Food Biophysics

Computational Investigation on the •OOH Scavenging Sites of Gnetin C

--Manuscript Draft--

Manuscript Number:	FOBI-D-20-00017
Full Title:	Computational Investigation on the •OOH Scavenging Sites of Gnetin C
Article Type:	Original Research
Keywords:	gnetin c; melinjo resveratrol; radical-scavenging activity; density-functional calculations
Corresponding Author:	Vera Khoirunisa Institut Teknologi Bandung Bandung, INDONESIA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Institut Teknologi Bandung
Corresponding Author's Secondary Institution:	
First Author:	Vera Khoirunisa
First Author Secondary Information:	
Order of Authors:	Vera Khoirunisa
	Febdian Rusydi
	Lusia Silfia Pulo Boli
	Adhitya Gandaryus Saputro
	Heni Rachmawati
	Hiroshi Nakanishi
	Hideaki Kasai
	Hermawan Kresno Dipojono
Order of Authors Secondary Information:	
Funding Information:	
Abstract:	Melinjo seed extract contains melinjo resveratrol compounds that exhibit antioxidant activity. The antioxidant activity requires radical scavenging sites, which yet to be located. We report a computational study that aimed to locate scavenging sites of the simplest resveratrol dimer, gnetin C. We consider the reaction of gnetin C and hydroperoxyl radical energetically with the basis of density-functional calculations, to be compared with the reaction of the resveratrol monomer and hydroperoxyl radical. The results show that OH group at the para position is the most reactive scavenging site for both molecules. Besides the OH group, gnetin C also provides two CH groups in the furan ring that are favorable as scavenging sites. Therefore, furan ring plays an important role in the scavenging activity, which is contrary to the experimental speculation that proposed resorcinol ring. Our study shows the prospect of density-functional calculation for studying the radical-scavenging reaction.
Suggested Reviewers:	Melanie Yadao David De La Salle University, Manila (DLSU) melanie.david@dlsu.edu.ph Dr. Melanie mainly uses density-functional calculations in her researches. We expect her can criticize our calculations methods and results discussion.
	Azizan Ahmad Universiti Kebangsaan Malaysia azizan@ukm.edu.my

	Prof. Ahmad is an experimental organic chemists and his works mainly on reaction kinetic. We expect him can review the chemistry aspect of our work.
	Allan Abraham Padama University of the Philippines at Los Baños abpadama@up.edu.ph Dr. Padama mainly uses density-functional calculations in his researches. We expect him can criticize our calculations methods and results discussion.
	Kazunari Yoshizawa Kyushu University kazunari@ms.ifoc.kyushu-u.ac.jp Prof. Kazunari Yoshizawa uses quantum mechanics in his work. We expect him can criticize our methods and results discussion.
	Yuji Kunisada Hokkaido University kunisada@eng.hokudai.ac.jp Dr. Yuji Kunisada uses first-principles calculation in his work. We expect him can criticize our computational model.

Computational Investigation on the •OOH Scavenging Sites of Gnetin C

Vera Khoirunisa,[1,2,3] Febdian Rusydi,[3,4*] Lusia Silfia Pulo Boli,[2,3] Adhitya Gandaryus Saputro,[2,5] Heni Rachmawati,[5,6] Hiroshi Nakanishi,[7] Hideaki Kasai,[7] Hermawan Kresno Dipojono[2,5*]

[1]*Engineering Physics Study Program, Institut Teknologi Sumatera (ITERA), Lampung 35365, Indonesia*

[2]*Advanced Functional Material Research Group, Institut Teknologi Bandung, Bandung 40132, Indonesia*

[3]*Research Center for Quantum Engineering Design, Faculty of Science and technology, Universitas Airlangga, Surabaya 601115, Indonesia*

[4]*Department of Physics, Faculty of Science and Technology, Universitas Airlangga, Surabaya 60115, Indonesia*

[5]*Research Center for Nanoscience and Nanotechnology, Institut Teknologi Bandung, Bandung 40132, Indonesia*

[6]*School of Pharmacy, Institut Teknologi Bandung, Bandung 40132, Indonesia*

[7]*National Institute of Technology, Akashi College, Hyogo 674-8501, Japan*

***Corresponding Authors:**

Email addresses: rusydi@fst.unair.ac.id (Febdian Rusydi), dipojono@gmail.com (Hermawan Kresno Dipojono).

ABSTRACT

Melinjo seed extract contains melinjo resveratrol compounds that exhibit antioxidant activity. The antioxidant activity requires radical scavenging sites, which yet to be located. We report a computational study that aimed to locate scavenging sites of the simplest resveratrol dimer, gnetin C. We consider the reaction of gnetin C and hydroperoxyl radical energetically with the basis of density-functional calculations, to be compared with the reaction of the resveratrol monomer and hydroperoxyl radical. The results show that OH group at the para position is the most reactive scavenging site for both molecules. Besides the OH group, gnetin C also provides two CH groups in the furan ring that are favorable as scavenging sites. Therefore, furan ring plays an important role in the scavenging activity, which is contrary to the experimental speculation that proposed resorcinol ring. Our study shows the prospect of density-functional calculation for studying the radical-scavenging reaction.

KEYWORDS: gnetin c, melinjo resveratrol, radical-scavenging activity, density-functional calculations

1. Introduction

Melinjo (*Gnetum gnemon* Linn) seeds carry bioactive compound with antioxidant [1, 2] and other beneficial pharmacological activities. In particular, the melinjo seed extract (MSE) confirms antimicrobial [1], anti-allergic [3], anti-angiogenesis [4], anti-melanogenesis [5], and anti-tumor [6] properties. Consuming MSE could reduce the serum uric acid levels [7] without serious adverse events both in the human [8] and toxicity studies [9]. It implies the potential of the seed for drugs, supplements, and functional foods that may benefit human health.

The main antioxidant in melinjo seed is resveratrol dimer (known as melinjo resveratrol). As antioxidants, melinjo resveratrol can act as radical scavengers. A study from Kato et al. [1] showed that melinjo resveratrol has comparable scavenging activity to dl-α-tocopherol. Their study also showed that melinjo resveratrol could maintain the scavenging activity longer than dl-α-tocopherol could. They proposed that resorcinol ring in resveratrol dimer plays an important role in the scavenging activity of melinjo resveratrol. However, no other studies have been reported to corroborate the findings. Further investigation in the radical-scavenging activity is significant to explain the antioxidant manner of melinjo resveratrol.

One preferred method to study the antioxidant activity is calculation method based on density functional theory (DFT) [10, 11]. DFT allows us to explore the chemical properties of molecules based on their quantum electronic structures [12] as applied in the study of reactions with the basis of orbital interaction [13, 14]. DFT also allows us to predict the antioxidant activity from the thermodynamic parameters. [15-21] Furthermore, the primary advantage of DFT is to predict the reaction pathways, including the determination of transition state (TS) that is very challenging to observe in experimental methods. Once the TS is predicted, we can extend the method into the study of reaction kinetics of antioxidants [22-24]. Therefore, the density-functional calculations could be reliable for investigating the activity of melinjo resveratrol.

In this study, we utilize density-functional computations to locate the active scavenging site of melinjo resveratrol. We evaluate the possible site energetically by using gnetin C (the simplest melinjo resveratrol) to scavenge hydroperoxyl radical (•OOH). Here, we assume that the scavenging reaction undergoes a one-step reaction mechanism. Besides the energetic results, we can propose another ring apart from that of Kato et al. [1] speculated.

2. Computational Model

2.1. Scavenging Reaction Model

The one-step reaction mechanism models the •OOH scavenging by melinjo resveratrol (YH) as it suggested to be the preferable mechanism of phenolic antioxidants [25-27]. The reaction is as follows:

$$X + YH \rightarrow [X - Y - H] \rightarrow XH + Y. \quad (1)$$

In our case, X is •OOH, YH is gnetin C, XH is H_2O_2, and Y is gnetin C radical. Besides gnetin C, we also consider trans-resveratrol as YH in the Eq. (1). The reasons are (1) trans-resveratrol is a well-studied monomer of resveratrol, and (2) the dimer form is gnetin C as shown in Fig. 1.

[Fig. 1 about here.]

The [X – H – Y] activated complex is the TS. It is the state where the hydrogen atom transfer (HAT) from melinjo resveratrol to •OOH occurs. While the energy difference between product (XH and Y) and reactant (X and YH) means the reaction energy (E_r), the energy difference between TS and reactant means the barrier energy (E_b).

The H in [X – H – Y] activated complex may derive from 22 possible sites of gnetin C. We consider all H atoms from hydroxyl sites since they are essential for antioxidant activity of resveratrol [28]. The remains of the H atoms are evaluated based on their bond dissociation energy (BDE). BDE calculation from a site follows the generic dissociation,

$$YH \rightarrow Y + H, \tag{2}$$

hence BDE is the energy difference between the product (Y and H) and the reactant (YH). The higher the BDE of a site means the least favor the H donation from the site.

2.2. Density-functional Calculation

The primary quantities here are BDE, E_r, and E_b. The ground state of reactants and products determines the first two energies. The optimization geometry calculation routine, based on DFT, obtains the geometry and energy of reactant (initial state) and product (final state) in the ground state. For E_b, we calculate the value from the energy difference between the TS and the reactant. The TS is obtained from the routine of optimization geometry at the saddle point of the potential surface. We identify the appropriate TS from a particular vibrational mode, which has imaginary frequency and involves the motion of hydrogen between the 22-possible sites and the •OOH.

We couple DFT with vibrational mode calculations at 298.15 K. The energy calculated by DFT is electronic energy at 0 K. The vibrational mode calculations allow us to correct the electronic energy with thermal energy at 298.15 K. As for E_r and E_b, we use Gibbs free-energy correction to get the standard Gibbs energy of reaction ($\Delta_r G^\circ$) and activation ($\Delta^{\ddagger} G^\circ$), respectively. For BDE, we use enthalpy correction to get BDE^*. In the current, the relevant quantity is BDE^* of YH relative to BDE^* of H-phenol (C_6H_5OH), equated as

$$\Delta BDE* = BDE*_{(YH)} - BDE*_{(phenol)} \tag{3}$$

BDE^* of H-phenol is a standard reference value for the hydrogen atomic bond dissociation energy. Besides calculating ΔBDE^*, we also calculate the spin density distribution as a qualitative method of checking the stability of Y. The more

delocalized the spin density, the more stable the Y is, hence, the lower BDE^* is. Furthermore, we also apply the spin density in term of single occupied molecular orbital (SOMO) at the TS to predict the reaction mechanism based on the Mayer's interpretation [29].

In using DFT method, we employ M05-2X exchange-correlation functional and 6-31++G(d,p) basis set that are integrated in Gaussian 09 software [30]. M05-2X functional has been recommended for thermochemistry and kinetic calculations [31, 32], and has performed well to predict internuclear distance at the TS, especially for hydrogen transfer reaction [33].

We couple DFT calculation with the polarized continuum model (PCM) [34, 35] for considering the solvent environment. PCM has been applied successfully to a significant number of systems in aqueous and non-aqueous media [36-38]. In this work, we consider water solvent since it is the primary cellular environment component.

3. Result and Discussion

3.1. The Bond Dissociation Energy

Fig. 2 shows the optimized geometry for trans-resveratrol and gnetin C, while Table S1 (Online Resource) lists the selected parameters. A gnetin C consists of one trans-resveratrol-like structure (ring A1 and B1) and one non-planar resveratrol structures (ring A2 and B2). Atom 13O and 12C of the planar trans-resveratrol are combined with atom 7'C and 8'C of non-planar resveratrol to form a new ring, namely furan ring (ring C).

[Fig. 2 about here]

Table 1 lists the ΔBDE^* of trans-resveratrol and gnetin C based on Fig. 1. Overall, ΔBDE^* of OH is less than that of CH in both molecules. Interestingly, our calculations show that two CH sites of gnetin C have a value of ΔBDE^* comparable with OH site's. They are site 7'-CH and site 8'-CH (in the furan ring). Therefore, we consider these two sites for the scavenging site of gnetin C in Eq. (1) in addition to the OH sites.

[Table 1 about here]

The spin density plots in Fig. 3 supports the ΔBDE^* of gnetin C radical calculations. The spin density at 8'-C is the most delocalized distribution since the spin density covers three rings, which indicates that the site has the lowest ΔBDE^*.

[Fig. 3 about here]

3.2. The Standard Gibbs Energy of Reaction

Table 2 provides the $\Delta_r G^\circ$ of the •OOH scavenging reaction by trans-resveratrol, according to Eq. (1). Out of three OH sites in trans-resveratrol, the •OOH scavenging reaction is exergonic only at site 4. Therefore, only the 4-OH site is favorable for scavenging •OOH. Another density-functional study of an identical system concluded in the same result [23], conducted by employing the same exchange-correlation functional but 6-311++G(d,p) and solvation model based on density. It supports the recommendation by Zhao et al. [31] that M05-2X is reliable for studying the scavenging reaction energetically.

[Table 2 about here]

As for gnetin C, Table 2 shows that the exergonic sites are not only at OH-group but also at CH-group. The scavenging sites of gnetin C is at 4-OH, 7'-CH, 8'-CH. Since gnetin C provides more scavenging site than trans-resveratrol does, the former is potent to have a higher antioxidant capacity than the latter. When we consider the rings in gnetin C, ring C provides more scavenging sites than other rings (A, phenol, and B, resorcinol ring). It indicates that furan ring plays more important role than other rings in the scavenging capacity of melinjo resveratrol.

Overall, ring A always provides the lowest $\Delta_r G^\circ$ value for OH site. It is valid for both trans-resveratrol and gnetin C. It implies that there is a relation between the position of the OH site and the $\Delta_r G^\circ$. Queiroz et al. [38] also reported this relation.

3.3. The Standard Gibbs Energy of Activation

We validate our work on reaction kinetics based on the trans-resveratrol case. Our predictions of $\Delta^{\ddagger}G^{\circ}$ are comparable with a theoretical work reported by Iuga et al. [24], which computed the rate constants at room temperature with the basis of transition-state theory, whose results are comparable with experimental results by Zinatullina et al. [40]. Consequently, our density-functional calculations on Eq. (1) is adequate to study •OOH scavenging by resveratrol system such as gnetin C.

Regarding gnetin C, Fig. 4 shows the TS of •OOH scavenging according to Eq. (1). The activated complexes are at their optimized structure, where the syn arrangement exists as expected from phenolic antioxidants. The syn arrangement also exists in trans-resveratrol, which is also a group of phenolic antioxidants, as we provide the optimized structure in Fig. S1 (Online Resource). It is also noteworthy that the distance between the H-atom of gnetin C and its scavenging site elongates to 0.16 Å on average (or at about 16%) relative to its ground state structure. It implies that H-atom's bonding to its scavenging site weakens at the TS for all scavenging sites. The reaction in Eq. (1) requires this condition.

[Fig. 4 about here]

The $\Delta^{\ddagger}G^{\circ}$ values of gnetin C in Table 2 show that the lowest $\Delta^{\ddagger}G^{\circ}$ is at site 4-OH. The site 4-OH in trans-resveratrol also has the lowest activation energy. These results agree with previous experimental findings which reported that site 4-OH is the most reactive one in trans-resveratrol and its derivatives. [41] However, $\Delta^{\ddagger}G^{\circ}$ at site 4-OH of gnetin C is lower than that of trans-resveratrol. It implies that resveratrol in its dimer form is expected to react faster with •OOH than its monomer form.

As for Δ_rG°, the $\Delta^{\ddagger}G^{\circ}$ values at OH-group also has a relation with its location. Both site 4-OH and 4'-OH have the lowest $\Delta^{\ddagger}G^{\circ}$ in their respective resveratrol unit, and they are at para position of ring A1 and A2, respectively. The difference is that ring A1 is in the first unit, while ring A2 is in the second one. The resveratrol is planar in the first unit, but not in the second unit. It implies that the planarity of resveratrol in gnetin C increases scavenging reactivity of an OH site.

Considering the $\Delta_r G^\circ$ value, it is also possible for site 7'-CH and 8'-CH to become a scavenging site. However, the reaction may be slower at these two CH sites than at 4-OH site due to their higher value of $\Delta^i G^\circ$. The high barrier is expected since geometrically ring A2 and B2 hinders •OOH to reach site 7' and 8'. The various value of $\Delta^i G^\circ$ make the three sites scavenge three •OOH radicals at different rates. It is revealed that resveratrol dimer gradually scavenges one radical from ring A1 (phenol) and two more radicals from ring C (furan) to reach the maximum scavenging activity after a sufficient time. This finding is contrary to the work by Kato et al [1] which proposed that it is ring B2 (resorcinol) that plays a crucial role in the scavenging activity of melinjo resveratrol.

All the three possible scavenging sites share similarities in their SOMO distribution. The 2p-like orbitals construct all SOMO distributions, as shown in Fig. S2 (Online Resource). The orbital interaction forms sigma bonding between O or C (from the scavenging site) and at O (from •OOH). The sigma bond allows hydrogen atom (both the proton and the electron) to transfer from one side to the other [29]. It implies that the •OOH scavenging at the three sites of gnetin C through the reaction in Eq. (1) is a hydrogen atom transfer.

4. Conclusion

We have demonstrated the use of a density-functional to investigate the scavenging activity of gnetin C with trans-resveratrol as the comparison. We utilized density-functional calculations and used a one-step mechanism for the •OOH scavenging reaction model. The OH-group at the para position in a phenol ring turns out to be a common scavenging site for both trans-resveratrol and gnetin C. The scavenging reaction energy at this particular site, as observed in this study, is -3.59 kcal/mol and -3.51 kcal/mol for trans-resveratrol and gnetin C respectively, which makes the reaction at OH site is exergonic.

We have shown the role of the furan ring in relation to the antioxidant capacity and activity of melinjo resveratrol. Furan ring increases the antioxidant capacity of melinjo resveratrol by providing two more scavenging sites, namely site 7'-CH and 8'-CH. Such sites should have a slower reaction with •OOH as they require higher activation energy compared to 4-OH site. The activation energy differs as much as 4.92 kcal/mol between 7'-CH and 4-OH and 3.53 kcal/mol between 8'-CH and 4-OH. Our results suggested that gnetin C scavenge radicals gradually with the following

sequence: 4-OH, 8'-CH, and 7'-CH, to reach its maximum scavenging activity. Thus, we propose the furan ring, not the resorcin ring as it is speculated from the experimental study, which plays a crucial role in the scavenging activity of melinjo resveratrol. Finally, this work demonstrates that density-functional calculations are a prospective approach for studying the system in question.

Acknowledgements

We thank to Research Center for Nanosciences and Nanotechnology (RCNN), Indonesia and Global Education Center of Akashi College, Japan for computer facilities support. VK thanks to Rizka Nur Fadilla, Nufida Dwi Aisyah, Susan Aspera, Ryo Kishida, and Ryan Lacdao Arevalo for insightful discussions. VK also thanks to Lembaga Pengelola Dana Pendidikan (LPDP) for the doctoral scholarship and Sandwich Program of Akashi college. FR appreciates partial financial support from Universitas Airlangga. This work is also supported by Directorate of Higher Education, Ministry of Research Technology and Higher Education (RISTEKDIKTI), Republic of Indonesia under grant scheme Penelitian Dasar Unggulan Perguruan Tinggi (PDUPT) 2019.

References

[1] E. Kato, Y. Tokunaga, F. Sakan, J. Agric. Food Chem. 57 (6), 2544–2549 (2009)

[2] R. Bhat, N. binti Yahya, Food Chem. 156, 42–49. (2014)

[3] H. Kato, M. Samizo, R. Kawabata, F. Takano, T. Ohta, Planta Med. 77, 1027–1034 (2011)

[4] K. Kunimasa, T. Ohta, H. Tani, E. Kato, R. Eguchi, K. Kaji, K. Ikeda, H. Mori, M. Mori, T. Tatefuji, Y. Yamori, Mol. Nutr. Food Res. 55 (11), 1730–1734 (2011)

[5] M. Yanagihara, M. Yoshimatsu, A. Inoue, T. Kanno, T. Tatefuji, K. Hashimoto, Biol. Pharm. Bull. 35 (6), 993–996 (2012)

[6] N.K. Narayanan, K. Kunimasa, Y. Yamori, M. Mori, H. Mori, K. Nakamura, G. Miller, U. Manne, A.K. Tiwari, B. Narayanan, Cancer Med. 4 (11), 1767–1780 (2015)

[7] H. Konno, Y. Kanai, M. Katagiri, T. Watanabe, A. Mori, T. Ikuta, H. Tani, S. Fukushima, T. Tatefuji, T. Shirasawa, Evid. Based Complement. Altern. Med. 2013, 589169 (2013)

[8] H. Tani, S. Hikami, S. Iizuna, M. Yoshimatsu, T. Asama, H. Ota, Y. Kimura, T. Tatefuji, K. Hashimoto, K. Higaki, J. Agric. Food Chem. 62 (8), 1999–2007 (2014)

[9] T. Tatefuji, M. Yanagihara, S. Fukushima, K. Hashimoto, Food Chem. Toxicol. 67, 230–235 (2014)

[10] P. Hohenberg, W. Kohn, Inhomogeneous electron gas, Phys. Rev. 136, B864–B871 (1964)

[11] W. Kohn, L. J. Sham, Phys. Rev. 140, A1133–A1138 (1965)

[12] R. G. Parr, W. Yang, Density-Functional Theory of Atoms and Molecules, (Oxford University Press, New York, 1994), pp. 47-69

[13] F. Rusydi, M. Kemal Agusta, A. Gandaryus Saputro, H. Kasai, J. Phys. Soc. Jpn 81 (12), 124301 (2012)

[14] A. G. Saputro, F. Rusydi, H. Kasai, H. K. Dipojono, J. Phys. Soc. Jpn 81 (3), 034703 (2012)

[15] Y. Rong, Z. Wang, B. Zhao, Food Biophys. 8, 90–94 (2013)

[16] T.J. Tsiepe, M.M. Kabanda, K.R.N. Serobatse, Food Biophys. 10, 342–359 (2015)

[17] A. Amić, B. Lučić, V. Stepanić, Z. Marković, S. Marković, J.M.D. Marković, D. Amić, Food Chem. 218, 144–151 (2017)

[18] A. Stobiecka, Food Biophys. 14, 1–12 (2018)

[19] N. Nenadis, K. Stavra, J. Phys. Chem. A 121 (9), 2014–2021 (2017)

[20] E. Nazarparvar, M. Zahedi, E. Klein, J. Org. Chem 77 (22), 10093–10104 (2012)

[21] Y. Rong, Z. Wang, B. Zhao, Food Biophys. 8, 250–255 (2013)

[22] J. Tošović, S. Marković, Food Chem. 278, 469–475 (2019)

[23] M. Cordova-Gomez, A. Galano, J.R. Alvarez-Idaboy, RSC Adv. 3, 20209–20218 (2013)

[24] C. Iuga, J. R. Alvarez-Idaboy, N. Russo, J. Org. Chem. 77 (8), 3868–3877 (2012) https://doi.org/10.1039/C3RA42923G

[25] J. S. Wright, E. R. Johnson, G. A. DiLabio, J. Am. Chem. Soc.123 (6), 1173–1183 (2001)

[26] F. Caruso, J. Tanski, A. Villegas-Estrada, M. Rossi, J. Agric. Food Chem. 52, 7279–7285 (2004)

[27] D. Mikulski, M. Szelag, M. Molski, R. Gorniak, J. Mol. Struct.:THEOCHEM 951, 37–48 (2010)

[28] L. Stivala, M. Savio, F. Carafoli, P. Perucca, L. Bianchi, G. Maga, L. Forti, U. M. Pagnoni, A. Albini, E. Prosperi, V. Vannini, J. Biol. Chem. 276, 22586–22594 (2001)

[29] J. M. Mayer, D. A. Hrovat, J. L. Thomas, W. T. Borde, J. Am. Chem. Soc. 124 (37), 11142–11147 (2002)

[30] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, J. R. Cheeseman, M. A. Robb, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson,H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian 09, revision E.01, (Gaussian, Inc., Wallingford CT, 2010)

[31] Y. Zhao, N. E. Schultz, D. G. Truhlar, J. Chem. Theory Comput. 2 (2), 364–382 (2006)

[32] Y. Zhao, D. G. Truhlar, Theor. Chem. Acc. 120 (1), 215–241 (2008)

[33] X. Xu, I. M. Alecu, D. G. Truhlar, J. Chem. Theory Comput. 7 (6), 1667–1676 (2011)

[34] E. Cancès, B. Mennucci, J. Tomasi, J. Chem. Phys. 107 (8), 3032–3041 (1997)

[35] B. Mennucci, E. Cances, J. Tomasi, J. Phys. Chem. B 101 (49), 10506–10517 (1997)

[36] M. Cossi, G. Scalmani, N. Rega, V. Barone, J. Chem. Phys. 117 (1), 43–54 (2002)

[37] B. Mennucci, Polarizable continuum model, Wiley Interdiscip. Rev. Comput. Mol. Sci. 2 (3), 386–404 (2012)

[38] F. Rusydi, A. G. Saputro, H. Kasai, J. Phys. Soc. Jpn 83 (8), 084802 (2014)

[39] A. N. Queiroz, B. A. Q. Gomez, W. M. J. Moraez, R. S. Borges, Eur. J. Med. Chem 44 (4), 644–1649 (2009)

[40] K. M. Zinatullina, N. P. Khrameeva, O. T. Kasaikina, B. I. Shapiro, V. A. Kuzmin, Russ Chem Bull 66 (11), 2145–2151 (2017)

[41] S. Petralia, C. Spatafora, C. Tringali, M. C. Foti, S. Sortino, New J. Chem. 28, 1484–1487 (2004)

Figure captions

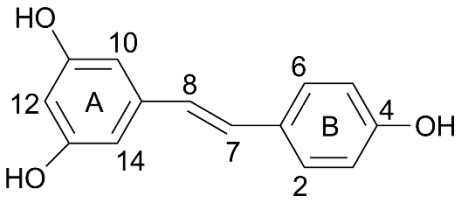
Fig. 1 Chemical structure of (a) trans-resveratrol and (b) gnetin C. Numbers in the figure represent the site numbering. A, B, C are resorcinol, phenol, and furan rings in resveratrol system respectively. The labeling number of atoms here is used throughout the manuscript

Fig. 2 Optimized structure of trans-resveratrol and gnetin C in water environment. Blue, red, and yellow atoms represent H, O, and C atom. Red marker indicates the scavenging site

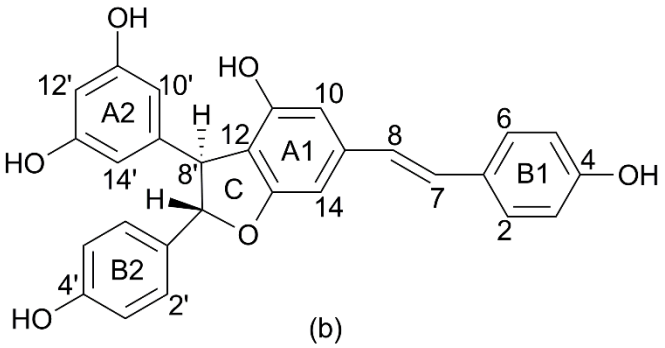
Fig. 3 The spin density distribution of gnetin C radical with isovalue 0.003. In their respective order, orange and purple colors indicate that α and β densities are dominant

Fig. 4 TS structure for •OOH scavenging reaction by gnetin C on each site. Markers d1 is the bond length of scavenging site, while d2 is the distance between O atom of •OOH and with the nearest scavenging site

Fig. 1


HO
10
12
A
8
6
B
4
OH
14
7
HO
2

(a)


OH
12'
10'
A2
H
HO
12
HO
10
A1
8
6
B1
4
OH
HO
14'
8'
C
H
14
7
2
O
B2
4'
2'
HO

(b)

Fig. 2

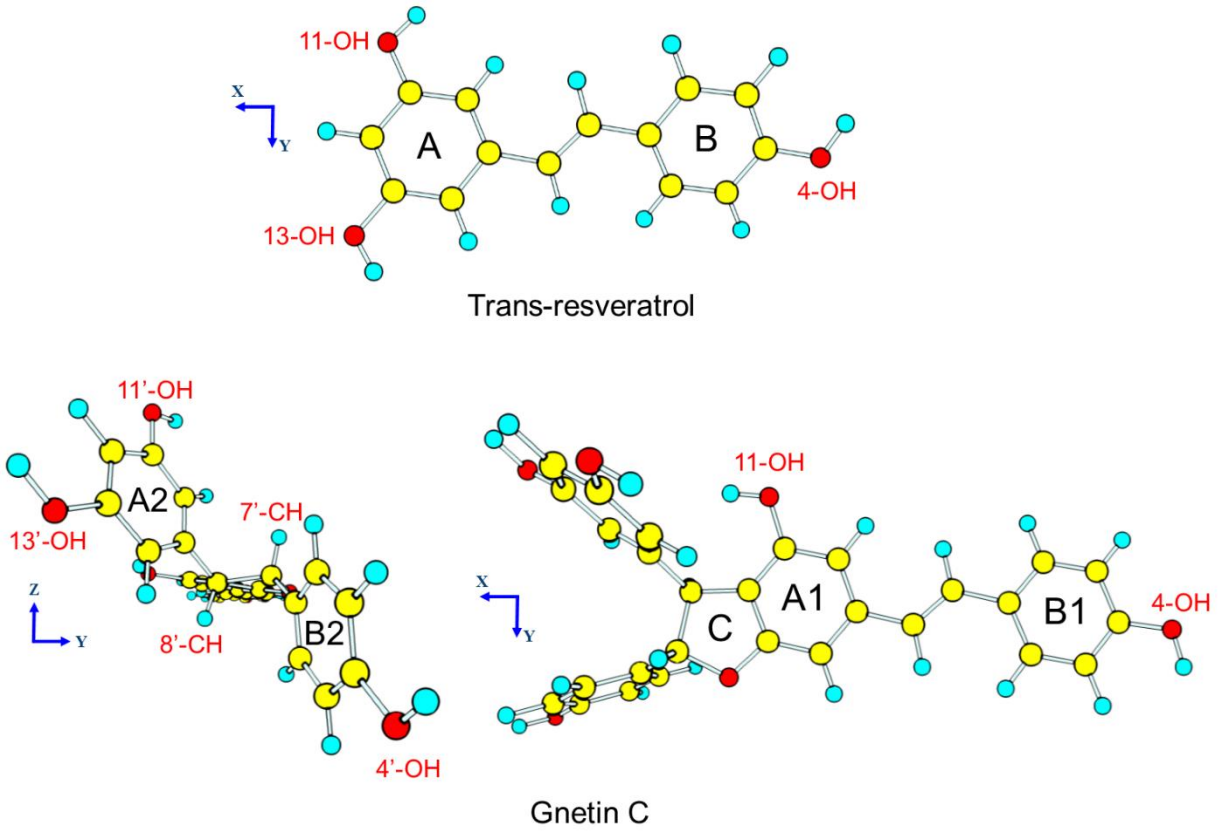

11-OH
X
Y
A
B
4-OH
13-OH
Trans-resveratrol
11'-OH
A2
7'-CH
13'-OH
Z
Y
8'-CH
B2
4'-OH
11-OH
X
Y
C
A1
B1
4-OH
Gnetin C

Fig. 3

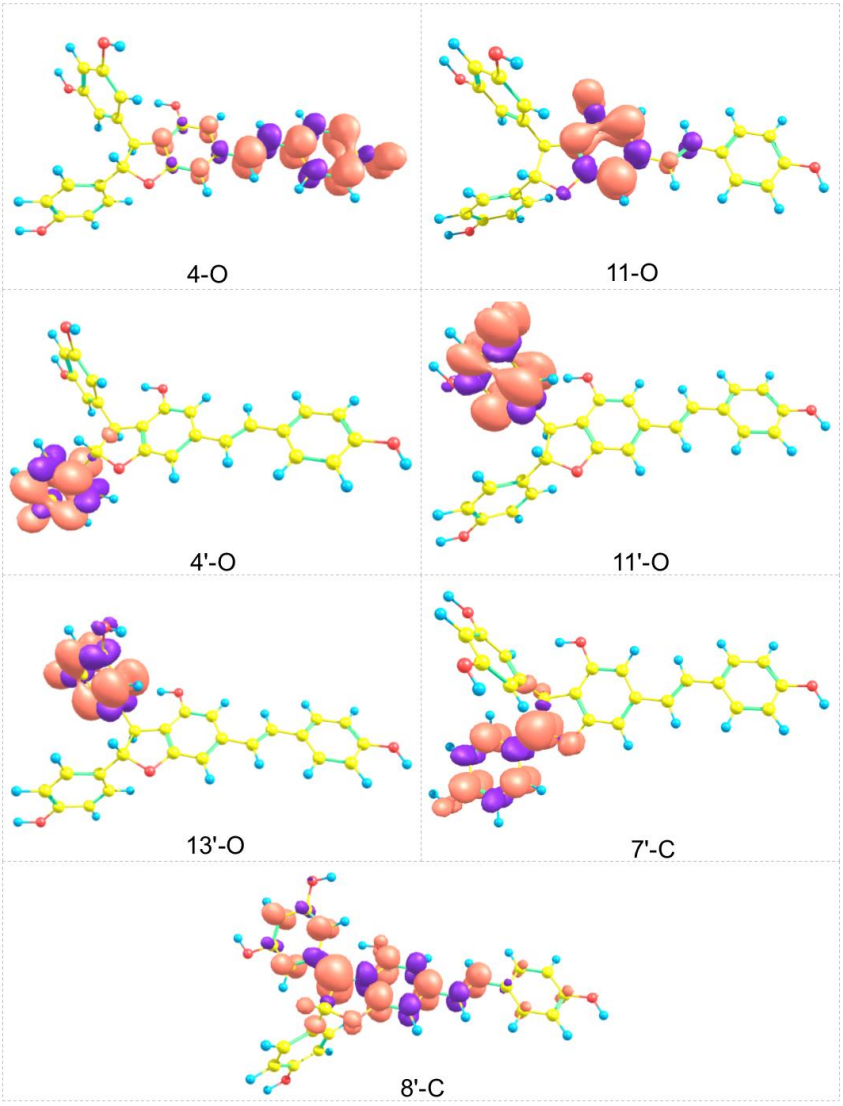


Fig. 4

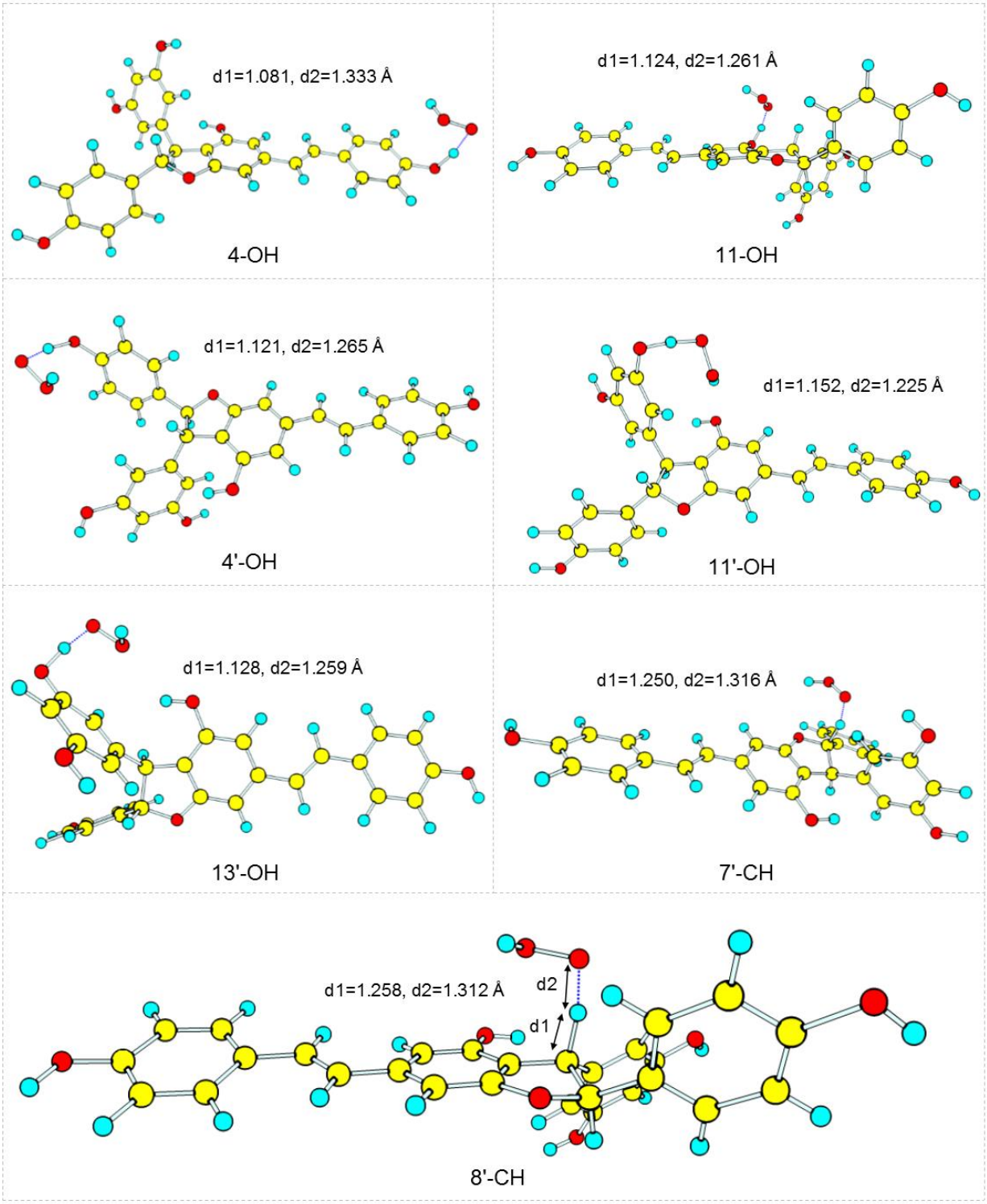

d1=1.081, d2=1.333 Å
4-OH
d1=1.124, d2=1.261 Å
11-OH
d1=1.121, d2=1.265 Å
4'-OH
d1=1.152, d2=1.225 Å
11'-OH
d1=1.128, d2=1.259 Å
13'-OH
d1=1.250, d2=1.316 Å
7'-CH
d1=1.258, d2=1.312 Å
d2
d1
8'-CH

Table 1

H-bond dissociation enthalpy of trans-resveratrol and Gnetin C relative to H-phenol (ΔBDE^*), at T=298.15 K

Reaction site	ΔBDE^* (kcal/mol)	Reaction site	ΔBDE^* (kcal/mol)
Trans-resveratrol			
4-OH	-4.95	6-CH	26.27
11-OH	1.13	7-CH	17.33
13-OH	1.47	8-CH	16.66
2-CH	25.14	10-CH	27.87
3-CH	27.48	12-CH	30.94
5-CH	28.12	14-CH	29.04
Gnetin C			
4-OH	-5.27	10-CH	27.75
11-OH	2.14	14-CH	29.80
4'-OH	-0.01	2'-CH	26.20
11'-OH	0.96	3'-CH	28.10
13'-OH	2.22	5'-CH	27.65
2-CH	24.99	6'-CH	26.39
3-CH	27.29	7'-CH	-3.98
5-CH	28.18	8'-CH	-6.56
6-CH	26.18	10'-CH	28.88
7-CH	16.53	12'-CH	30.22
8-CH	16.97	14'-CH	29.82

Table 2

The standard Gibbs energies of reaction ($\Delta_r G^\circ$) and activation ($\Delta^{\ddagger} G^\circ$) for the •OOH scavenging reaction based on Eq.(1)

Reaction site	$\Delta_r G^\circ$ (kcal/mol)	$\Delta^{\ddagger} G^\circ$ (kcal/mol)	$\Delta^{\ddagger} G^\circ$ (kcal/mol)[a]
Trans-resveratrol			
4-OH	-3.59	18.69	17.96
11-OH	2.09	21.31	20.25
13-OH	1.83	20.70	19.77
Gnetin C			
4-OH	-3.51	17.22	-
11-OH	2.69	21.55	-
4'-OH	0.86	19.86	-
11'-OH	4.03	21.29	-
13'-OH	3.07	21.72	-
7'-CH	-2.43	22.14	-
8'-CH	-5.02	20.85	-

[a]Calculated using M05-2X functional and 6-311++G** basis set [24]

Suplementary material