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Quest For the Best Antioxidant Component Present in *Aloe vera*: A Theoretical Study

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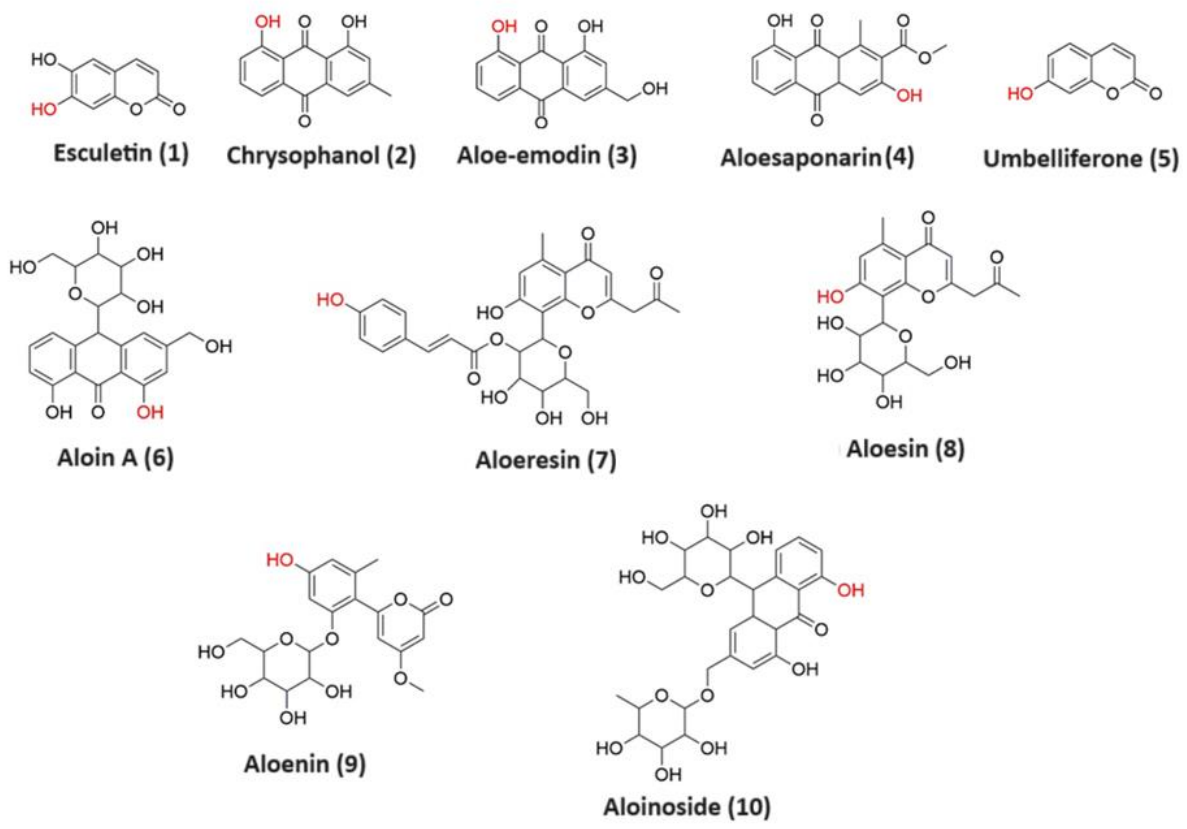
Abstract: Aloe vera is known to have many antioxidants. However, the best component is not known yet. In this study, a search for the best candidate to show antioxidant ability is made through quantum chemical calculations. Antioxidant behavior at different solvent medium including the lipid environment has been explored. Our study reveals that out of ten major components of Aloe vera, three of them, namely esculetin, umbelliferone and aloinoside A have been found to possess superior ability. Moreover, these three components have shown similar antioxidant ability as that of resveratrol and gallic acid while they perform better than fumaric acid.

Keywords: Aloe vera; Antioxidants; Bioavailability; Theoretical

1. Introduction

Antioxidants trap unwanted free radicals which are produced by oxidation in our body. The demand for antioxidants in day-to-day life is growing at an exponential rate. Over several decades, researchers have been searching for new antioxidants from natural sources [1-20]. The oxidative stress in the body is sometimes balanced by internally produced antioxidants such as enzymes or by those obtained from dietary sources such as vitamin C and E. However, when the body is under excessive oxidative stress, the internally produced antioxidants may not tackle the situation and therefore, more efficient antioxidants from dietary sources are gaining much attention these days.

Aloe vera is known for decades as a super antioxidant which is due to the presence of polyphenols. There are ten major phenolic compounds such as esculetin (**1**), chrysophanol (**2**), aloe-emodin (**3**), aloesaponarin I (**4**) and umbelliferone (**5**), aloin A (**6**), aloeresin A (**7**), aloesin (**8**), aloenin (**9**) and aloinoside A (**10**) as shown in Scheme 1. All these phenolic compounds are known to be the active components present in Aloe vera and are known to trap unwanted radicals generated in our body and thereby serve as antioxidants. However, it is not known to us which among them performs the best. Are all of them equally capable? Is there a particular component which performs better than the others? Can we distinguish the best component which can be synthesized alone in the laboratory? To answer these pertinent questions, we have undertaken a theoretical study to search for the best antioxidant component present in Aloe vera.



Scheme 1. Phenolic compounds present in Aloe vera

The study focusses on O-H bond dissociation enthalpy (BDE), ionization potential (IE) and radical stabilization enthalpy (RSE) using quantum chemical method. These chemical properties are associated with the four accepted mechanisms of antioxidants' action, [21-23] such as (i) hydrogen atom transfer (HAT), (ii) single electron transfer (SET), (iii) single electron transfer followed by proton transfer (SET-PT), and (iv) sequential proton loss electron transfer (SPLET) [2,8,18].

2. Computational Details

Structures were fully optimized at M06-2X/def2-TZVP level [24]. This functional provides good thermochemistry of main group compounds [24]. Harmonic vibrational frequency calculations confirm them to be local minimum. Transition states were located with one imaginary value of the Hessian matrix by intrinsic reaction coordinate (IRC) analysis. Unrestricted formalism was employed for the open shell calculations. Spin contaminations were found to be negligible (less than 1%). Further, bond dissociation energies of some phenols considered in this study were also evaluated by running single point calculations at CCSD(T)/def2-TZVP level on M06-2X optimized geometries. Universal solvation model (SMD) [25] were used for solvent phase calculations using n-octanol, water, and benzene on the gas phase optimized geometries. Pentyl ethanoate as solvent was also used to model lipid environment.

Rate constants were calculated using standard transition state theory at 298 K and 1 atm pressure.

The lipophilicity (LogP) was calculated using the following equation, Eq. (1) [26].

$$LogP = (\Delta G_{water} - \Delta G_{n-octanol})/RT \quad (1)$$

where ΔG values are the free energies in respective solvent.

Electronic structure analyses were performed using natural bond orbital (NBO) [27]. All the other calculations were performed using Gaussian 16 suite of program [28].

3. Results and Discussion

3.1. Lipophilicity

Lipophilicity is an indication of the physiological activity of the compounds [21, 29]. It is measured in terms of LogP values calculated in two different solvent medium, water and n-octanol. This partition functions provides important information regarding the bioavailability of a compound. Higher the LogP values, higher is the biological availability of the compounds. Figure 1 shows the logP values of the studied molecules. It is evident from Figure 1 that aloinoside A (**10**) has the highest value of LogP indicating higher physiological activity. This is expected due to its high molecular weight among all the polyphenols. Similarly, high molecular weight containing polyphenols (**6-10**) have higher LogP values indicating higher physiological activity. Interestingly, umbelliferone (**5**) have also significant value of logP despite of its smaller molecular weight.

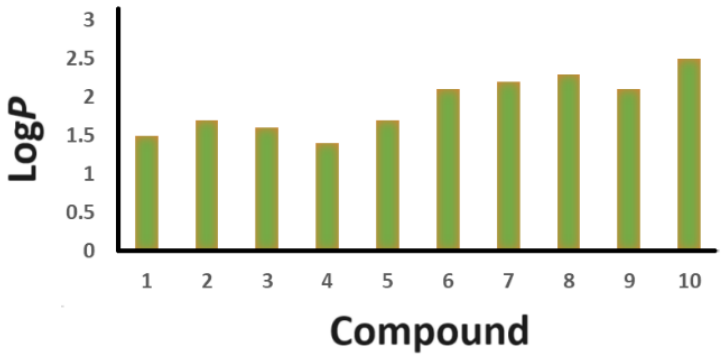


Figure 1. Calculated Log*P* values of the compounds

We then turned our attention to investigate chemical properties of these compounds by calculating the O-H bond dissociation energies (BDE), ionization energies, electron transfer enthalpy (ETE), radical stabilization energies (RSE) and finally the activation energies associated with trapping of OH free radical (as a test case). These parameters are very important to determine antioxidant ability following HAT, SET, SET-PT and SPLET discussed above.

Table 1 contains the O-H bond dissociation energies. The O-H bond is broken which produced the lowest BDE values and are marked red in Scheme 1. Calculated values of BDE

for **1**, **2** and **5** at M06-2X and CCSD(T) levels are very close (within 3.0 kcal/mol) indicating the reliability of the method used. It is evident from Table 1 that BDE values increase from gas phase to water, n-octanol and lipid medium which are more realistic model for the biological system. It is interesting to note that esculetin (**1**), umbelliferone (**5**) and aloinoside A (**10**) showed the lowest O-H BDE indicating that these three compounds are best to show antioxidant ability through hydrogen atom transfer (HAT) pathway. Moreover, the calculated BDE of these two compounds is lower than trans-resveratrol, gallic acid and fumaric acid which are known to be good antioxidants. Thus, these three compounds (**1**, **5** and **10**) present in Aloe vera are the best performers according to HAT mechanism.

Table 1. Calculated O-H bond dissociation energies (BDE, kcal/mol) [The O-H bonds marked red are broken as shown in Scheme 1; values within parenthesis refer to CCSD (T)/ def2-TZVP values]

Compound	BDE			
	Gas	**Water**	**n-octanol**	**Lipid**
1	77.7 (79.3)	87.5 (89.1)	87.2 (89.3)	88.3 (90.3)
2	101.7 (103.2)	107.3 (108.4)	107.9 (109.2)	109.2 (111.3)
3	101.6	109.3	107.9	105.2
4	94.1	102.2	102.4	104.6
5	88.0 (90.1)	96.0 (97.8)	96.9 (98.3)	97.2 (99.3)
6	91.0	94.2	97.2	97.6
7	88.2	90.2	91.2	92.3
8	92.1	93.2	94.3	94.1
9	90.1	91.4	91.8	92.4
10	76.1	77.3	78.2	78.5
Trans Resveratrol	86.7	96.0	95.9	96.3
Gallic Acid	88.1	93.5	93.9	94.2
Fumaric Acid	112.0	121.9	122.7	122.8

Ionization potential is another important parameter to understand the feasibility of electron transfer to the other radical centre. This is important as lower the ionization energy, higher will be its tendency to release electron and thereby trap the unwanted radical. Table 2 contains the numerical information of adiabatic ionization potential. In every case, IP values decrease in water and n-octanol medium owing to their high polarity which helps in stabilizing the cation formed after release of electron, thereby helping in electron transfer to the unwanted radical. It is evident from Table 2 that out of ten phenolic compounds considered in this study which are active components of Aloe vera, compound **1**, **5** and **10** have lower IP values indicating that these three may trap the radicals through single electron transfer mechanism. Interestingly, all the phenolic compounds have lower IP values compared to fumaric acid. This implies that all these phenolic compounds present in Aloe vera are better antioxidants than fumaric acid.

We then turned our attention to the kinetic barrier of these compounds to trap radicals. We have considered OH radical as a representative case. Table 2 also contains the activation

barriers of these compounds to trap OH radical. The activation barriers were found to be much lower for compound **1, 5** and **10** compared to other phenolic compounds indicating that these three are the best to readily trap radicals. Interestingly, the activation energies of these two compounds are very close to *trans*-resveratrol and gallic acid which are known to show excellent antioxidant abilities. Thus, out of ten phenolic compounds present in *Aloe vera* compound **1**, **5** and **10** are the best in trapping radicals. The transition states are shown in Figure 2. Moreover, Gibbs free energy change (ΔG^{298}) for the reaction between these phenolic compounds with OH radical also indicates that compound **1**, **5** and **10** have more negative values of ΔG^{298}. Therefore, the reactions of **1**, **5** and **10** with OH radical are expected to be more spontaneous.

Table 2. Calculated adiabatic ionization potential (IP, eV) of the compounds in different media [Activation energy (E_a, kcal/mol) and Gibbs free energy change (ΔG^{298}, kcal/mol) associated with the trapping of OH radical calculated in gas phase]

Compound	IP				E_a	ΔG^{298}
	Gas	Water	n-octanol	Lipid		
1	8.1	6.2	6.4	6.6	16.6	-21.3
2	8.4	7.0	7.1	7.2	31.2	-17.6
3	8.5	7.0	7.1	7.3	30.9	-18.3
4	8.5	7.1	7.3	7.4	18.2	-23.2
5	8.5	6.6	6.7	6.5	17.6	-24.1
6	8.3	6.9	6.8	6.7	23.1	-19.2
7	8.7	7.1	7.3	7.6	28.2	-18.7
8	8.4	7.3	7.5	7.2	26.1	-15.3
9	8.3	6.9	7.1	7.3	24.2	-16.3
10	7.8	6.1	6.3	6.4	14.5	-29.2
Trans-Resveratrol	7.3	5.9	6.0	6.2	17.3	-27.2
Gallic Acid	8.4	6.5	6.7	6.6	17.7	-25.4
Fumaric Acid	11.2	9.2	9.3	9.4	21.3	-24.2

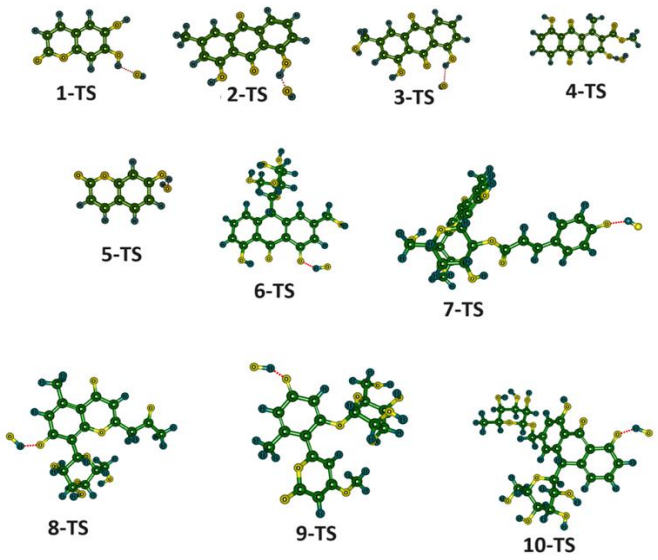


Figure 2. Transition state structures for the reaction between OH radical and the polyphenols

We then calculated the rate constant for the reaction between OH radical and phenolic compounds. Table 3 contains the rate constant *k* in $M^{-1}S^{-1}$ for all the reactions. The calculated rate constants for **1**, **5** and **10** are higher and are closer to the conventional antioxidants *trans* resveratrol, Gallic and Fumaric acid. Thus, the kinetic study also indicates that **1**, **5** and **10** are better antioxidants among the phenolic components present in aloe vera.

Table 3. Rate constant *k* ($M^{-1}S^{-1}$) for the reaction of OH radical with the phenolic compounds calculated at 298 K and 1 atm pressure

Compound	*k*	Compound	*k*
1	1.82	7	3.93×10^{-2}
2	3.42×10^{-1}	8	4.12×10^{-1}
3	3.91×10^{-1}	9	3.67×10^{-2}
4	2.12×10^{-1}	10	1.87
5	1.91	*Trans* Resveratrol	1.62
6	3.72×10^{-2}	Gallic Acid	1.81
		Fumaric Acid	1.67×10^{-1}

Stability of the radicals formed after H atom transfer is very crucial to determine. Distribution of spin density is important to render stability to the radical. We therefore, plotted the spin density of the radicals (Figure 3) and calculated the radical stabilization energy (RSE) using NBO program [27]. It is evident from Figure 3 that spin density is most delocalized in **1**, **5** and **10** radicals which render more stability to the radical after H atom transfer. This has also been reflected in the second-order perturbation energy E^2 (Table 4) computed using NBO program. Calculated RSE values of **1**, **5** and **10** radicals are almost similar to those of *trans*-resveratrol and gallic acid and slightly higher than that of fumaric acid. Thus, radicals of compound **1**, **5** and **10** have higher stability which may render them better antioxidant ability.

Table 4. Calculated RSE (kCal mol^{-1}) values

Compound	RSE			
	Gas	Water	n-octanol	Lipid
1	28.2	30.1	28.9	27.8
2	22.1	24.1	22.7	21.0
3	21.7	22.4	22.2	20.6
4	23.4	25.1	23.9	22.1
5	29.1	30.4	29.5	28.4
6	28.6	29.1	29.5	28.2
7	24.2	23.4	24.1	23.7
8	23.3	22.4	22.5	21.3
9	27.6	27.2	26.9	24.1
10	31.2	29.5	29.1	30.2
Trans Resveratrol	29.5	30.2	30.2	28.2
Gallic Acid	28.7	29.1	29.3	27.1
Fumaric Acid	25.2	26.1	26.1	24.2

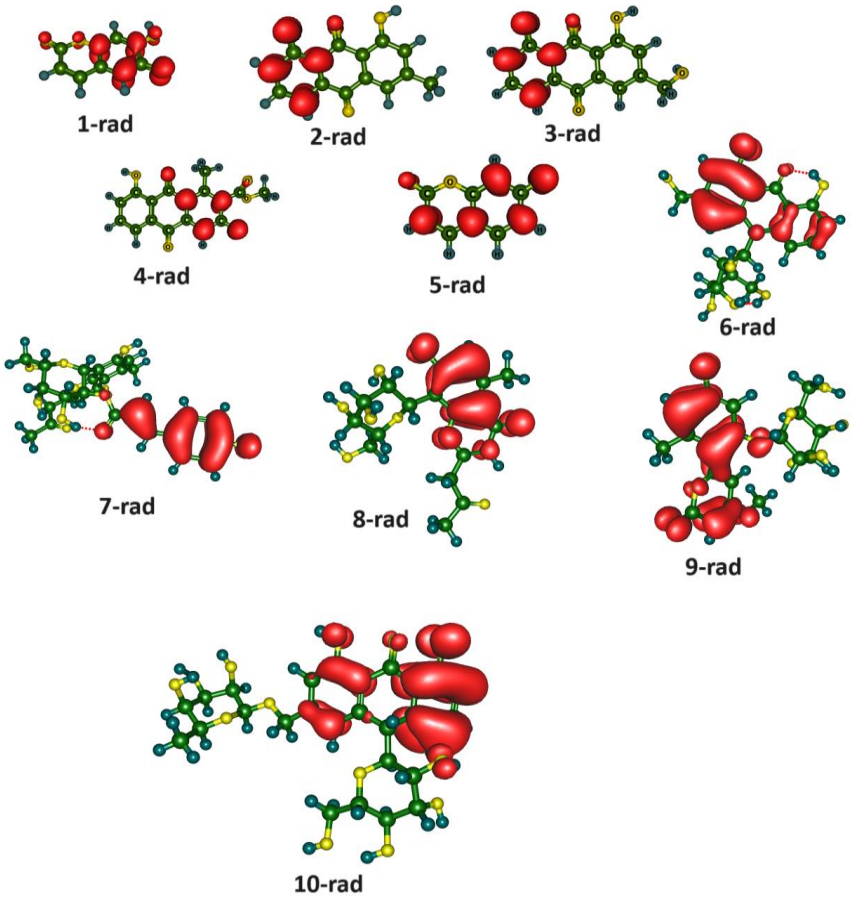


Figure 3. Spin density plots [Contour value used: 0.003 au]

4. Conclusions

Calculations were performed to search for the best phenolic antioxidants present in *Aloe vera*. Different parameters such as O-H bond dissociation energy, ionization potential and radical stabilization energies were evaluated for ten different phenolic compounds present in *Aloe vera*. Our study reveals that esculetin (**1**), umbelliferone (**5**) and aloinoside A (**10**) are the best phenolic compounds to show antioxidant behavior. The present study also checked the bioavailability through the calculation of lipophilicity. Although compound **1** has lower lipophilicity compared to others, compound **5** has comparable lipophilicity to others. The activation barrier for **1**, **5** and **10** related to the H atom transfer reaction with OH radical are lower compared to others. Thus, kinetics also favors **1**, **5** and **10** to trap unwanted free radicals generated in our body. The antioxidant ability of these two compounds is quite comparable to the well- known antioxidants such as *trans*-resveratrol and gallic acid. In conclusion, esculetin, umbelliferone and aloinoside A are the best three phenolic compounds present in *Aloe vera* having superior antioxidant behavior.

Multidisciplinary Domains

This research covers the domains: (a) Antioxidant, and (b) Theoretical.

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Conflicts of Interest

Authors declare no conflict of interest.

References

[1] Borgohain, R; Guha, A.K; Pratihar, S; Handique, J.G. Antioxidant activity of some phenolic aldehydes and their diimine derivatives: A DFT study. *Comput Theor Chem.* **2015**, *17*, 1060, DOI: 10.1016/j.comptc.2015.02.014.

[2] Borpujari, M.P.; Rohman, R.; Kar. R. Antioxidant properties can be tuned in the presence of an external electric field: accurate computation of O–H BDE with range-separated density functionals. *RCS Adv*. **2015**, *5*,78229, DOI: 10.1039/C5RA13462E

[3] Marchand, L. Cancer preventive effects of flavonoids—a review. *Biomed Pharmacother.* **2002**, *56*, 296, DOI: https://www.sciencedirect.com/science/article/abs/pii/S0753332202001865

[4] Shabaan, S.; Ba, L.A.; Abbas, M.; Burkholz, T.; Denkert, A.; Gohr, A.; Wessjohann, L.A.; Sasse, F.; Weber, W.; Jacob, C. Multicomponent reactions for the synthesis of multifunctional agents with activity against cancer cells. *Chem Commun*. **2009**, 4702, DOI: 10.1039/B823149D

[5] Amorati, R.; Valgimigli, L.; Dinér, P.; Bakhtiari, K.; Saeedi, M.; Engman, L. Catalytic Chain-Breaking Pyridinol Antioxidants. *Chem Eur J*. **2013**, *19*, 7510 DOI: 10.1021/jo902226t

[6] Marino, T.; Galano, A.; Mazzone, G.; Russo, N.; Idaboy, J.R.A. Chemical Insights into the Antioxidant Mechanisms of Alkylseleno and Alkyltelluro Phenols: Periodic Relatives Behaving Differently. *Chem Eur J*. **2018**, *24*, 8686. DOI: 10.1002/chem.201800913

[7] Anto, R.J.; Sukumarana, K.; Kuttana, G.; Raob, M.N.A.; Subbarajuc, V.; Kuttana, R. Anticancer and antioxidant activity of synthetic chalcones and related compounds. *Cancer Lett.* **1995**, *97*, 33. DOI: 10.1016/0304-3835(95)03945-s

[8] Borgohain, R.; Guha, A.K.; Pratihar, S.; Handique, J.G. A theoretical study on antioxidant activity of ferulic acid and its ester derivatives. *J Theor Comput Chem*, **2016**, *15*, 1650028. DOI:10.1142/S0219633616500280

[9] Trouillas, P.; Marsal, P.; Svobodova, A.; Vostalova, J.; Gazak, R.; Hrbac, J.; Sedmera, P.; Kren, V.; Lazzaroni, R.; Duroux, J.L.; Walterova. D. Mechanism of the Antioxidant Action of Silybin and 2,3-Dehydrosilybin Flavonolignans: A Joint Experimental and Theoretical Study. *J Phys Chem A.* **2008**, *112*, 1054, DOI: 10.1021/jp075814h

[10] Matxain, J.M.; Ristilä, M.;Strid, A.; Eriksson, L.A. Theoretical study of the antioxidant properties of pyridoxine. *J Phys Chem A* **2006**, *110*, 13068, DOI: 10.1021/jp065115p

[11] Borges, E.L.; Ignasiak, M.T.; Velichenko, Y.; Perin, G.; Hutton, C.A.; Davies, M.J.; Schiesser, C.H. Synthesis and antioxidant capacity of novel stable 5-tellurofuranose derivatives. *Chem Commun* **2018**, *54*, 2990, DOI: 10.1039/C8CC00565F

[12] Nogueira, C.W.; Zeni, G.; Rocha, J.B.T. Organoselenium and organotellurium compounds: toxicology and pharmacology. *Chem Rev*. **2004**, *104*, 6255,DOI: 10.1021/cr0406559 and references therein

[13] Storkey, C.; Davies, M.L.; White, J.M.; Schiesser, C.H. Synthesis and antioxidant capacity of 5-selenopyranose derivatives. *Chem Commun*. **2011**, *47*, 9693, DOI: 10.1039/C1CC13652F

[14] Kimani, M.M.; Wang, H.C.; Brumaghim, J.L. Investigating the copper coordination, electrochemistry, and Cu(ii) reduction kinetics of biologically relevant selone and thione compounds. *Dalton Trans*. 2012, *41*, 5248, DOI: 10.1039/C2DT11731B

[15] Luna, P.D.; Bushnell, E.A.C.; Gauld, J.W. A Density Functional Theory Investigation into the Binding of the Antioxidants Ergothioneine and Ovothiol to Copper. *J Phys Chem A*. **2013**, *117*, 4057.DOI:10.1021/jp402514w

[16] Storkey, C.; Pattison, D.I.; White, J.M.; Schiesser, C.H.; Davies, M.J. Preventing protein oxidation with sugars: scavenging of hypohalous acids by 5-selenopyranose and 4-selenofuranose derivatives. *Chem Res Toxicol*. **2012**, *25*, 2589. DOI: 10.1021/tx3003593

[17] Storkey, C.; Pattison, D.I.; Ignasiak, M.T.; Schiesser, C.H.; Davies, M.J. Kinetics of reaction of peroxynitrite with selenium- and sulfur-containing compounds: absolute rate constants and assessment of biological significance. *Free Radic Biol Med*. **2015**, *89*, 1049. DOI: 10.1016/j.freeradbiomed.2015.10.424

[18] Galano, A.; Arriaga, R.C.; González, A.P.; Tan, D.X.; Reiter, R.J. Phenolic Melatonin-Related Compounds: Their Role as Chemical Protectors against Oxidative Stress. *Molecules*, **2016**, *21*, 1442, DOI: 10.3390/molecules21111442 and references therein.

[19] Iuga, C.; Idaboy, J.R.A.; Russo, N. Antioxidant Activity of trans-Resveratrol toward Hydroxyl and Hydroperoxyl Radicals: A Quantum Chemical and Computational Kinetics Study. *J Organomet Chem*. **2012**, *77*, 3868. DOI: 10.1021/jo3002134

[20] Gomez, C.M.; Galano, A.; Idaboy, J.R.A. Piceatannol, a better peroxyl radical scavenger than resveratrol. *RSC Adv*. **2013**, *3*, 20209. DOI: 10.1039/C3RA42923G

[21] Wright, J.S.; Johnson, E.R.; DiLabio, G.A. Predicting the Activity of Phenolic Antioxidants: Theoretical Method, Analysis of Substituent Effects, and Application to Major Families of Antioxidants. *J Am Chem Soc*. **2001**, *123*, 1173. DOI: 10.1021/ja002455u

[22] Vafiadis, A.P.; Bakalbassis, E.G. A DFT study on the deprotonation antioxidant mechanistic step of ortho substituted phenolic cation radicals. *Chem Phys*, **2005**, *316*, 195. DOI: 10.1016/j.chemphys.2005.05.015

[23] Musialik, M.; Litwinienko, G. Acidity of Hydroxyl Groups: An Overlooked Influence on Antiradical Properties of Flavonoids. *Org Lett*, **2005**, *7*, 4952. DOI: 10.1021/jo802716v

[24] Zhao, Y. Truhlar, D.G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc*., **2008**, *120*, 215. DOI:10.1007/s00214-007-0310-x

[25] Marenich, A.V.; Cramer, C.J.; Truhlar, D.G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Chem. Phys.* **2009**, *113*, 6378. DOI: 10.1021/jp810292n

[26] Michalik, M.; Lukes, V. The validation of quantum chemical lipophilicity prediction of alcohols. *Acta Chim. Slov.* **2016**, *9*, 89. DOI: 10.1515/acs-2016-0015

[27] Reed, E.D.; Winhold, F.; Curtiss, L.A. Intermolecular Interactions from a Natural Bond Orbital, Donor Acceptor Viewpoint. *Chem. Rev.* **1998**, *88*, 899. DOI: 10.1021/cr00088a005

[28] Gaussian 16, Revision B.01, Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Petersson, G.A.; Nakatsuji, H. et al. Gaussian, Inc., Wallingford CT, **2016**.

[29] G. W. Burton, K. U. Ingold, Vitamin E: application of the principles of physical organic chemistry to the exploration of its structure and function. *Acc Chem Res*, **1986**, *19*, 19. DOI: DOI: 10.1021/cr00088a005