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## Original Article

# An investigation of the olive phenols activity as a natural medicine



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## ARTICLE INFO

## Article history:

Received 23 May 2017

Received in revised form

10 July 2017

Accepted 11 July 2017

Available online 25 July 2017

## Keywords:

1,4-Hydroquinone

Semiquinone

1,4-Benzoquinone

Blood

DFT

## ABSTRACT

The natural antioxidants of olive oil have phenolic structure and their activities are related to the formation of stable derivatives. In this study, the single components of the phenolic fraction of olive oil (1,4-hydroquinone, Semiquinone and 1,4-benzoquinone) have been studied as theoretical by using DFT (Density functional Theory). The behaviors of phenolic compounds of olive against to the alkyl peroxy radicals were investigated. Our data show that 1,4-benzoquinone is the best electron transfer agent in primary metabolic processes to human life. The frontier orbital gap, namely HOMO (highest occupied molecular orbital) –LUMO (lowest unoccupied molecular orbital) gap is the smallest for 1,4-benzoquinone. Hence, it is more stable than the others in blood. The natural phenolic compound's mechanism of many plants can be explained by using DFT method without consuming time and money. In this study, we have indicated the behaviors of natural antioxidants of olive oil's single components phenolic structure in blood phase.

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## 1. Introduction

Olive phenols have been studied to indicate healthy effects recently [1–4]. The chemical composition of EVOO and the phenolic compounds of it were effective to decrease the risk of cardiovascular disease [4]. Furthermore, some studies related to the Olive phenols showed that the daily consumption of it was too beneficial to be healthy for human because of the reduction in the peroxidation of blood lipids due to having phenolic functional groups. The most important antioxidants in olive were lipophilic and hydrophilic phenols [7], and the other effective structures such as carotenoids.

Phenolic acids, phenolic alcohols, hydroxy-isochromans, flavonoids, lignans and secoiridoids were effective phenolic

compounds in these olive oils [1,4]. Phenolic acids, vanillic, syringic, p-coumaric, o-coumaric, protocatechuic, sinapic acid, p-hydroxybenzoic and gallic acid were the initially discovered phenolic compounds in olive oil [7,8].

Antioxidants, were the mainly part of olive oil because of their biological activity effecting oxidation processes. The phenolic compounds of olive acted as chain breakers by donating radical hydrogen to alkylperoxyl radicals, which were produced by lipid oxidation. The formation of stable derivatives of olive phenols were given in Fig. 1 [4].

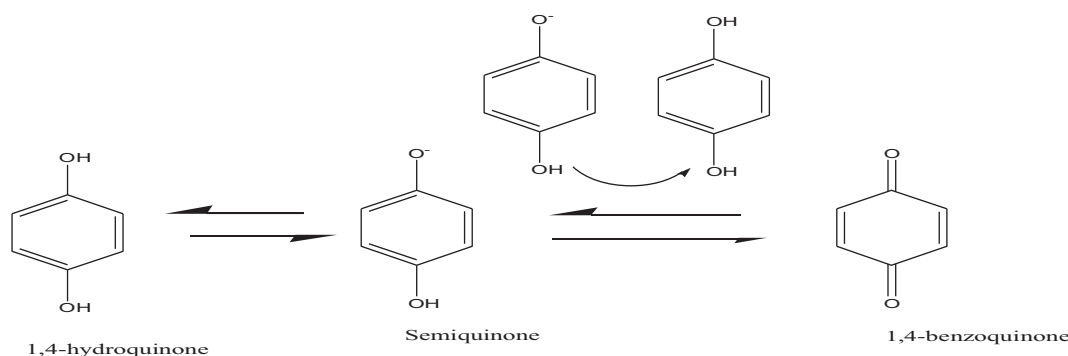
The reaction mechanism of 1,4-hydroquinone against the free radical as antioxidant could be explained in Fig. 2 [5].

1,4-hydroquinone, Semiquinone and 1,4-benzoquinone's electron transfer mechanism that allows the formation of the stable free radicals is given in Fig. 3 [6].

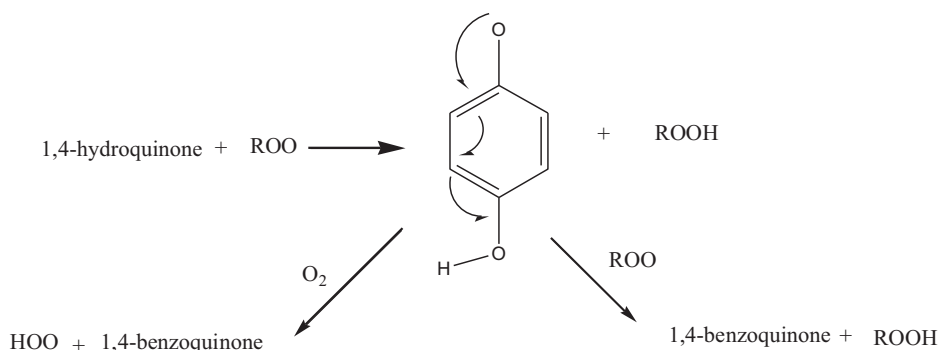
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<http://dx.doi.org/10.1016/j.jfda.2017.07.003>

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**Fig. 1 – The mechanism of the antioxidant activity of Olive phenols.**



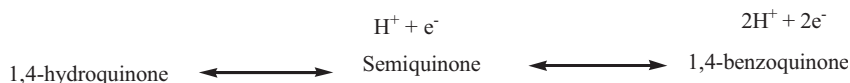
**Fig. 2 – The reaction mechanism of 1,4-hydroquinone against the free radical as antioxidant.**

The cananga tree alkaloid sampangine had been investigated for having antimicrobial and antitumor potential effects. The biological activities formed as the reduction of cellular oxygen, the induction of reactive oxygen species (ROS) in vivo [9]. “Ubiquinone was possible that this compound was reduced to more reactive Semiquinone form by mitochondria then readily reduces oxygen to superoxide. In support of this idea, ascorbate, an electron donor for a variety of compounds. For the heme biosynthesis can be coupled to the mitochondrial electron transport chain for energy production, oxidative stress disregulates heme production, ROS induced by the herbicide paraquat disrupts heme biosynthesis, and ROS suppresses uroporphyrinogen III synthase gene expression. Redox cycling appears responsible for the observed immediate increase of cellular oxygen consumption, but defects in heme biosynthesis may disrupt an array of biochemical processes. ROS-mediated side effects and toxicity may significantly limit the clinical potential of sampangine and its analogs as antifungal and antitumor agents” [9].

There were two major groups as determining antioxidant capacity. One of them is single electron transfer and the other is hydrogen atom transfer reaction. The main important method for single electron transfer is the Trolox equivalent

antioxidant capacity [10]. The oxygen radical absorbance capacity is the most applied method for hydrogen atom transfer reaction. Phenolic compounds are acted as effective radical chain-breaking antioxidants by the hydrogen atom transfer reaction [11,12]. With this mechanism, it is effected to the alkylperoxyl radicals, formed during the initiation step of lipid oxidation. In this step phenolics groups play important role as strong antioxidant [13] correlated to the total phenolics of it [10].

The risk of atherosclerosis may be decreased by the consumption of olive oil having a lot of phenolic compounds by decreasing inflammation and improving the antioxidant profile in the vascular endothelium [15]. Moreover, the high concentration of phenolic compounds have postprandial anti-inflammatory effects and decreases the gene expression of genes related to inflammation and oxidative stress [15,16]. “It may reduce the risk of developing atherosclerosis in metabolic syndrome patients by decreasing inflammation and improving the antioxidant profile in the vascular endothelium. These results provide further evidence of the reduction in the risk factors for developing cardiovascular disease observed in Mediterranean regions, where the main source of dietary fat is virgin olive oil” [14].



**Fig. 3 – Electron transfer mechanism of 4-hydroquinone, Semiquinone and 1,4-benzoquinone.**

## 2. Materials and methods

The electronic structures of the single components of the phenolic fraction of olive oil (1,4-hydroquinone, Semiquinone and 1,4-benzoquinone) are commonly studied by DFT, included in DFT method, containing Becke's gradient correction for exchange, and RB3LYP methods were used for quantum chemical calculations and geometry optimization. In the case of the RB3LYP functional, the non-local correlation was provided by the LYP expression, and the correction was carried by 6–31 + g (d, p) basis set. The thermodynamic values in blood were calculated by using DFT method. The correction was carried out by means of the 6–31 + g (d, p) functional basis set [17]. These methods and fully optimized geometric structure of the compounds by using this method were determined and evaluated. The electric constant is 58 at 37 °C for blood [23]. Theoretical investigations had important roles to determine the structural basis of selectivity [27].

## 3. Result and discussions

The 1,4-hydroquinone, Semiquinone and 1,4-benzoquinone values of  $\Delta G$ , HOMO, LUMO,  $\Delta$  (HOMO–LUMO) and Dipole Moment are given in Table 1.

A molecule had a small frontier orbital gap hence, it was more polarizable and had a high chemical reactivity, low kinetic stability and named as soft molecule [25]. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular (LUMO) orbital energies show that charge transfer occurs within the molecule and [24] According to the values in Table 1: The most stable compound is 1,4-hydroquinone because of having large band between the HOMO–LUMO difference. 1,4-benzoquinone has small the HOMO–LUMO difference hence, it is more polarizable and had a high chemical reactivity as mentioned in literature [21,25]. The lowest HOMO–LUMO band gap is the indication of increasing in electron donating character of the substituents [26]. Phenolic structures have big value of LUMO so that it is good acceptor of proton from the radicalic forms. It is too important to determine the HOMO–LUMO of the molecule to support the

reduction and oxidation mechanism in a more accurate way [28]. 1,4-benzoquinone is less stable and has big HOMO so that it is acceptor of proton or electrons from the radicalic forms. The 1,4-hydroquinone, Semiquinone and 1,4-benzoquinone's values of dihedral angles are given in Table 2. Dipole moment order of 1,4-hydroquinone, Semiquinone and 1,4-benzoquinone from big to small; Semiquinone, 1,4-hydroquinone, 1,4-benzoquinone so The polarity of Semiquinone is better than the others.

Dihedral angles increase top to bottom in Table 2. We can assume that the stability order from big to small; 1,4-benzoquinone, Semiquinone and 1,4-hydroquinone. Dihedral angles indicated the position of the pendant carbon chain relative to the benzene ring of the structure and all a planar geometry had minimum energy, probably due to the stabilizing effect of p-electron delocalization of benzene ring and C [18]. In Table 2; The comparison dihedral angles of 1,4-hydroquinone, Semiquinone and 1,4-benzoquinone; 1,4-benzoquinone is up to 180°, having the minimum energy and the most active form of phenolic derivatives.

The atomic charges of 1,4-hydroquinone is given in Fig. 4.

The atomic charges of Semiquinone is given in Fig. 5.

The atomic charges of 1,4-benzoquinone is given in Fig. 6.

The Mulliken charges order from Fig. 4 (1,4-hydroquinone), Fig. 5 (Semiquinone) and Fig. 6 (1,4-benzoquinone): For the right O;  $-0.593$ ,  $-0.623$ ,  $-0.512$ ; the left O;  $-0.593$ ,  $-0.900$ ,  $-0.512$ . For C3 on the right:  $-0.107$ ,  $-0.101$ ,  $-0.026$  and C6 on the left;  $-0.107$ ,  $-0.110$ ,  $-0.026$ . 1,4-benzoquinone has the smallest Mulliken charge for C6, C3 and O8, O7. Mohamed and Elssamani emphasized that the compounds had higher charges, therefore chelation by metal occur in the 13th position Furan ring. The stability of the bifuran free radical generated after H abstraction for the antioxidant. In generally, the factors enhancing the stability of the free radical would increase the antioxidant activity [19].

Atomic charges were affected by the presence of the substituent of rings. The highest atomic charge of compound indicated that these atoms were the most reactive toward the addition, substitution reactions and bonding with the metals [20]. As shown in Figs. 4–6; the Mulliken charge of Semiquinone for O is higher than the others. So, it is the most reactive derivatives forms of phenolic

**Table 1 – The 1,4-hydroquinone, Semiquinone and 1,4-benzoquinone values of  $\Delta G$ , HOMO, LUMO,  $\Delta$  (HOMO–LUMO) and Dipole Moment.**

DFT (in blood)	$\Delta G$ (Hartree)	HOMO (eV)	LUMO (eV)	$\Delta$ (HOMO–LUMO) (eV)	Dipole moment (Debye)
1,4-Hydroquinone	–382.650056	–0.21754	–0.02489	–0.19265	3.6558
Semiquinone	–382.179781	–0.15902	0.00100	–0.15802	9.7219
1,4-Benzoquinone	–381.432065	–0.28646	–0.14260	–0.14386	0.0001

**Table 2 – The dihedral angles of 1,4-hydroquinone, Semiquinone and 1,4-benzoquinone.**

DFT (in blood)	Dihedral angles			
	H13-O7-C6-C1	H13-O7-C6-C5	H14-O8-C3-C2	H14-O8-C3-C4
1,4-Hydroquinone	179.98614	–0.01672	179.98584	0.01706
Semiquinone	179.98949	–0.01377	179.99240	0.00090
1,4-Benzoquinone	179.99256	0.00801	179.98734	0.01816

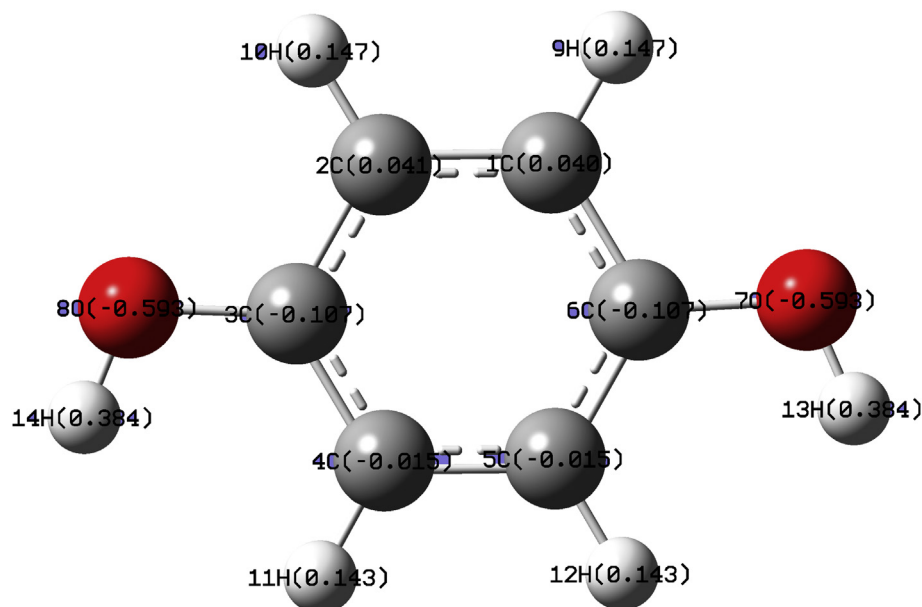


Fig. 4 – The atomic charges of 1,4-hydroquinone.

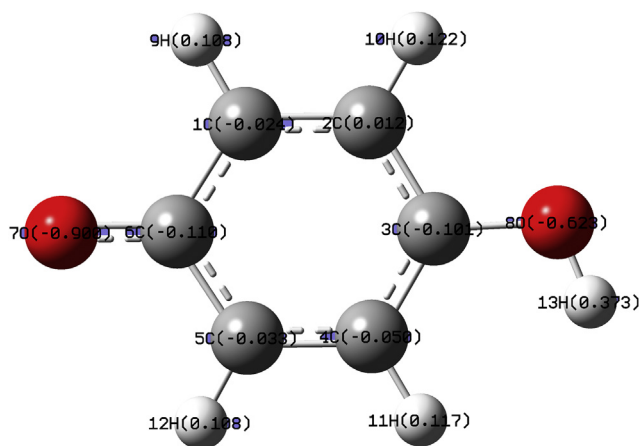


Fig. 5 – The atomic charges of Semiquinone.

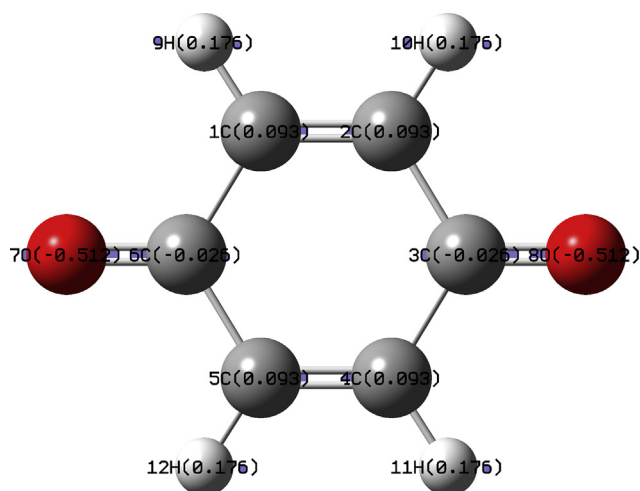


Fig. 6 – The atomic charges of 1,4-benzoquinone.

structure of olive oil. Klein et al. indicated that the easier hydrogen atom transfer from the deprotonated flavonoids as phenolic antioxidants [22]. The important agents against hydroxyl radicals come from antioxidants. Antioxidants are the mainly reducing agents; they participate in redox reactions by donating electrons or hydrogen atoms [29]. The chemical structure of individual flavor compounds is associated with the chemical reaction that is responsible for its stability. The presence of active functional groups, such as carbonyl, hydroxyl, functional groups, affects the chemical reactivity of these compounds [30]. In this study; 1,4-hydroquinone oxidized to 1,4-benzoquinone by donating electrons or hydrogen as the presence of functional groups (hydroxyl).

#### 4. Conclusion

The natural antioxidants of olive oil have phenolic structure and the phenolic derivatives activity have been investigated by using DFT. 1,4-benzoquinone has small the HOMO–LUMO difference hence, it is more stable than the others. The comparison dihedral angles of 1,4-hydroquinone, Semiquinone and 1,4-benzoquinone; 1,4-benzoquinone is up to 180°, having the minimum energy and the most active form of them. For the Mulliken charge of Semiquinone for O is higher than the others. So, it is the most reactive derivatives forms of phenolic structure of olive oil. The polarity of Semiquinone is also well in blood.

#### Acknowledgment

The calculations are carried out in the Computing Center and Gaussian 09W64 programs of Kırkkale University. This study

is supported by the Scientific Research Projects of Kırıkkale University (BAP-2017/019).

## REFERENCES

- [1] Servili M, Selvaggini R, Esposto S, Taticchi A, Montedoro GF, Morozzi GJ. Health and sensory properties of virgin olive oil hydrophilic phenols: agronomic and technological aspect of production that affect their occurrence in the oil. *J Chromatogr* 2004;1054:113–27.
- [2] Servili M, Esposto S, Fabiani R, Urbani S, Taticchi A, Mariucci F, et al. Phenolic compounds in olive oil: antioxidant, health and organoleptic activities according to their chemical structure. *Inflammopharmacology* 2009;17:1–9.
- [3] Omar SH. Oleuropein in olive and its pharmacological effects. *Sci Pharm* 2010;78:133–54.
- [4] Servili M, Sordini B, Esposto S, Urbani S, Veneziani G, Maio ID, et al. Biological activities of phenolic compounds of extra virgin olive oil. *Antioxidants* 2014;3:1–23.
- [5] Bendary E, Francis RR, Ali HMG, Sarwat MI, El Hady S. Antioxidant and structure–activity relationships (SARs) of some phenolic and anilines compounds. *Ann Agric Sci* 2013;58(2):173–81.
- [6] Blakley RL, Henry DD, Smith CJ. Lack of correlation between cigarette mainstream smoke particulate phase radicals and hydroquinone yield. *Food Chem Toxicol* 2001;39(4):401–6.
- [7] Servili M, Montedoro GF. Contribution of phenolic compounds to virgin olive oil quality. *Eur J Lipid Sci Technol* 2002;104:602–13.
- [8] Tsimidou M, Lytridou M, Boskou D, Pappa-Louisi A, Kotsifaki F, Petrakis C. On the determination of minor phenolic acids of virgin olive oil by RP-HPLC. *Grasas Aceites* 1996;47:151–7.
- [9] Mahdi F, Morgan JB, Liu W, Agarwal AK, Jakobsons MB, Liu Y, et al. Sampangine (a copyrine alkaloid) exerts biological activities through cellular redox cycling of its quinone and semiquinone intermediates. *J Nat Prod* 2015;78:3018–23.
- [10] Ballus CA, Meinhart AD, Campos Jr FAS, Godoy HT. Total phenolics of virgin olive oils highly correlate with the hydrogen atom transfer mechanism of antioxidant capacity. *J Am Oil Chemists' Soc* 2015;92:843–51.
- [11] Huang D, Ou B, Prior RL. The chemistry behind antioxidant capacity assays. *J Agric Food Chem* 2005;53:1841–56.
- [12] Tabart J, Kevers C, Pincemail J, Defraigne J-O. Comparative antioxidant capacities of phenolic compounds measured by various tests. *Food Chem* 2009;113:1226–33.
- [13] Carrasco-Pancorbo A, Cerretani L, Bendini A, Segura-Carretero A, Del Carlo M, Gallina-Toschi T, et al. Evaluation of the antioxidant capacity of individual phenolic compounds in virgin olive oil. *J Agric Food Chem* 2005;53:8918–25.
- [14] Meza-Miranda ER, Rangel-Zúñiga OA, Marín C, Pérez-Martínez P, Delgado-Lista J, Haro C, et al. Virgin olive oil rich in phenolic compounds modulates the expression of atherosclerosis-related genes in vascular endothelium. *Eur J Nutr* 2016;55:519–27.
- [15] Bogani P, Galli C, Villa M, Visioli F. Postprandial anti-inflammatory and antioxidant effects of extra virgin olive oil. *Atherosclerosis* 2007;190:181–6.
- [16] Konstantinidou V, Covas MI, Munoz-Aguayo D, Khymenets O, de la Torre R, Saez G, et al. In vivo nutrigenomic effects of virgin olive oil polyphenols within the frame of the Mediterranean diet: a randomized controlled trial. *FASEB J* 2010;24:2546–57.
- [17] Gökalp F. A study on the chemical properties of eugenol and eugenol acetate, clove essential oils. *Sigma J Eng Nat Sci* 2016;34(3):407–14.
- [18] Besien EV, Marques MPM. Ab initio conformational study of caffeic acid. *J Mol Struct (Theochem)* 2003;625:265–75.
- [19] Mohamed ME, Elssamani AO. Density functional theory (DFT) B3LYP study of antioxidant activity of 6-(2,2'-bithiophen-5yl) pyridine-3-carboximidamide, new model bichalcophenes derivatives. *J Appl Industrial Sci* 2015;3(4):126–32.
- [20] Kadhum AA, Al-Amiery AA, Musa AY, Mohamad AB. The antioxidant activity of new coumarin derivatives. *Int J Mol Sci* 2011;12:5747–61.
- [21] Veeraiiah A, Solomon KA, Krishna GG, Reddy JS, Veeraiiah V, Chaitanya K. Vibrational and electronic absorption spectra of (Z)-2-(4-nitrobenzylidene)-1-benzofuran-3(2H)-one. *J Mol Struct* 2012;1026:36–43.
- [22] Klein E, Rimarcík J, Senajová E, Vagánek A, Lengyel J. Deprotonation of flavonoids severely alters the thermodynamics of the hydrogen atom transfer. *Comput Theor Chem* 2016;1085:7–17.
- [23] Miscellaneous dielectric constants, available at <https://www.microwaves101.com/encyclopedias/miscellaneous-dielectric-constants>. [Accessed 09 May 2017].
- [24] Sundaraganesan N, Elango G, Meganathan C, Karthikeyan B, Kurt M. Molecular structure, vibrational spectra and HOMO, LUMO analysis of 4-piperidone by density functional theory and ab initio Hartree–Fock calculations. *Mol Simul* 2009;35(9):705–13.
- [25] Poonam R, Singh RN, Alok R, Sartaj A, Rajat S. Antimycobacterial, antimicrobial activity, experimental (FT-IR, FT-Raman, NMR, UV-Vis, DSC) and DFT (transition state, chemical reactivity, NBO, NLO) studies on pyrrole-isonicotinyl hydrazine. *Spectrochim Acta Part A Mol Biomol Spectrosc* 2017;179:1–10.
- [26] Manju P, Muthu S, Nanje G NM. Quantum mechanical and spectroscopic (FT-IR, FT-Raman, <sup>1</sup>H, <sup>13</sup>C NMR, UV-Vis) studies, NBO, NLO, HOMO, LUMO and Fukui function analysis of 5-Methoxy-1H-benzo[d]imidazole-2(3H)-thione by DFT studies. *J Mol Struct* 2017;1130:511–21.
- [27] Zhanga L, Zhang L. Molecular simulation of HDAC1/3 inhibitor: insights into the structural basis of selectivity. *Lett Drug Des Discov* 2016;13:43–6.
- [28] Taşdemir İH. Electrochemistry and determination of cefdinir by voltammetric and computational approaches. *J Food Drug Analysis* 2014;22:527–36.
- [29] Fu PP, Xia O, Hwang HM, Ray PC. Mechanisms of nanotoxicity: generation of reactive oxygen species. *J Food Drug Anal* 2014;22:64–75.
- [30] Weerawatanakorn M, Wu JC, Pan MH, Ho CT. Reactivity and stability of selected flavor compounds. *J Food Drug Anal* 2015;23:176–90.