significant. However, the oxidation values for menthol in polar and non-polar solvents are not significantly different. Due to the wide peak in menthol (Fig. 1), the mechanism of oxidation seems to be several-stages [49] (Scheme 3).

The first step is to liberate OH-oxidation into a radical form, which can be called the stage of deprotonation. The second stage is the formation of the C=O functional group and the oxidation of the composition.

Stability of Intermediate does not change with change of solvent, so the solvent changes will not have a significant effect on the oxidation process. However, it is suggested that the oxidation mechanism of carvacrol is as follows (Scheme 4).

Electrification of the methyl group at para position increases the stability of the final species in carvacrol resulting in a more stable intermediate. Therefore, carvacrol will tend to oxidize more than menthol. As shown in Table 1, the redox potential increases as solvent polarity increases. The reason of this observation can be hypothesized to be the interaction of the polar solvent with the electron cloud of the aromatic ring of the carvacrol, which prevents its easy oxidation in these solvents. As a result, carvacrol has the least redox potential in the non-polar solvent of heptane. In other words, it is easier to lose electrons and be more potent antioxidant.

All of oxidation and reduction forms of studied compounds are calculated in the gas and solution phases using 6-311+g (d,p) basis set at DFT level of theory with two models CPCM and IEFPCM. Free energy, $\Delta\Delta G^0_{solv}$ and ΔG_{tot} of menthol and carvacrol species studied in four solvent (MeOH, EtOH, DMSO and Heptane) by CPCM and IEFPCM models are included in (Tables 2,3). $\mathbf{E_{1/2}}$ for both the menthol and carvacrol compounds in methanol, DMSO, ethanol and heptan solvents were calculated using both CPCM and IEFPCM models (Table 3) .

By comparing $E_{1/2}$ of the studied species in various computational models of CPCM and IEFPCM, it is understood that the method does not have much effect

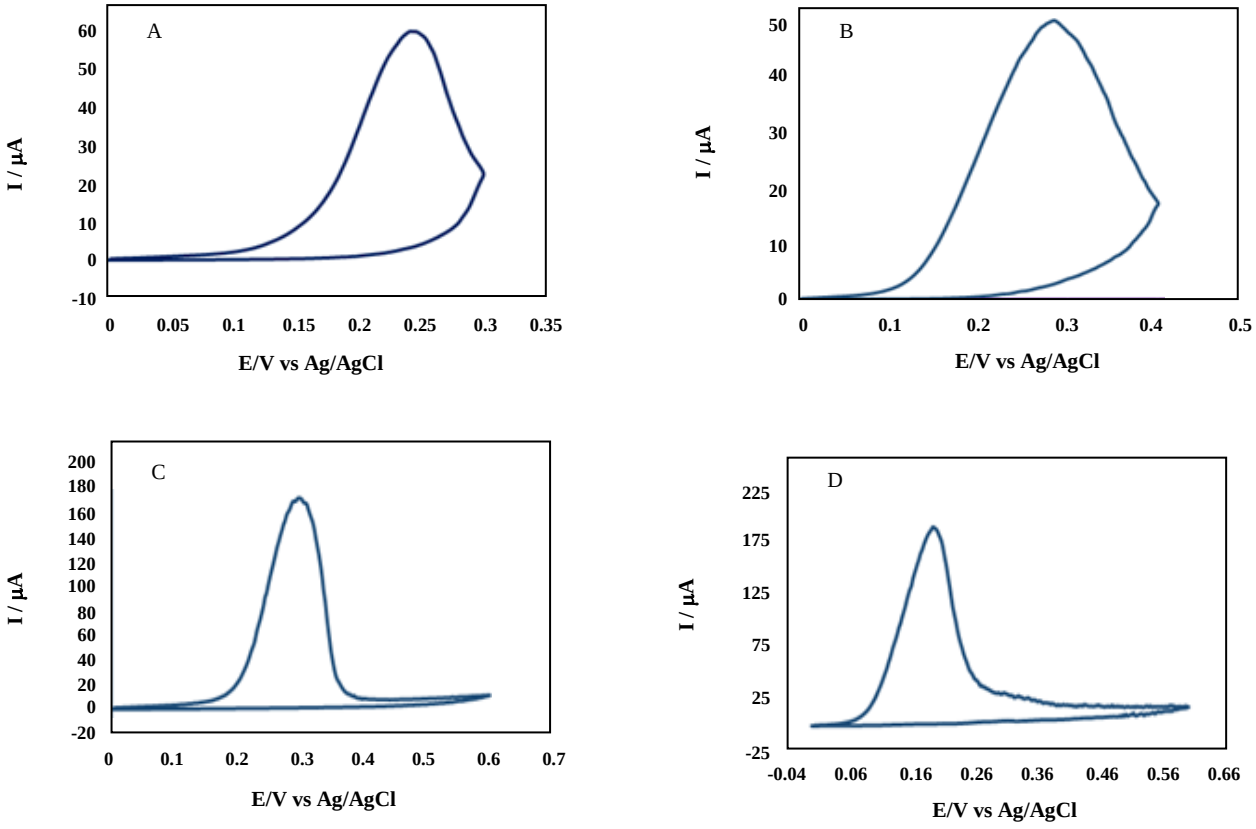
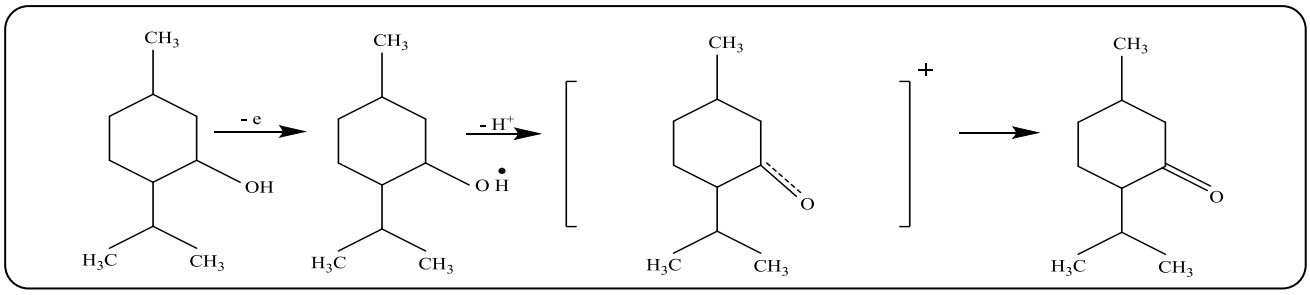


Fig. 2: Cyclic voltammogram of 1.0 mM of carvacrol in (A): methanol (B): DMSO (C): ethanol D: Heptane solvents at a glassy carbon electrode. Scan rate; 100 mV/s.



Scheme 3: The oxidation mechanism of menthol compound.

on computational results for menthol and carvacrol species (Table 4). The observed diversity in the electrochemical behavior of antioxidant compounds such as menthol and carvacrol shows that only one solvent parameter, such as polarity, cannot effect the amount of solvent-soluble interaction in molecular discussion. Even the stability of the resulting intermediates for oxidation can play an effective role in this regard.

The lack of significant differences in experimental and computational amounts shows that computational models can provide an accurate indication of the electrochemical behavior of antioxidant species. Based on this, one can simulate the electrochemical behavior and, finally, the antioxidant properties of different species using computer calculations in different solvents.

Structural, electronic properties and orbital distributions

Fig. 3 shows the optimized structures, HOMO, LUMO distribution and electrostatic potential (ESP) maps calculated at the B3LYP/6-311+G(d,p) level of theory

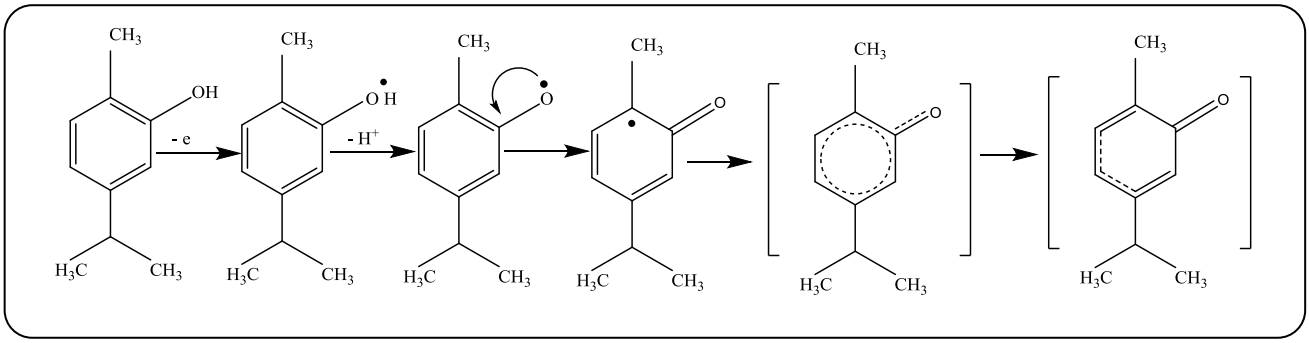
Table 1: Results of half-wave potentials experimental.

Comp.	Solvent	E_{ap}	$E_{1/2}$ Exp.
	Methanol	0.290	0.276
Menthol	DMSO	0.284	0.270
	Ethanol	---------	---------
	Heptane	0.298	0.280
	Methanol	0.240	0.240
Carvacrol	DMSO	0.278	0.278
	Ethanol	0.288	0.288
	Heptane	0.187	0.187

Table 2: Gibbs energy, $\Delta\Delta G^0_{solv}$ and ΔG_{tot} of menthol and carvacrol for both reduced (AH) and oxidized (A) forms in the gas and solution phases calculated using 6-311+g(d,p) basis set at DFT level of theory with CPCM model.

Comp.	Solvent	G^0_{gas} (A) (a.u)	G^0_{gas} (AH) (a.u)	G^0_{sol} (A) (a.u)	G^0_{sol} (AH) (a.u)	$\Delta\Delta G^0_{solv}$ (kJ/mol)	ΔG_{tot} (kJ/mol)
Menthol	Methanol	-467.052700	-468.235600	-467.059611	-468.241430	4.6760	-3101.0095
	DMSO	-467.052700	-468.235600	-467.059694	-468.241494	2.8880	-3102.8160
	Ethanol*	---------	----------	----------	----------	----------	----------
	Heptane	-467.052700	-468.235600	467.055605	-468.229826	22.7867	3082.9174
Carvacrol	Methanol	-464.056703	-464.683181	-464.064437	-464.689525	3.6494	-1641.1686
	DMSO	-464.056703	-464.683181	-464.064536	-464.689596	3.7229	-1641.0952
	Ethanol	-464.056703	-464.683181	-464.056703	-464.689452	3.5680	-1641.2822
	Heptane	-464.056703	-464.683181	-464.686063	-464.059988	1.0580	-1645.8761

** In experimental eny peak seen for Ethanol so not performed calculation in this solvent.*



Scheme 4: The oxidation mechanism of carvacrol compound

for menthol and carvacrol. The highest occupied molecular orbitals (HOMOs) and the lowest occupied ones (LUMOs) of the two studied compounds are also presented in Fig. 3. We can see that both frontier orbitals are distributed at the rings and the OH groups. For that reason, the electron transfer reactions may occur at the rings. Finally, Fig. 3 also displays ElectroStatic Potential (ESP) maps of two compounds. In principal, the electrostatic potential levels are represented by different ranges of colors: the red color as the most negative electrostatic potential while the blue one as the most positive potential. As can be seen in Fig. 3, the most negative electrostatic potential regions are located at oxygen atom positions, while the positive electrostatic potential areas contain the C atoms of rings.

Table 3: Gibbs energy, $\Delta\Delta G^0_{solv}$ and ΔG_{tot} of menthol and carvacrol for both reduced(AH) and oxidized (A) forms in the gas and solution phases calculated using 6-311+g (d,p) basis set at DFT level of theory with IEFPCM model.

Comp.	Solvent	G^0_{gas} (A) (a.u)	G^0_{gas} (AH) (a.u)	G^0_{sol} (A) (a.u)	G^0_{sol} (AH) (a.u)	$\Delta\Delta G^0_{solv}$ (kJ/mol)	ΔG_{tot} (kJ/mol)
Menthol	Methanol	-467.052700	-468.235600	-467.059616	-468.232995	31.8368	-3073.8673
	DMSO	-467.052700	-468.235600	-464.059720	-468.233101	31.8368	-3080.7120
	Ethanol*	---------	---------	---------	---------	---------	---------
	Heptan	-467.052700	-468.235600	-467.055231	-468.229152	23.5743	-3082.1298
Carvacrol	Methanol	-464.056703	-464.683181	-464.064812	-464.689460	4.8020	-1640.0160
	DMSO	-464.056703	-464.683181	-464.064812	-464.689590	4.4633	-1637.7619
	Ethanol	-464.056703	-464.683181	-464.064512	-464.689367	4.2611	-1640.5569
	Heptan	-464.056703	-464.683181	-464.059503	-464.685508	1.2418	-1643.5762

Table 4: Comparison of results of half-wave potentials calculated with experimental and obtained MUE from calculated Redox potentials in two methods CPCM and IEFPCM.

Comp.	Solvent	$E_{1/2}$ CPCM	$E_{1/2}$ IEFPCM	$E_{1/2}$ Exp.	MUE CPCM	MUE IEFPCM
Menthol	Methanol	0.229	0.228	0.276	0.047	0.048
	DMSO	0.229	0.228	0.270	0.041	0.042
	Ethanol	---------	---------	---------	---------	---------
	Heptane	0.228	0.228	0.280	0.052	0.052
Carvacrol	Methanol	0.214	0.213	0.240	0.026	0.027
	DMSO	0.214	0.213	0.278	0.064	0.065
	Ethanol	0.214	0.214	0.288	0.074	0.074
	Heptane	0.214	0.214	0.187	-0.027	-0.027

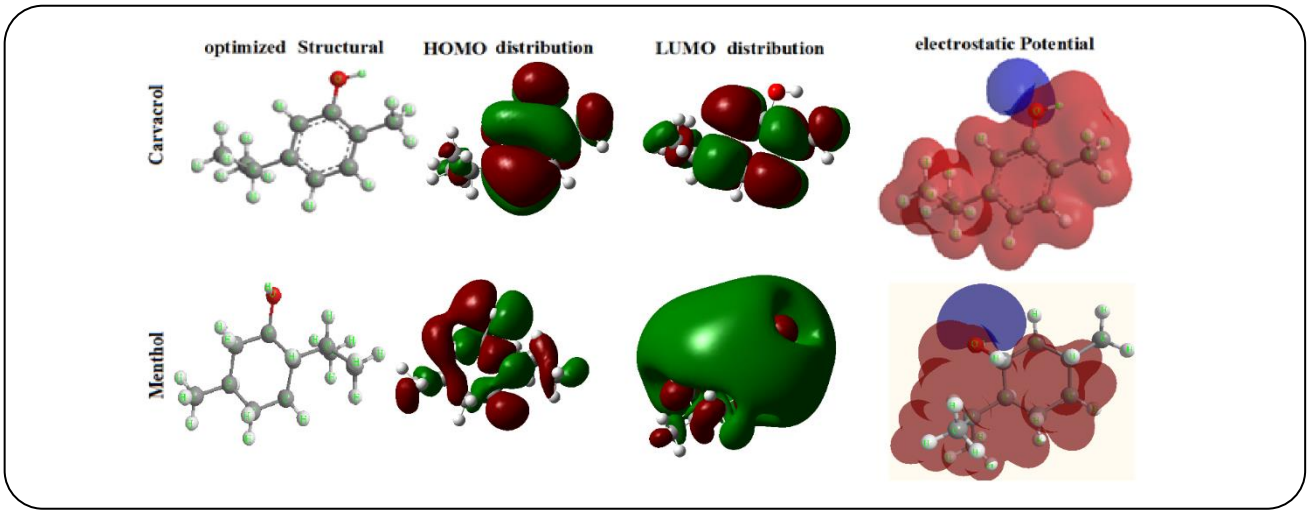


Fig. 3: Optimized structures, HOMO, LUMO distribution and electrostatic potential (ESP) map.

Table 5: BDE, IP and EA values of menthol and carvacrol calculated at the B3LYP/6-311+G(d,p) model in the gas phase.

Comp.	BDE (kcal/mol)	IP (ev)	EA (ev)
Carvcarol	80.19	6.12	0.35
Menthol	98.91	7.31	0.00

Table 6: BDE, IP and EA values of menthol and carvacrol calculated using 6-311+g (d,p) basis set at DFT level of theory with CPCM model.

Comp.	Solvent	BDE (kcal/mol)	IP (ev)	EA (ev)
	Methanol	99.06	7.3654	-0.1055
Menthol	DMSO	99.06	7.3660	-0.1061
	Ethanol	99.06	7.3649	-0.1053
	Heptane	99.02	7.3363	-0.0633
	Methanol	79.29	6.2746	0.4666
Carvacrol	DMSO	79.27	6.2765	0.4682
	Ethanol	79.31	6.2729	0.4650
	Heptane	79.89	6.1940	0.3942

BDE, IP and EA values of menthol and carvacrol calculated at the B3LYP/6-311+G(d,p) model in the gas phase are shown in Table 5. In comparison with the BDEs values of other well-known antioxidants such as phenol (87.2 kcal/mol) [50], α-terpinene (74.4 kcal/mol) [51] BDE in the gas phase being 98.91 and 80.19 kcal/mol for menthol and carvacrol respectively. The calculated adiabatic ionization potentials (IP) are obtained 7.31 and 6.12 eV for menthol and carvacrol were and electron affinity (EA) also calculated 0.00 and 0.35 eV for menthol and carvacrol (Table 5). From this results understand that carvacrol trend to farther oxidation compared with menthol. Values of BDE, IE and EA of menthol and carvacrol in different solvents are calculated (Table 6 and 7). These results emphasis antioxidant properties of carvacrol compared with menthol at different solvents is farther. Literatures shows by employing the different methods and models, redox potentials of different organic compounds in several solvents were calculated (Table 8). Table shows that obtained MUE from calculated Redox potentials of this work as previously other works were calculated values of MUE.

CONCLUSIONS

In this work, we studied electrochemical and antioxidant properties of two spaces menthol and carvacrol by two method of computational: $E_{1/2}$ calculation by thermodynamic cycle and Hot/Set mechanism and results compared with redox potentials of obtained cyclo vaoltamety. The results of cyclo voltammetry showed:

1- Redox potentials of menthol compared with carvacrol are high.

2- Electrochemical mechanism of carvacrol oxidation in spite of menthol depended on solvent polarity.

3- Computational data showed that the modification of the method for menthol and carvacrol compounds did not have much effect. Electrochemical results approximately are same in CPCM and IEPCM method.

4- BDE, IP and EA values of menthol and carvacrol calculated at the B3LYP/6-311+G (d,p) level in the gas phase show this values is adapted to calculation of $E_{1/2}$ and cyclo voltametry results.

5- Antioxidant properties of carvacrol were due to smaller presence of $E_{1/2}$ in non-polar solvents is more likely to be a criterion for selecting this compound in chemical and biochemical reactions as an antioxidant.

We hope that the methods described in this work serve as a helpful tool to choose appropriate computational methods for redox-potential predictions in areas of chemistry, biology, and mineralogy of many spaces such carvacrol and menthol.

Table 7: BDE, IP and EA values of menthol and carvacrol calculated using 6-311+g (d,p) basis set at DFT level of theory with IEFPCM model.

Comp.	Solvent	BDE (kcal/mol)	IP (ev)	EA (ev)
	Methanol	99.03	7.3632	0.1058
Menthol	DMSO	99.04	7.3646	0.1061
	Ethanol	99.02	7.3622	0.1053
	Heptane	98.97	7.3232	0.5686
	Methanol	79.28	6.2691	0.4609
Carvacrol	DMSO	79.27	6.2724	0.4642
	Ethanol	79.29	6.2656	0.4576
	Heptane	79.82	6.1668	0.3676

Table 8: Studied compound in literatures compared with this work.

Comp.	MUE (ev)	Model	Ref.
Quinones	0.03	B3LYP/PCM	[52]
Nitroxide	0.05	B3LYP/PCM	[53]
Aazaphenalene nitroxide	0.06	B3LYP/PCM	[54]
Polyaromatic hydrocarbons	0.03	B3LYP/SMD	[54]
Polyaromatic hydrocarbons	0.07	B3LYP/ CPCM	[55]
Cyclic nitroxide	0.2–0.50	CBS-QB3/ CPCM	[56]
Flavonoids	0.06	CPCM	[57]
Flavonoids	0.04	M06-L DFT/SM6	[58]
Menthol and Carvacrol	0.02-0.07	B3LYP/CPCM/IEPCM	-

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