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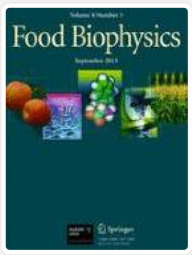

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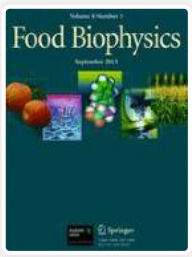

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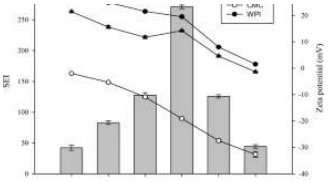

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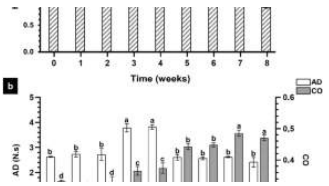

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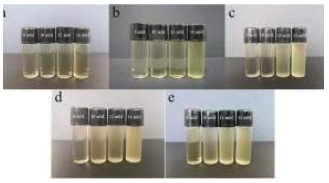

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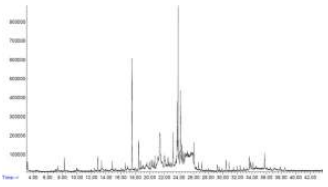

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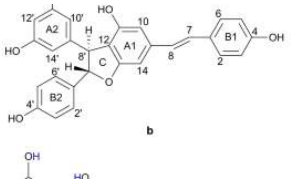

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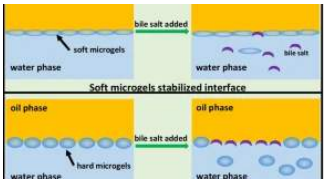

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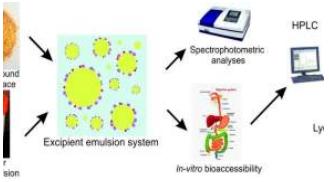

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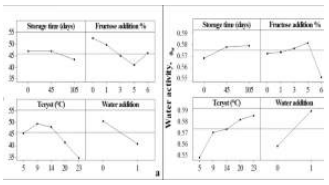

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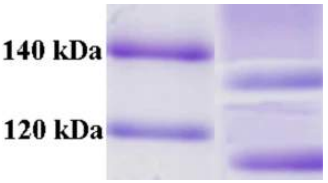

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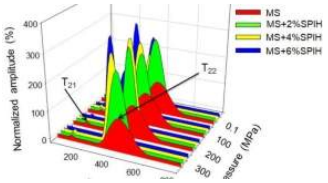

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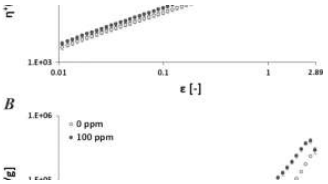

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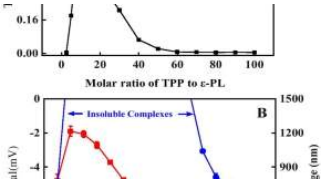

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Computational Investigation on the •OOH Scavenging Sites of Gnetin C

--Manuscript Draft--

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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

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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.

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Figure captions

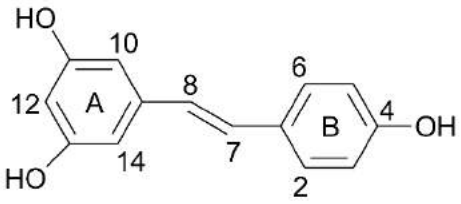
Fig. 1 Chemical structure of (a) trans-resveratrol and (b) gnetin C. Numbers in the figure represent the site numbering. A, B, C are resorcinol, phenol, and furan rings in resveratrol system respectively. The labeling number of atoms here is used throughout the manuscript

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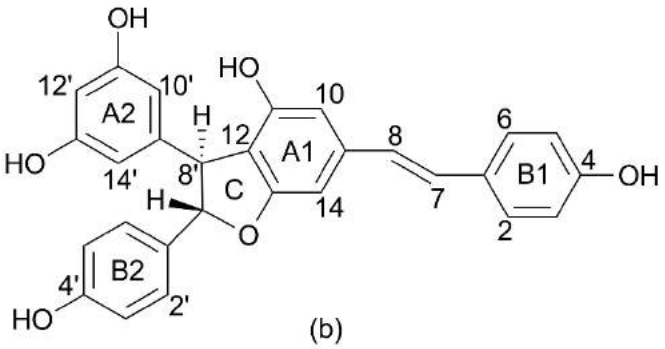
10
12
A
8
6
B
4
OH
14
7
HO
2

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

(b)

Fig. 2

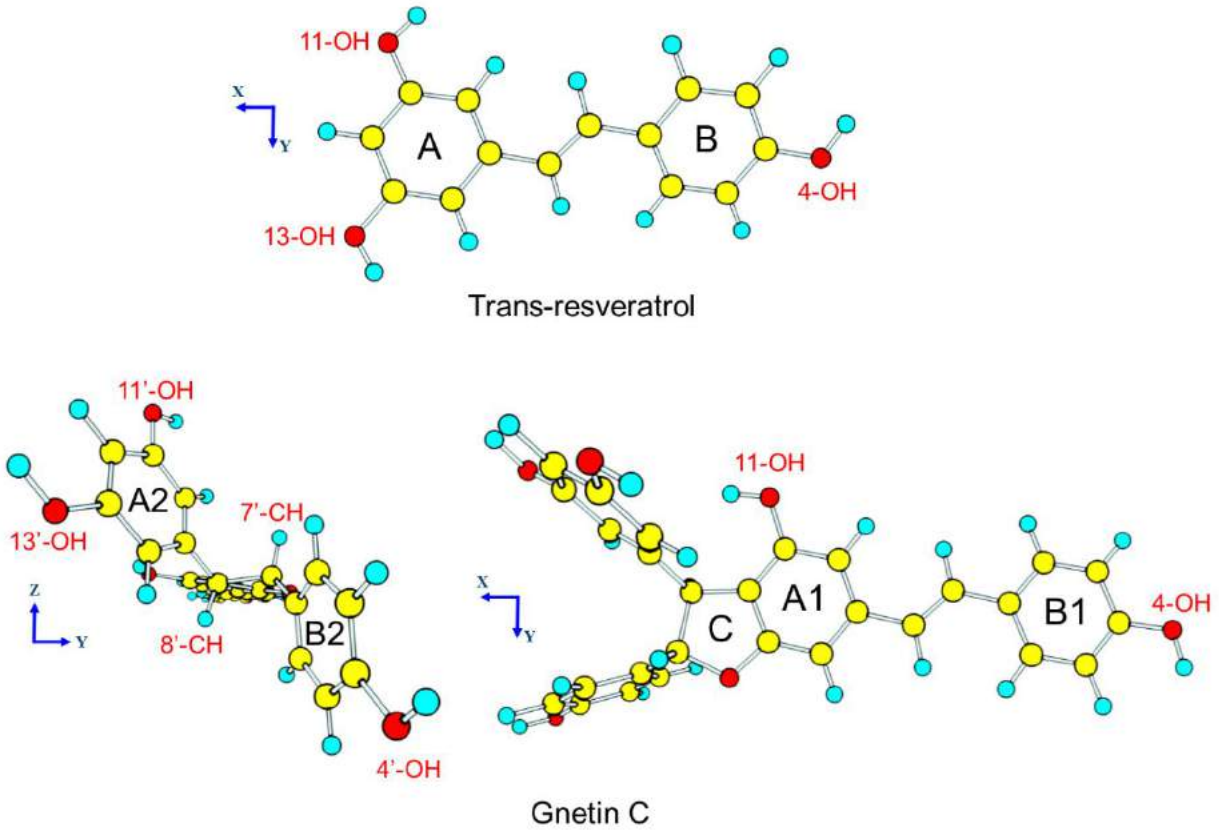

11-OH
X
Y
A
B
4-OH
13-OH
Trans-resveratrol
11'-OH
A2
7'-CH
13'-OH
Z
Y
8'-CH
B2
4'-OH
11-OH
X
Y
A1
C
B1
4-OH
Gnetin C

Fig. 3

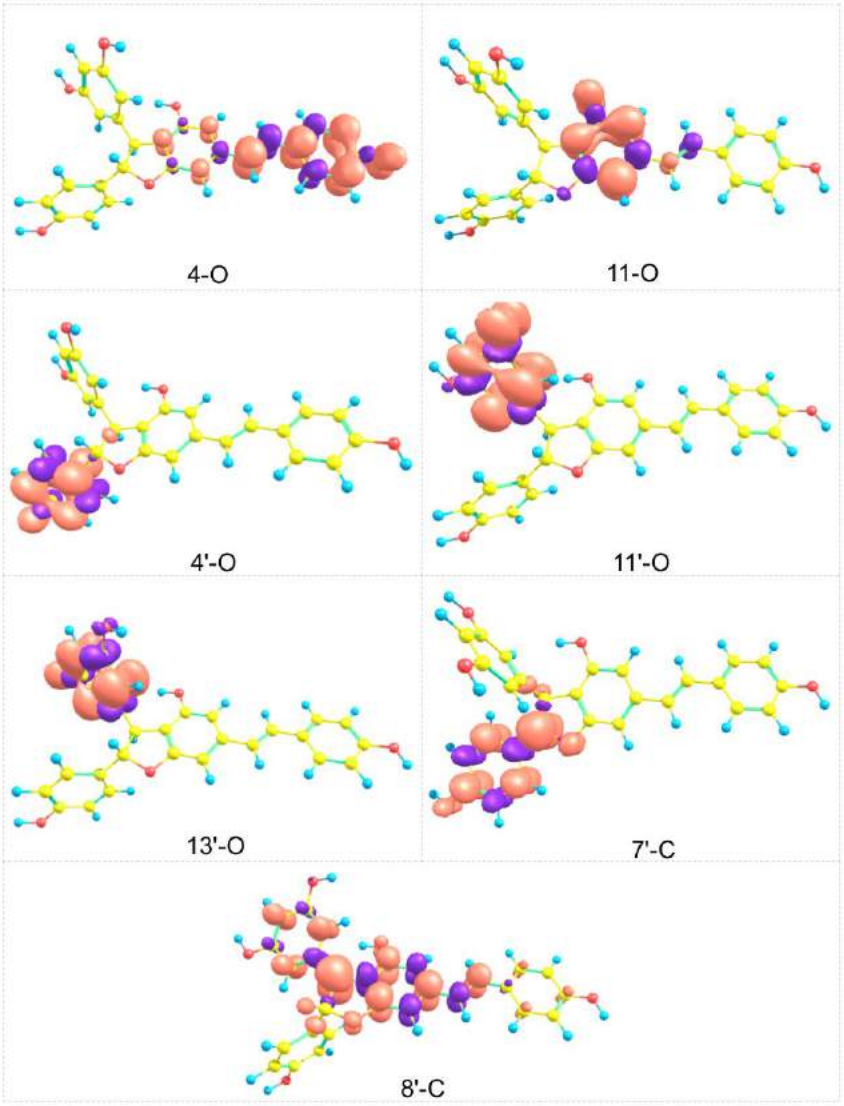
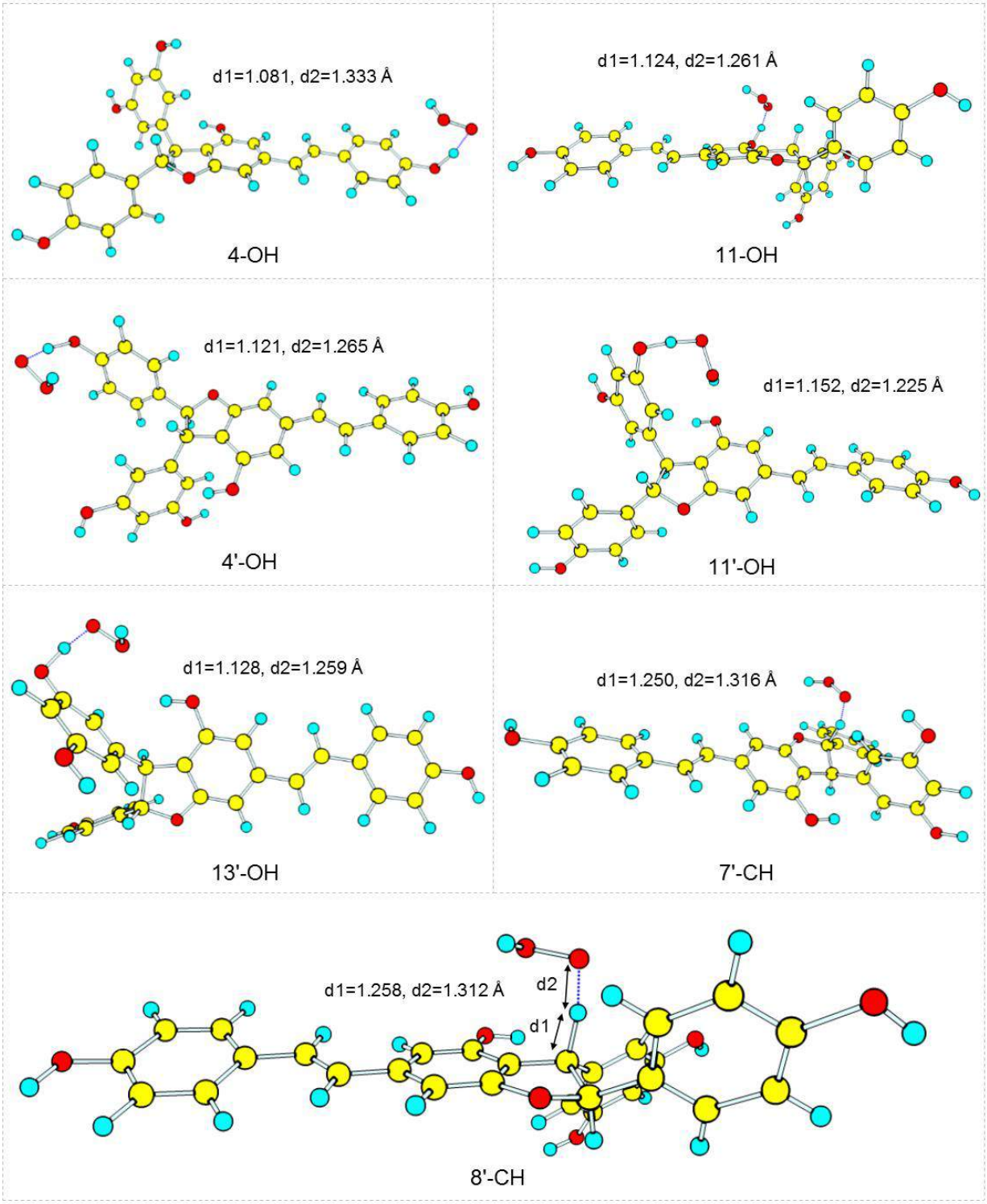


Fig. 4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11-OH
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4'-OH
d1=1.152, d2=1.225 Å
11'-OH
d1=1.128, d2=1.259 Å
13'-OH
d1=1.250, d2=1.316 Å
7'-CH
d1=1.258, d2=1.312 Å
d2
d1
8'-CH

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

4. Review Manuskrip

- Komentar Reviewer
- Pertanyaan dan Jawaban
- Revisi Draf Manuskrip

Vera Khoirunisa <vera.khoirunisa@tf.itera.ac.id>

Decision on your Manuscript #FOBI-D-20-00017

2 messages

John W. Brady <em@editorialmanager.com> Tue, Aug 11, 2020 at 3:37 AM
Reply-To: "John W. Brady" <jwb7@cornell.edu>
To: Vera Khoirunisa <vera.khoirunisa@tf.itera.ac.id>

Dear Dr. Khoirunisa:

We have received the reports from our advisors on your manuscript, "Computational Investigation on the •OOH Scavenging Sites of Gnetin C", which you submitted to Food Biophysics.

Based on the advice received, I feel your manuscript could be accepted for publication should you be prepared to incorporate minor revisions.
We encourage you to re-submit your article within one month.
When preparing your revised manuscript, you are asked to carefully consider the reviewer comments which are attached, and submit a list of responses to the comments. Your list of responses should be uploaded as a file in addition to your revised manuscript.

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Best regards,

John W. Brady, Ph.D.
Associate Editor
Food Biophysics

COMMENTS FOR THE AUTHOR:

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.
https://www.editorialmanager.com/fobi/l.asp?i=54473&l=DJLNMNOZ

Reviewer #1: Manuscript ID: FOBI-D-20-00017

The authors of the manuscript "Computational Investigation on the *OOH Scavenging Sites of Gnetin C "present a DFT study at the M05-2X/ 6-31++G(d,p) level of theory the investigate the scavenging sites of gnetin C. The manuscript is well written and presents the studied system in a clear and clear manner.

Comments:
- On page 4 line 12 the author talk about the activated complexes and 22 active scavenging sites, a figure would be helpful to the readers to illustrate that.
- The manuscript would benefit from a more detailed discussion of the experimental results.

Our flexible approach during the COVID-19 pandemic

If you need more time at any stage of the peer-review process, please do let us know. While our systems will continue to remind you of the original timelines, we aim to be as flexible as possible during the current pandemic.

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Vera Khoirunisa <vera.khoirunisa@tf.itera.ac.id> Tue, Aug 11, 2020 at 3:44 AM
To: febdian@gmail.com, rusydi@fst.unair.ac.id

[Quoted text hidden]

Food Biophysics

Computational Investigation on the •OOH Scavenging Sites of Gnetin C

--Manuscript Draft--

Manuscript Number:	FOBI-D-20-00017R1
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
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Corresponding Author's Secondary Institution:	
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	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 has antioxidant activity. The radical-scavenging sites required for the antioxidant activity, however, is yet to be located. We report a computational study that aims 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, trans-resveratrol, 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 propose resorcinol ring. Our study shows the prospect of density-functional calculation for studying the radical-scavenging reaction.

To: Reviewer 1
Subject: response and revision to the comments and questions

We appreciate the reviewer's comments and concern on our work. Here we respond the reviewer's questions point by point. We also added a new figure and reference [1] in the revised manuscript. We expect the revised manuscript meets the reviewer's expectation.

Sincerely,

on the behalf of the authors
Vera Khoirunisa

BEGIN

Question 1

On page 4 line 12 the author talk about the activated complexes and 22 active scavenging sites, a figure would be helpful to the readers to illustrate that.

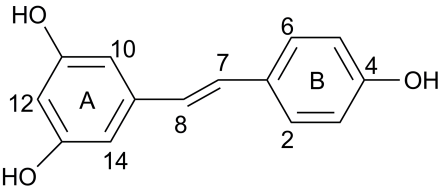
We agree with the reviewer's concern. Therefore, we add Fig. 1(c) and revise the caption of Fig. 1 to illustrate the activated complex and 22 possible scavenging sites.

Question 2

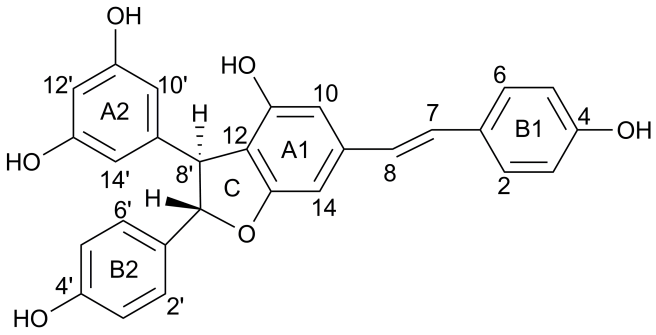
The manuscript would benefit from a more detailed discussion of the experimental results.

We have already provided detailed discussions (blue font) that are related to experimental work by Tani et al.[1] and Kato et al. [2]. For the former, we give the reason why gnetin C has a higher antioxidant capacity than trans-resveratrol does. While for the latter, we explain the experimental observation from Kato et al. [2] which showed that melinjo extract gradually scavenged radicals and reached a maximum effect after sufficient time.

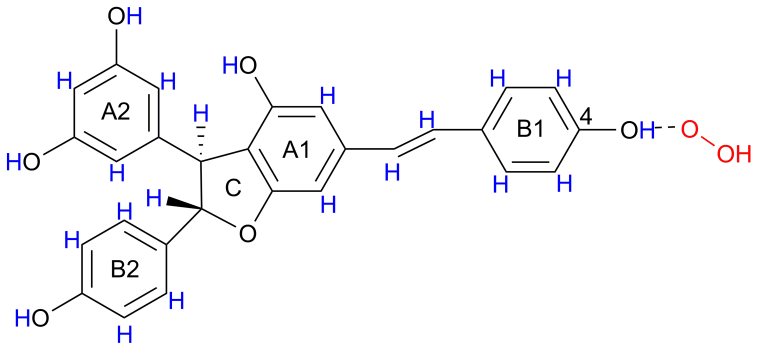
However, we realize that we have not clearly mentioned it in the manuscript. Therefore, we add a sentence (red font) in the second paragraph of "3.2 The Standard Gibbs Energy of Reaction",



(a)



(b)



(c)

Fig. 1 Molecular model for (a) trans-resveratrol, (b) gnetin C, and (c) activated complex of gnetin C and •OOH for 4-OH site. The nomenclature is used throughout manuscript. A, B, C, are resorcinol, phenol, and furan rings in resveratrol system respectively. Red atom and blue atom labels indicate •OOH and the 22 possible scavenging sites respectively.

In the manuscript

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 are 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 later. These results support the experimental findings which reported that gnetin C has better antioxidant capacity than trans-resveratrol in ORAC assay [1]. Furthermore, by considering the ring in gnetin C, ring C provides more scavenging sites than other rings (A, phenol, and B, resorcin ring). It indicates that furan ring plays a more important role than other rings in the scavenging capacity of melinjo resveratrol.

and in the fifth paragraph of "The Standard Gibbs Energy of Activation" section,

In the manuscript

Considering the $\Delta_r G^0$ 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 $\Delta^{\ddagger} G^0$. The high barrier is expected since geometrically ring A2 and B2 hinders $^{\bullet}$OOH to reach site 7′ and 8′. The various value of $\Delta^{\ddagger} G^0$ make the three sites scavenge three $^{\bullet}$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 gradual increase in scavenging activity was observed in the experiment done by Kato et al. [2]. However, this finding is contrary to their speculation which proposed that it is ring B2 (resorcinol) that plays a crucial role n the scavenging activity of melinjo resveratrol.

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[2] E. Kato, Y. Tokunaga, F. Sakan, J. Agric. Food Chem., Stilbenoids isolated from the seeds of melinjo (Gnetum gnemon L.) and their biological activity, 57 (6), 2544–2549 (2009)

To: Reviewer 2
Subject: response and revision to the comments and questions

We are grateful for the question and comments on our manuscript. We respond to the reviewer's concerns point by point. We revised our manuscript and added more data in the supplementary material to give insight on our manuscript. We expect the revised manuscript meets the reviewer's expectations.

Sincerely,

on the behalf of the authors
Vera Khoirunisa

BEGIN

Question 1

Please revise grammar as numerous sentences contain grammatical errors.

We are aware of our English limitation. Therefore, we use professional proofreading service before resubmitting our manuscript to Food Biophysics.

Question 2

On page 4 paragraph 1 "[X-H-Y]" is used which is different from what is shown in Equation (1). Please be consistent to avoid confusion if these are the same TS.

We apologize for our inconsistency. We revise Eq. (1) in "2.1 Scavenging Reaction" section to avoid confusion.

In the manuscript

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

Question 3

For gnetin C, the 7'-CH and 8'-CH energies are even lower than the OH site, what is the reason for this? (Table 1)

The reason for the lower ΔBDE* in the 7′-CH and 8′-CH sites is the contribution of sp^n hybrid orbital in the C-H bonding. As we can see in Table S2, most of C-H bonds in gnetin C have n≈2 in their sp^n hybrid orbital, except for C-H bonds in the 7′-CH and 8′-CH sites (highlighted in yellow). These exceptional C-H bonds have n≈3 in their sp^n hybrid orbital. The sp^3 bonding has less electron density than the sp^2 bonding result in the weaker bonding between atom C and H. Therefore, the C-H bonds in the 7′-CH and 8′-CH have lower ΔBDE* than the other C-H bonds.

Since O-H bonds in gnetin C also possesses sp^n hybrid orbital with $n \approx 3$ in their bonding, it is reasonable that C-H bonds in 7′-CH and 8′-CH sites has comparable ΔBDE* with or even lower than the O-H sites.

We are glad the reviewer pointed out this issue. Here, we revise the discussion of Table 1 in the second paragraph of the "3.1 Bond Dissociation Energy" section and provide Table S2 in supplementary material.

In the manuscript

Table 1 shows the ΔBDE* in all possible sites of trans-resveratrol and gnetin C based on Fig. 1. Overall, ΔBDE* in the O-H site is less than that in the C-H site in both molecules. Interestingly, 7′-CH and 8′-CH sites of gnetin C have comparable ΔBDE* with the O-H sites. The lower ΔBDE* in 7′-CH and 8′-CH sites is explained by the contribution of sp^n hybrid in their bonding orbital (as shown in Table S2). The C-H bond in these sites has n≈3, instead of n≈2 as the other C-H bonds in gnetin C. It suggests that the weaker sp^3 bonding than sp^2 bonding is the reason of the lower ΔBDE* in 7′-CH and 8′-CH sites. Therefore, we consider 7′-CH and 8′-CH for the scavenging sites of gnetin C in addition to the OH sites.

Table S2 The calculated sp^n hybrid orbital contribution of C-H and O-H bonding in gnetin C. The data was obtained from the natural bond orbital analysis (NBO) calculations.

Site	Coefficient	sp^n	Atom
4-OH	0.876	3.25	O4
11-OH	0.877	3.12	O11
4′-OH	0.876	3.25	O4′
11′-OH	0.876	3.24	O11′
13′-OH	0.876	3.25	O13′
2-CH	0.793	2.30	C2
3-CH	0.795	2.24	C3
5-CH	0.797	2.20	C5
6-CH	0.794	2.32	C6
7-CH	0.789	2.50	C7
8-CH	0.790	2.47	C8
10-CH	0.795	2.21	C10
14-CH	0.797	2.17	C14
2′-CH	0.796	2.29	C2′
3′-CH	0.797	2.21	C3′
5′-CH	0.796	2.23	C5′
6′-CH	0.795	2.30	C6′
7′-CH	0.794	2.93	C7′
8′-CH	0.803	3.18	C8′
10′-CH	0.797	2.21	C10′
12′-CH	0.798	2.15	C12′
14′-CH	0.797	2.19	C14′

Question 4

Please elaborate more on Fig. 3 and explains the significance and/or difference of each of the subplot.

We revise the discussion for Fig. 3 in the last paragraph of the "3.1 Bond Dissociation Energy" section to address the request from the reviewer.

In the manuscript

The spin density plots in Fig. 3 shows the stability of gnetin C radical. The most stable radical is 8′-C gnetin C radical since the spin density covers two resorcinol and one furan rings. The stability of radical reduces as the number of rings covered decreases. The second and third most stable radicals are 4′-O and 7′-C gnetin C radical. The former has two rings covered, while the latter has one and a half rings covered. The stability of 8′-C, 4′-O, and 7′-C radicals are inversely proportional to the ΔBDE* at site 8′-CH, 4′-OH, and 7′-CH. Therefore, the stability of gnetin C radical supports the hydrogen atom transfer process in site 8′-CH, 4′-OH, and 7′-CH.

Question 5

Please clarify what is the difference in the method in calculating the values in column 2 and 3 of Table 2.
-It is not very clear from the description of the table or from the discussion.
-Also please state clearly why are those values not calculated for gnetin C.

The difference is in the basis set that is used to calculate $\Delta^{\ddagger}G^{0}$ values in column 2 and 3 (column 3 and 4 in the revised manuscript). 6-31++G(d,p) basis set is used for calculating $\Delta^{\ddagger}G^{0}$ value in column 2. While a higher basis set, 6-311++G(d,p), is used for $\Delta^{\ddagger}G^{0}$ value in column 3.

We revise and add the description of Table 2 to clarify this issue.

END

Table 2 The calculation results of the standard Gibbs free energy of reaction ($\Delta_r G^0$, in kcal/mol) and activation ($\Delta^{\ddagger} G^0$, in kcal/mol) for the $^{\bullet}$OOH scavenging reaction based on Eq. (1). The values in column 3 and 4 are obtained from our calculations. The values from Iuga's calculations [1] in column 5 are used as benchmark for $\Delta^{\ddagger} G^0$.

Molecule	Reaction site	$\Delta_r G^{0a}$	$\Delta^{\ddagger} G^{0a}$	$\Delta^{\ddagger} G^{0b}$
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	n/a[c]
	11-OH	2.69	21.55	n/a
	4′-OH	0.86	19.86	n/a
	11′-OH	4.03	21.29	n/a
	13′-OH	3.07	21.72	n/a
	7′-CH	-2.43	22.14	n/a
	8′-CH	-5.02	20.85	n/a

[a] Using M05-2X/6-31++G(d,p), this work.

[b] Using M05-2X/6-311++G(d,p), reported by Iuga et al. [1].

[c] n/a means not available value.

References

[1] C. Iuga, J. R. Alvarez-Idaboy, N. Russo, Antioxidant activity of trans-resveratrol toward hydroxyl and hydroperoxyl radicals: A quantum chemical and computational kinetics study, J. Org. Chem., 77 (8), 3868–3877 (2012)

[2] K. M. Zinatullina, N. P. Khrameeva, O. T. Kasaikina, B. I. Shapiro, V. A. Kuzmin, Kinetic characteristics of the reaction of resveratrol with peroxyl radicals and natural thiols in aqueous medium, Russ Chem Bull 66 (11), 2145–2151 (2017)

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Computational Investigation on the $^{\bullet}$OOH Scavenging Sites of Gnetin C

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Abstract Melinjo seed extract contains melinjo resveratrol compounds that has antioxidant activity. The radical-scavenging sites required for the antioxidant activity, however, is yet to be located. We report a computational study that aims 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, trans-resveratrol, 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 propose 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

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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 needed 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, DFT can 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 a reliable method 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 ($^{\bullet}$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.

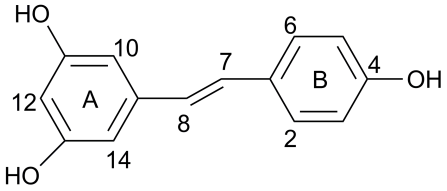
2 Computational Model

2.1 Scavenging Reaction Model

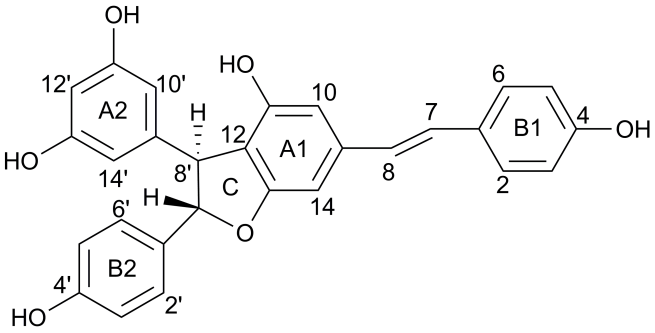
The one-step reaction mechanism models the $^{\bullet}$OOH scavenging by melinjo resveratrol (YH) has been suggested to be the preferable mechanism of phenolic antioxidants [25–27]. The reaction is as follows:

$$\mathrm{X} + \mathrm{YH} \rightarrow [\mathrm{X} - \mathrm{H} - \mathrm{Y}] \rightarrow \mathrm{XH} + \mathrm{Y}. \tag{1}$$

In our case, X is $^{\bullet}$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.



(a)



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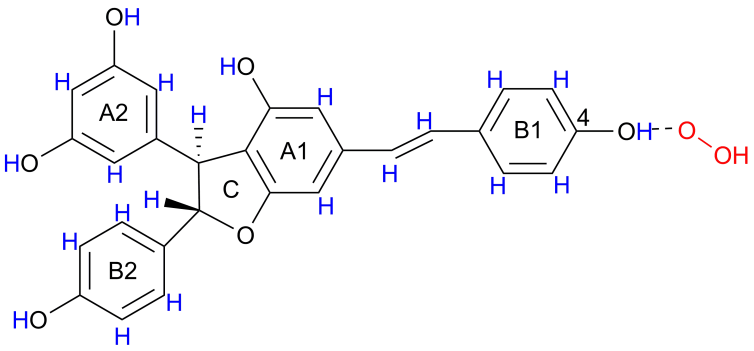

(c)

Fig. 1 Molecular model for (a) trans-resveratrol, (b) gnetin C, and (c) activated complex of gnetin C and •OOH for 4-OH site. The nomenclature is used throughout manuscript. A, B, C, are resorcinol, phenol, and furan rings in resveratrol system respectively. Red atom and blue atom labels indicate •OOH and the 22 possible scavenging sites respectively.

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) describes the reaction energy (E_r), the energy difference between TS and reactant determine the barrier energy (E_b).

The H in [X–H–Y] activated complex may derive from 22 possible sites of gnetin C [see Fig. 1(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 H donation from the site.

2.2 Density-functional Calculation

The primary quantities here are 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 [29]. 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 ($\Delta_r G^0$) and activation ($\Delta^{\ddagger} G^0$), 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

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

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. 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 [30].

In using the DFT method, we employ M05-2X exchange-correlation functional and 6-31++G(d,p) basis set that are integrated into the Gaussian 09 software [31]. M05-2X functional has been recommended for thermochemistry and kinetic calculations [32,33], and has performed well to predict internuclear distance at the TS, especially for hydrogen transfer reaction [34].

We couple DFT calculation with the polarized continuum model (PCM) [35,36] for considering the solvent environment. PCM has been applied successfully to a significant number of systems in aqueous and non-aqueous media [36,37,39]. 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).

Table 1 shows the ΔBDE* in all possible sites of trans-resveratrol and gnetin C based on Fig. 1. Overall, ΔBDE* in the O-H site is less than that in the C-H site in both molecules. Interestingly, 7′-CH and 8′-CH sites of gnetin C have comparable ΔBDE* with the O-H sites. The lower ΔBDE* in 7′-CH and 8′-CH sites is explained by the contribution of sp^n hybrid in their bonding orbital (as shown in Table S2). The C-H bond in these sites has n≈3, instead of n≈2 as the other C-H bonds in gnetin C. It suggests that the weaker sp^3 bonding than sp^2 bonding is the reason of the lower ΔBDE* in 7′-CH and

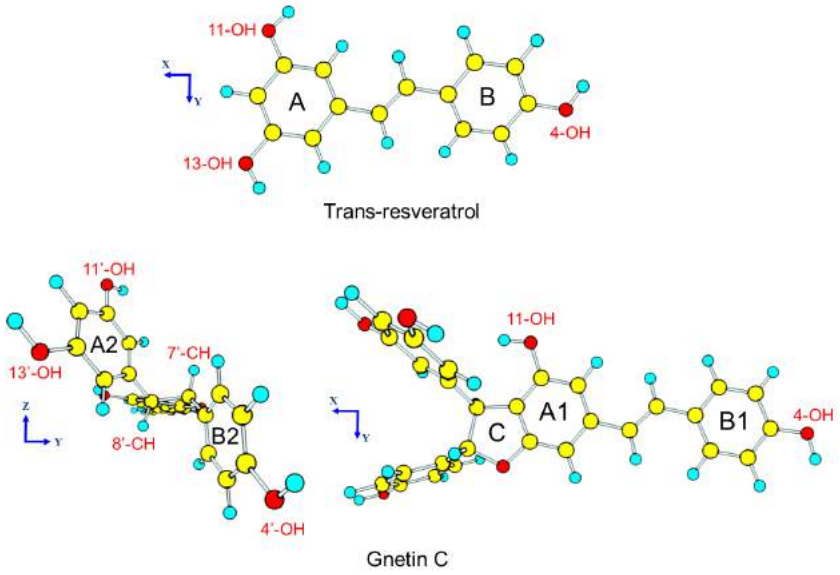

Fig. 2 Optimized structure of trans-resveratrol and gnetin C in water environment. Blue, red, and yellow atoms represent H, O, and C atom. Red marker indicates scavenging site.

8′-CH sites. Therefore, we consider 7′-CH and 8′-CH for the scavenging sites of gnetin C in addition to the OH sites.

The spin density plots in Fig. 3 shows the stability of gnetin C radical. The most stable radical is 8′-C gnetin C radical since the spin density covers two resorcinol and one furan ring. The stability of the radical reduces as the number of rings covered decreases. The second and third most stable radicals are 4′-O and 7′-C gnetin C radical. The former has two rings covered, while the latter has one and a half rings covered. The stability of 8′-C, 4′-O, and 7′-C radicals are inversely proportional to the ΔBDE* at site 8′-CH, 4′-OH,

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

and 7′-CH. Therefore, the stability of gnetin C radical supports the hydrogen atom transfer process in site 8′-CH, 4′-OH, and 7′-CH.

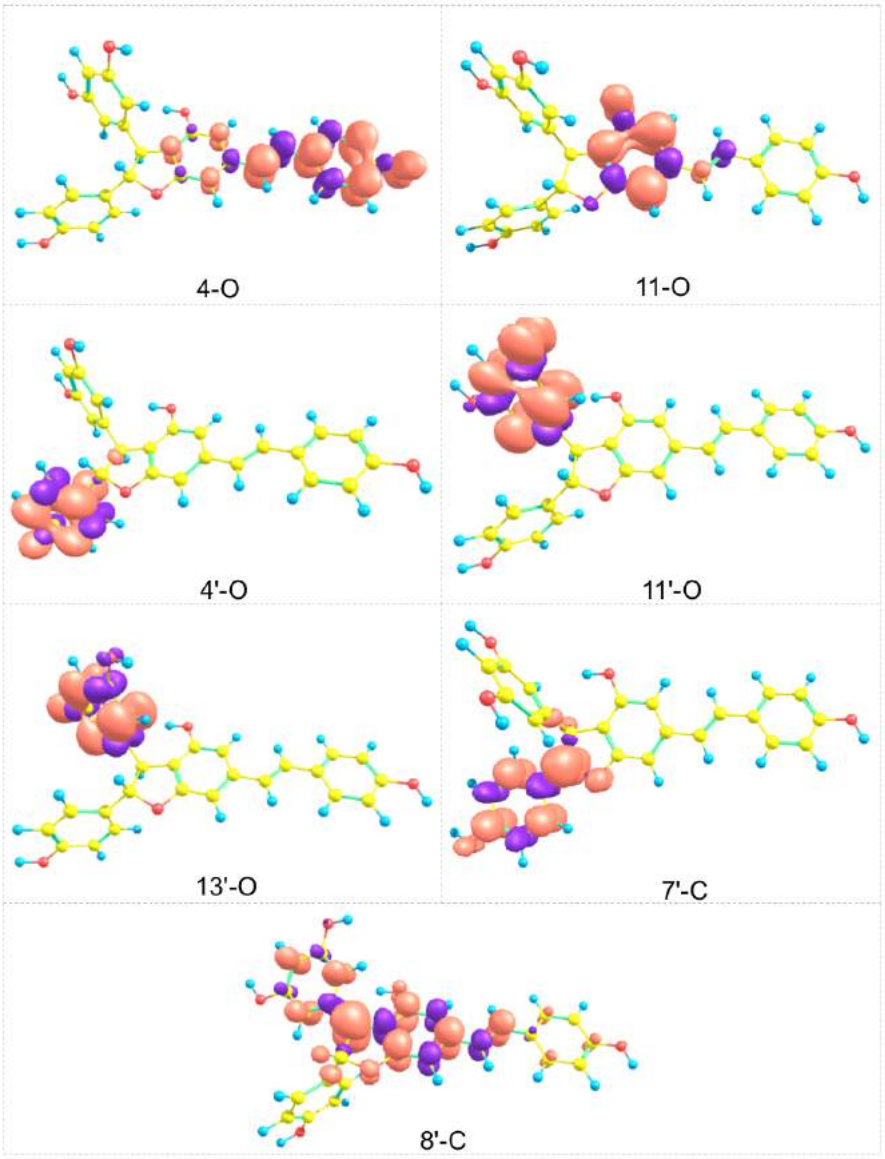

Fig. 3 The spin density distribution of gnetin C radical with isovalue 0.003. Orange and purple colors indicate α and β densities are dominant, respectively.

3.2 The Standard Gibbs Energy of Reaction

Table 2 provides the $\Delta_r G^0$ of the $^\bullet$OOH scavenging reaction by trans-resveratrol, according to Eq. (1). Out of three OH sites in trans-resveratrol, the $^\bullet$OOH scavenging reaction is exergonic only at site 4. Therefore, only the 4-OH site is favorable for scavenging $^\bullet$OOH. Another density-functional study on the identical system, employing the same exchange-correlation functional but 6-311++G(d,p) and solvation model based on density, concluded the same result [23]. It supports the recommendation by Zhao et al. [32,33] that M05-2X is reliable for studying the scavenging reaction energetically.

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 are 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 later. These results support the experimental findings which reported that gnetin C has better antioxidant capacity than trans-resveratrol in ORAC assay [40]. Furthermore, by considering the ring in gnetin C, ring C provides more scavenging sites than other rings (A, phenol, and B, resorcin ring). It indicates that furan ring plays a more important role than other rings in the scavenging capacity of melinjo resveratrol.

Overall, ring A always provides the lowest $\Delta_r G^0$ value for OH site. It is valid for both trans-resveratrol and gnetin C. It implies, there is a relation between the position of the OH site and the $\Delta_r G^0$. Queiroz et al. [41] also reported this relation.

Table 2 The calculation results of the standard Gibbs free energy of reaction ($\Delta_r G^0$, in kcal/mol) and activation ($\Delta^{\ddagger} G^0$, in kcal/mol) for the •OOH scavenging reaction based on Eq. (1). The values in column 3 and 4 are obtained from our calculations. The values from Iuga's calculations [24] in column 5 are used as benchmark for $\Delta^{\ddagger} G^0$.

Molecule	Reaction site	$\Delta_r G^{0\,a}$	$\Delta^{\ddagger} G^{0\,a}$	$\Delta^{\ddagger} G^{0\,b}$
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	n/a[c]
	11-OH	2.69	21.55	n/a
	4′-OH	0.86	19.86	n/a
	11′-OH	4.03	21.29	n/a
	13′-OH	3.07	21.72	n/a
	7′-CH	-2.43	22.14	n/a
	8′-CH	-5.02	20.85	n/a

[a] Using M05-2X/6-31++G(d,p), this work.

[b] Using M05-2X/6-311++G(d,p), reported by Iuga et al. [24].

[c] n/a means not available value.

4 The Standard Gibbs Energy of Activation

We validate our work on reaction kinetics based on the trans-resveratrol case. Our predictions of $\Delta^{\ddagger} G^0$ are comparable with a theoretical work reported by Iuga et al. [24] (see Table 2), which computed the rate constants at room temperature with the basis of transition-state theory, whose results are comparable with the experimental results by Zinatullina et al. [42]. Consequently,

our density-functional calculations on Eq. (1) is adequate to study $^{\bullet}$OOH scavenging by resveratrol system such as gnetin C.

Regarding gnetin C, Figure 4 shows the TS of $^{\bullet}$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 shown in 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 $\mathring{A}$ 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.

The $\Delta^{\ddagger}G^{0}$ values of gnetin C in Table 2 show that the lowest $\Delta^{\ddagger}G^{0}$ is at site 4-OH. The site 4-OH in trans-resveratrol also has the lowest activation energy. These results agree with the previous experimental findings reporting that site 4-OH is the most reactive one in trans-resveratrol and its derivatives [43]. However, $\Delta^{\ddagger}G^{0}$ 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 $^{\bullet}$OOH than its monomer form.

As for $\Delta_{r}G^{0}$, the $\Delta^{\ddagger}G^{0}$ values at OH-group also has a relation with its location. Both site 4-OH and 4′-OH have the lowest $\Delta^{\ddagger}G^{0}$ 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

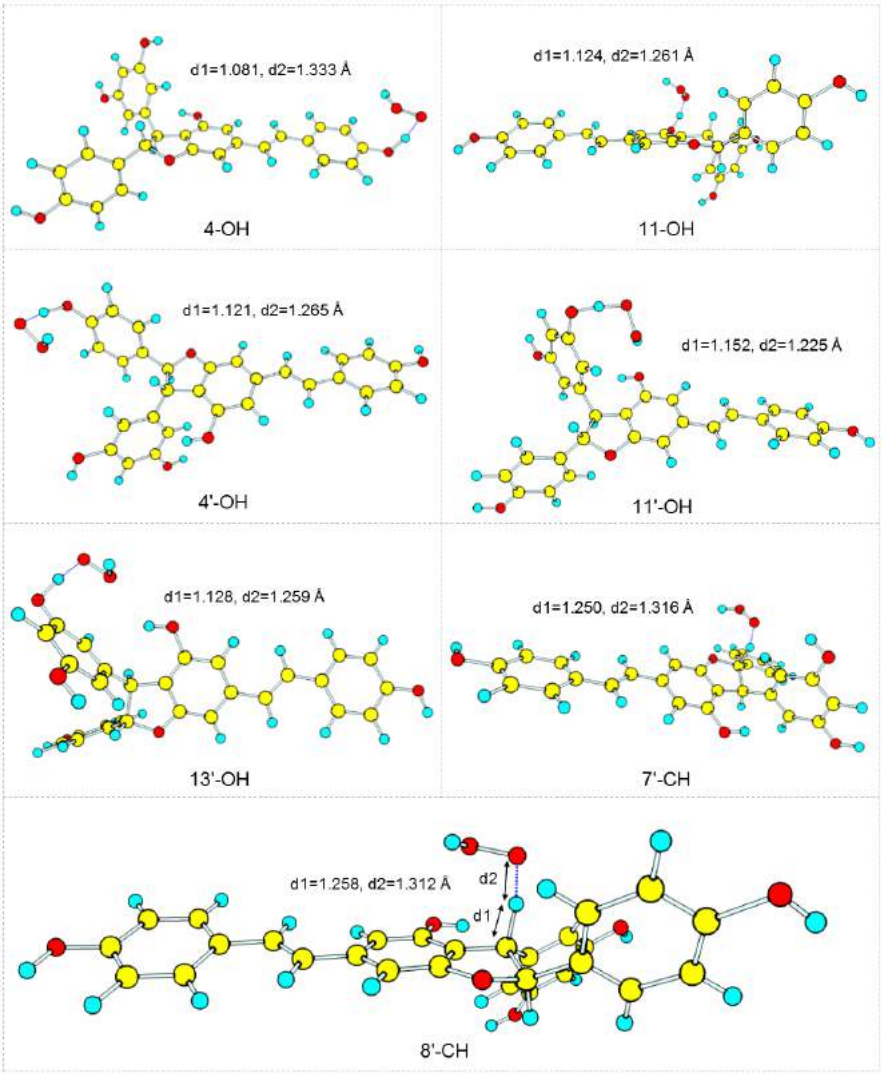

Fig. 4 TS structure for •OOH scavenging reaction by gnetin C on each site. Markers d1 is bond length of scavenging site, while d2 is the distance between O atom of •OOH with the nearest scavenging site.

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 the scavenging reactivity of an OH site.

Considering the $\Delta_r G^0$ 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 that of at 4-OH site due to their higher value of $\Delta^{\ddagger} G^0$. The high barrier is expected since geometrically ring A2 and B2 hinder $^{\bullet}$OOH to reach site 7′ and 8′. The various value of $\Delta^{\ddagger} G^0$ make the three sites scavenge three $^{\bullet}$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 gradual increase in scavenging activity was observed in the experiment done by Kato et al.[1]. However, this finding is contrary to their speculation proposing that it is ring B2 (resorcinol) that plays a crucial role n 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 $^{\bullet}$OOH). The sigma bond allows hydrogen atom (both the proton and the electron) to transfer from one side to another [30]. It implies that the $^{\bullet}$OOH scavenging at the three sites of gnetin C through the reaction in Eq. (1) is a hydrogen atom transfer.

5 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 as the one playing a crucial role in the scavenging activity of melinjo resveratrol, not the resorcin ring as has been speculated in the experimental study. Finally, this work demonstrates that density-functional calculations are a prospective approach for studying the system in question.

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Author's contributions

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Abstract	Melinjo seed extract contains melinjo resveratrol compounds that has antioxidant activity. The radical-scavenging sites required for the antioxidant activity, however, is yet to be located. We report a computational study that aims 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, trans-resveratrol, 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 propose resorcinol ring. Our study shows the prospect of density-functional calculation for studying the radical-scavenging reaction.
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ORIGINAL ARTICLE

Computational Investigation on the •OOH Scavenging Sites of Gnetin C

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Abstract

Melinjo seed extract contains melinjo resveratrol compounds that has antioxidant activity. The radical-scavenging sites required for the antioxidant activity, however, is yet to be located. We report a computational study that aims 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, trans-resveratrol, 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 propose 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

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 needed 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

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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, DFT can 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 a reliable method 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.

Computational Model

Scavenging Reaction Model

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

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

In our case, X is •OOH, YH is gnetin C, XH is ~~H2O2~~, 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.

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) describes the reaction energy (E_r), the energy difference between TS and reactant determine the barrier energy (E_b).

The H in [X – H – Y] activated complex may derive from 22 possible sites of gnetin C [see Fig. 1(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,

$$YH \rightarrow Y + H, \quad (2)$$

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 H donation from the site.

Density-Functional Calculation

The primary quantities here are 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 [29]. 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 ($\Delta_r G^0$) and activation ($\Delta^{\ddagger} G^0$), 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 (~~C6H5OH~~), equated as

$$\Delta BDE^* = BDE^*_{(YH)} - BDE^*_{(phenol)}. \quad (3)$$

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. 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 [30].

In using the DFT method, we employ M05-2X exchange-correlation functional and 6-31++G(d,p) basis set that are integrated into the Gaussian 09 software [31]. M05-2X functional has been recommended for thermochemistry and kinetic calculations [32, 33], and has performed well to predict internuclear distance at the TS, especially for hydrogen transfer reaction [34].

We couple DFT calculation with the polarized continuum model (PCM) [35, 36] for considering the solvent environment. PCM has been applied successfully to a significant number of systems in aqueous and non-aqueous media [36, 37, 39]. In this work, we consider water solvent since it is the primary cellular environment component.

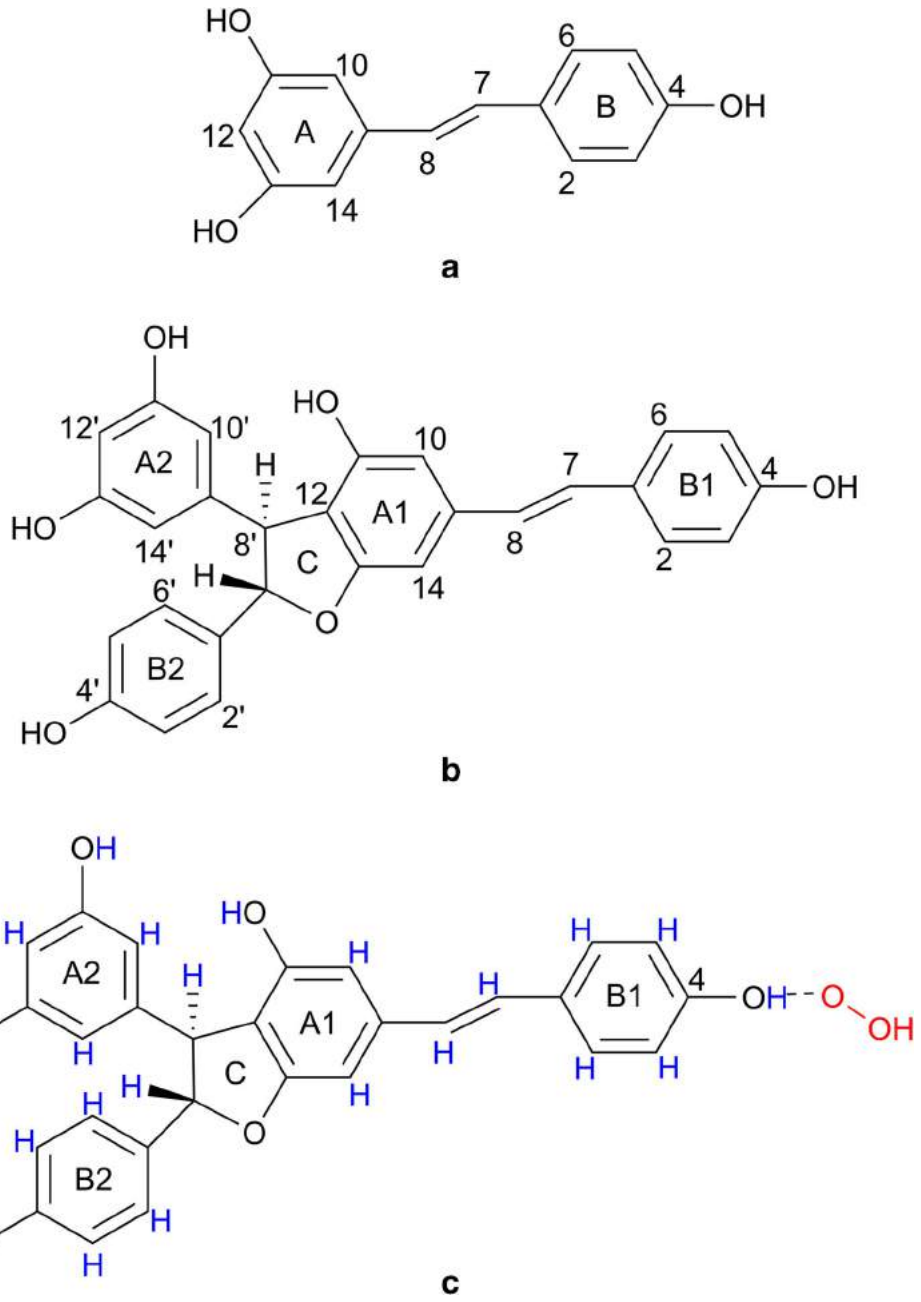

Fig. 1 Molecular model for **a** trans-resveratrol, **b** gnetin C, and **c** activated complex of gnetin C and •OOH for 4-OH site. The nomenclature is used throughout manuscript. A, B, C, are resorcinol, phenol, and furan rings in resveratrol system respectively. Red atom and blue atom labels indicate •OOH and the 22 possible scavenging sites respectively

Result and Discussion

The Bond Dissociation Energy

Figure 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).

Table 1 shows the ΔBDE* in all possible sites of trans-resveratrol and gnetin C based on Fig. 1. Overall, ΔBDE* in the O-H site is less than that in the C-H site in both molecules. Interestingly, 7′-CH and 8′-CH sites of gnetin C have comparable ΔBDE* with the O-H sites. The lower ΔBDE* in 7′-CH and 8′-CH sites is explained by the contribution of sp^n hybrid in their bonding orbital (as shown in Table S2). The C-H bond in these sites has n≈3, instead of n≈2 as the other C-H bonds in gnetin C. It suggests that the weaker sp^3 bonding than sp^2 bonding is the reason of the lower ΔBDE* in 7′-CH and 8′-CH sites. Therefore, we consider 7′-CH and 8′-CH for

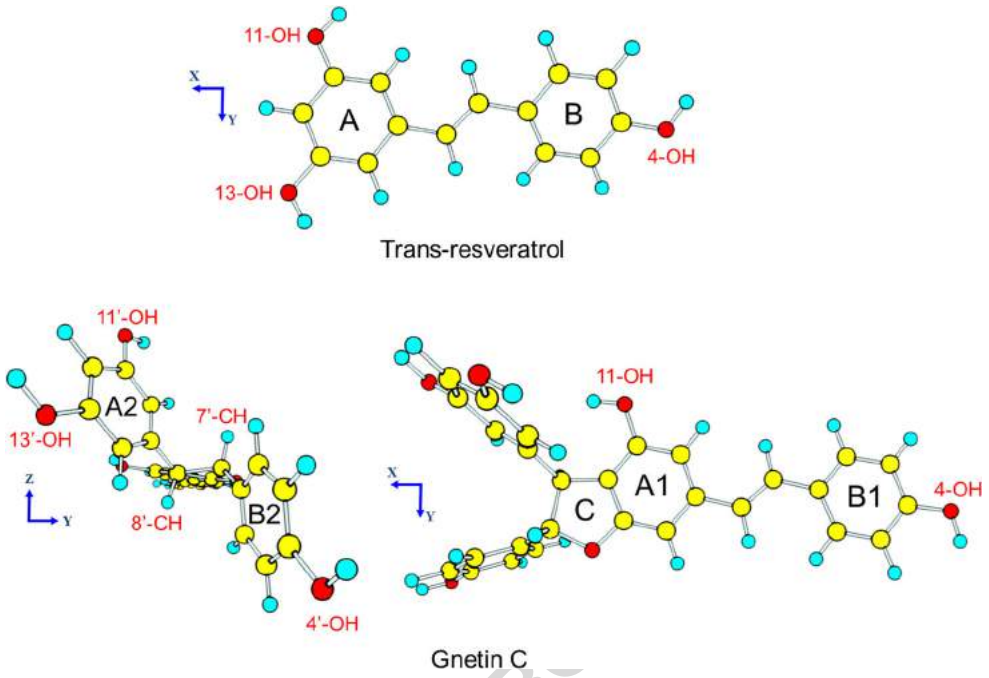

Fig. 2 Optimized structure of trans-resveratrol and gnetin C in water environment. Blue, red, and yellow atoms represent H, O, and C atom. Red marker indicates scavenging site

the scavenging sites of gnetin C in addition to the OH sites.

The spin density plots in Fig. 3 shows the stability of gnetin C radical. The most stable radical is 8′-C gnetin C radical since the spin density covers two resorcinol and one furan ring. The stability of the radical reduces as the number of rings covered decreases. The second and third most stable radicals are 4′-O and 7′-C gnetin C radical. The former has two rings covered, while the latter has one and a half rings covered. The stability of 8′-C, 4′-O, and 7′-C radicals are inversely proportional to the ΔBDE* at site 8′-CH, 4′-OH, and 7′-CH. Therefore, the stability of gnetin C radical

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

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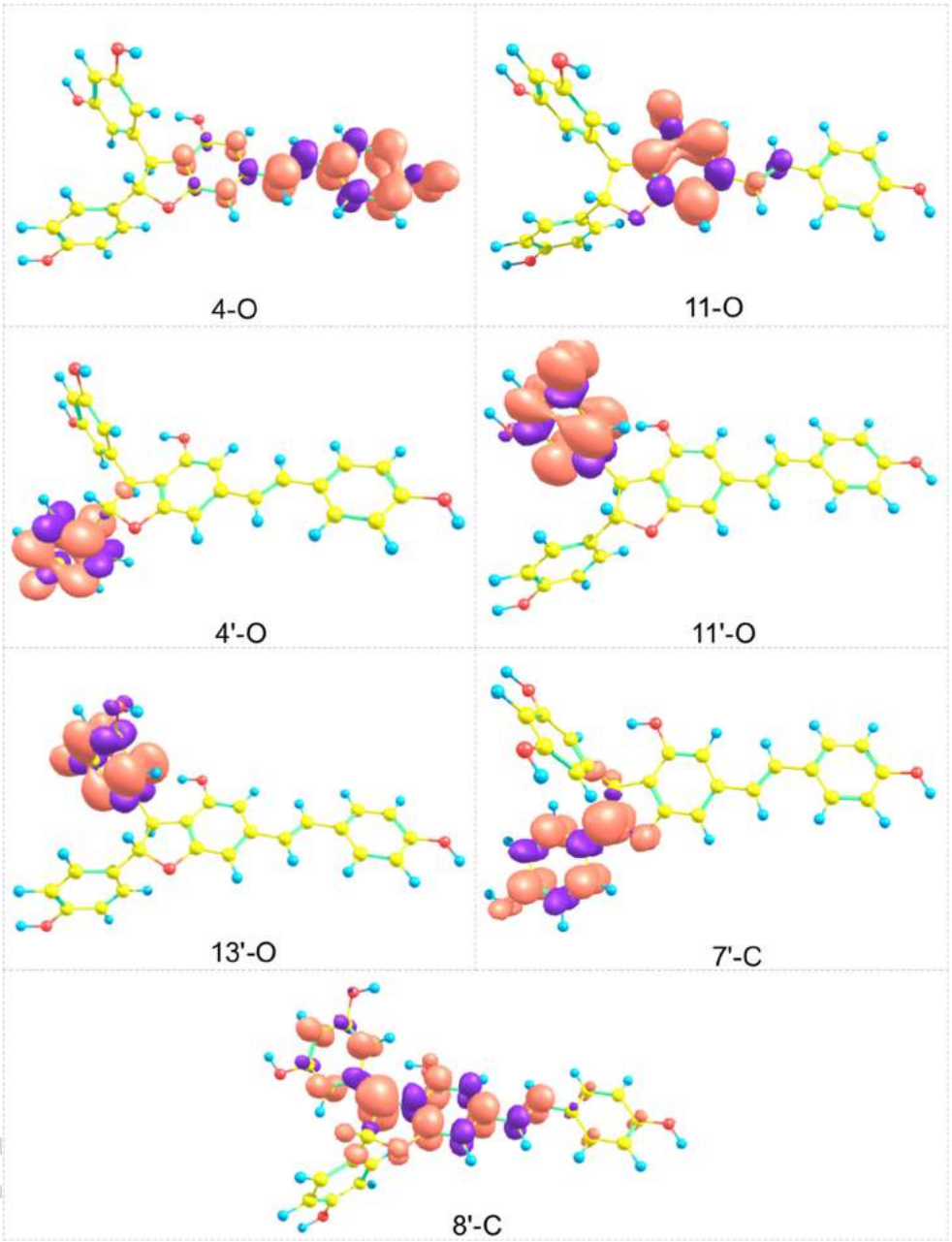

Fig. 3 The spin density distribution of gnetin C radical with isovalue 0.003. Orange and purple colors indicate α and β densities are dominant, respectively

supports the hydrogen atom transfer process in site 8′-CH, 4′-OH, and 7′-CH.

The Standard Gibbs Energy of Reaction

Table 2 provides the $\Delta_r G^0$ 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 on the identical system, employing the same exchange-correlation functional but 6-311++G(d,p) and solvation model based on density, concluded the same result [23]. It supports the recommendation by Zhao et al. [32, 33] that M05-2X is reliable for studying the scavenging reaction energetically.

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 are 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 later. These results support the experimental findings which reported that gnetin C has better antioxidant capacity than trans-resveratrol in ORAC assay [40]. Furthermore, by considering the ring in gnetin C, ring C provides more scavenging sites than other rings

Table 2 The calculation results of the standard Gibbs free energy of reaction ($\Delta_r G^0$, in kcal/mol) and activation ($\Delta^{\ddagger} G^0$, in kcal/mol) for the •OOH scavenging reaction based on Eq. (1)

Molecule	Reaction site	$\Delta_r G^{0a}$	$\Delta^{\ddagger} G^{0a}$	$\Delta^{\ddagger} G^{0b}$
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	n/a[c]
	11-OH	2.69	21.55	n/a
	4′-OH	0.86	19.86	n/a
	11′-OH	4.03	21.29	n/a
	13′-OH	3.07	21.72	n/a
	7′-CH	-2.43	22.14	n/a
	8′-CH	-5.02	20.85	n/a

The values in column 3 and 4 are obtained from our calculations. The values from Iuga's calculations [24] in column 5 are used as benchmark for $\Delta^{\ddagger} G^0$

[a]Using M05-2X/6-31++G(d,p), this work.

[b]Using M05-2X/6-311++G(d,p), reported by Iuga et al. [24].

[c]n/a means not available value.

(A, phenol, and B, resorcin ring). It indicates that furan ring plays a more important role than other rings in the scavenging capacity of melinjo resveratrol.

Overall, ring A always provides the lowest $\Delta_r G^0$ value for OH site. It is valid for both trans-resveratrol and gnetin C. It implies, there is a relation between the position of the OH site and the $\Delta_r G^0$. Queiroz et al. [41] also reported this relation.

The Standard Gibbs Energy of Activation

We validate our work on reaction kinetics based on the trans-resveratrol case. Our predictions of $\Delta^{\ddagger} G^0$ are comparable with a theoretical work reported by Iuga et al. [24] (see Table 2), which computed the rate constants at room temperature with the basis of transition-state theory, whose results are comparable with the experimental results by Zinatullina et al. [42]. Consequently, our density-functional calculations on Eq. (1) is adequate to study •OOH scavenging by resveratrol system such as gnetin C.

Regarding gnetin C, Figure 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 shown in the optimized structure in Fig. S1 (~~Online Resource~~ 1). 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.

The $\Delta^{\ddagger} G^0$ values of gnetin C in Table 2 show that the lowest $\Delta^{\ddagger} G^0$ is at site 4-OH. The site 4-OH in trans-resveratrol also has the lowest activation energy. These results agree with the previous experimental findings reporting that site 4-OH is the most reactive one in trans-resveratrol and its derivatives [43]. However, $\Delta^{\ddagger} G^0$ 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 $\Delta_r G^0$, the $\Delta^{\ddagger} G^0$ values at OH-group also has a relation with its location. Both site 4-OH and 4′-OH have the lowest $\Delta^{\ddagger} G^0$ 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 the scavenging reactivity of an OH site.

Considering the $\Delta_r G^0$ 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 that of at 4-OH site due to their higher value of $\Delta^{\ddagger} G^0$. The high barrier is expected since geometrically ring A2 and B2 hinder •OOH to reach site 7′ and 8′. The various value of $\Delta^{\ddagger} G^0$ 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 gradual increase in scavenging activity was observed in the

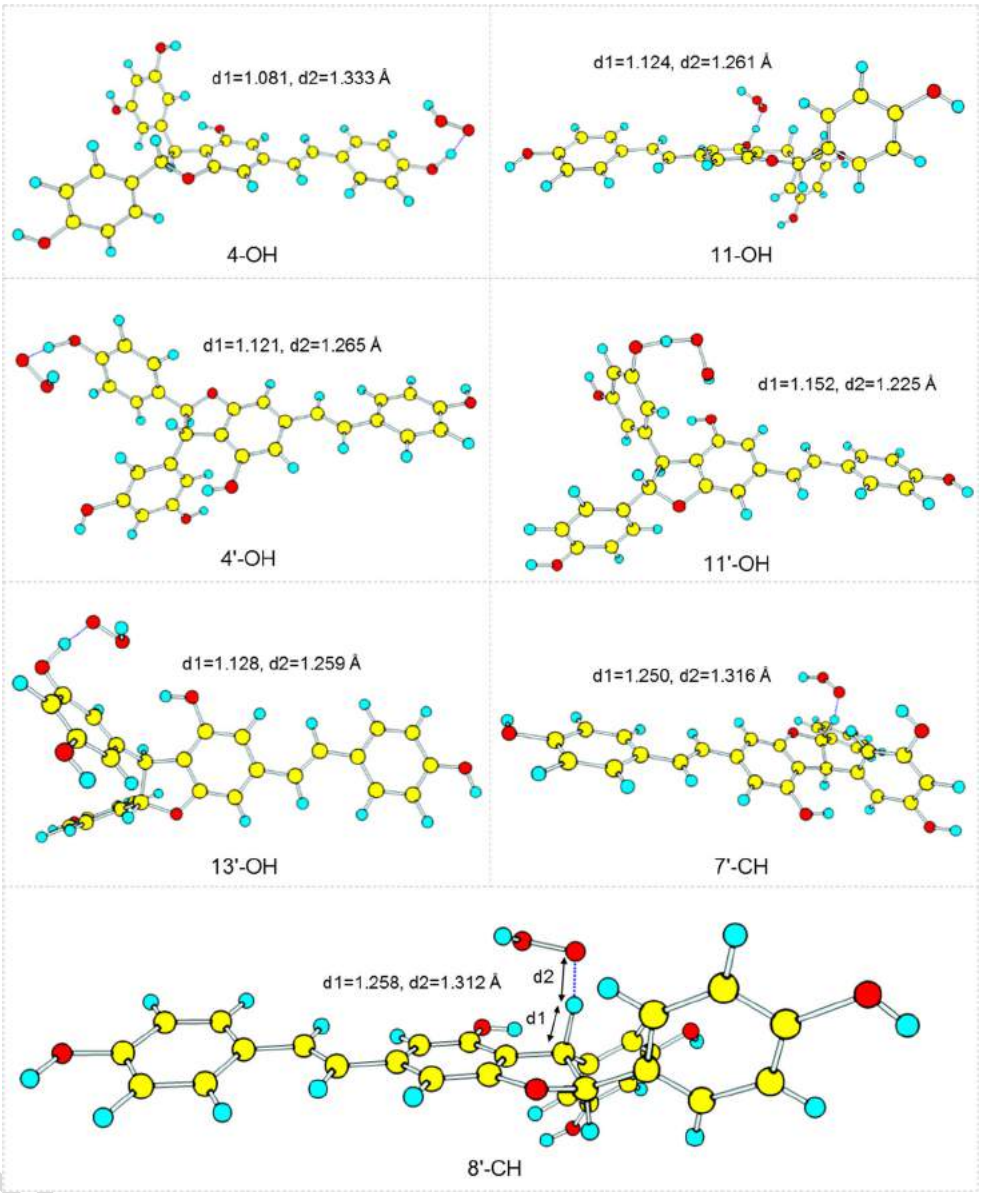

Fig. 4 TS structure for •OOH scavenging reaction by gnetin C on each site. Markers d1 is bond length of scavenging site, while d2 is the distance between O atom of •OOH with the nearest scavenging site

experiment done by Kato et al.[1]. However, this finding is contrary to their speculation proposing that it is ring B2 (resorcinol) that plays a crucial role ~~n~~ 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 another [30]. It implies that the •OOH scavenging at the three sites of gnetin C through the reaction in Eq. (1) is a hydrogen atom transfer.

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 as the one playing a crucial role in the scavenging activity of melinjo resveratrol, not the resorcin ring as has been speculated in the experimental study. Finally, this work demonstrates that density-functional calculations are a prospective approach for studying the system in question.

Supplementary Information The online version contains supplementary material available at 10.1007/s11483-021-09666-y.

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Author Contributions Conceptualization: Febdian Rusydi; Methodology: Febdian Rusydi and Vera Khoirunisa; Formal analysis: Vera Khoirunisa, Lusia Silfia Pulo Boli; Investigation: Vera Khoirunisa; Writing - original draft preparation: Vera Khoirunisa; Writing - review and editing: Febdian Rusydi, Heni Rachmawati and Hermawan Kresno Dipojono; Resources: Hideaki Kasai and Hiroshi Nakanishi.

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Author(s) [Please list all named Authors]:	Febdian Rusydi, Vera Khoirunisa, Lusia S. P. Bol, Adhitya G. Saputro, Heni Rachmawati, Hiroshi Nakanishi, Hideaki Kasai, Hermawan K. Dipojono	(the 'Author')
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ORIGINAL ARTICLE

Computational Investigation on the •OOH Scavenging Sites of Gnetin C

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Abstract
Melinjo seed extract contains melinjo resveratrol compounds that has antioxidant activity. The radical-scavenging sites required for the antioxidant activity, however, is yet to be located. We report a computational study that aims 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, trans-resveratrol, 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 propose 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

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 needed 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

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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, DFT can 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 a reliable method 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 ($^{\bullet}$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.

Computational Model

Scavenging Reaction Model

The one-step reaction mechanism models the $^{\bullet}$OOH scavenging by melinjo resveratrol (YH) has been suggested to be the preferable mechanism of phenolic antioxidants [25–27]. The reaction is as follows:

$$\mathrm{X} + \mathrm{YH} \rightarrow [\mathrm{X} - \mathrm{H} - \mathrm{Y}] \rightarrow \mathrm{XH} + \mathrm{Y}. \tag{1}$$

In our case, X is $^{\bullet}$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.

The [X - H - Y] activated complex is the TS. It is the state where the hydrogen atom transfer (HAT) from melinjo resveratrol to $^{\bullet}$OOH occurs. While the energy difference between product (XH and Y) and reactant (X and YH) describes the reaction energy (E_r), the energy difference between TS and reactant determine the barrier energy (E_b).

The H in [X – H – Y] activated complex may derive from 22 possible sites of gnetin C [see Fig. 1(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,

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

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 H donation from the site.

Density-Functional Calculation

The primary quantities here are 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 [29]. 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 $^{\bullet}$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 ($\Delta_r G^0$) and activation ($\Delta^{\ddagger} G^0$), 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

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

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. 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 [30].

In using the DFT method, we employ M05-2X exchange-correlation functional and 6-31++G(d,p) basis set that are integrated into the Gaussian 09 software [31]. M05-2X functional has been recommended for thermochemistry and kinetic calculations [32, 33], and has performed well to predict internuclear distance at the TS, especially for hydrogen transfer reaction [34].

We couple DFT calculation with the polarized continuum model (PCM) [35, 36] for considering the solvent environment. PCM has been applied successfully to a significant number of systems in aqueous and non-aqueous media [36–39]. In this work, we consider water solvent since it is the primary cellular environment component.

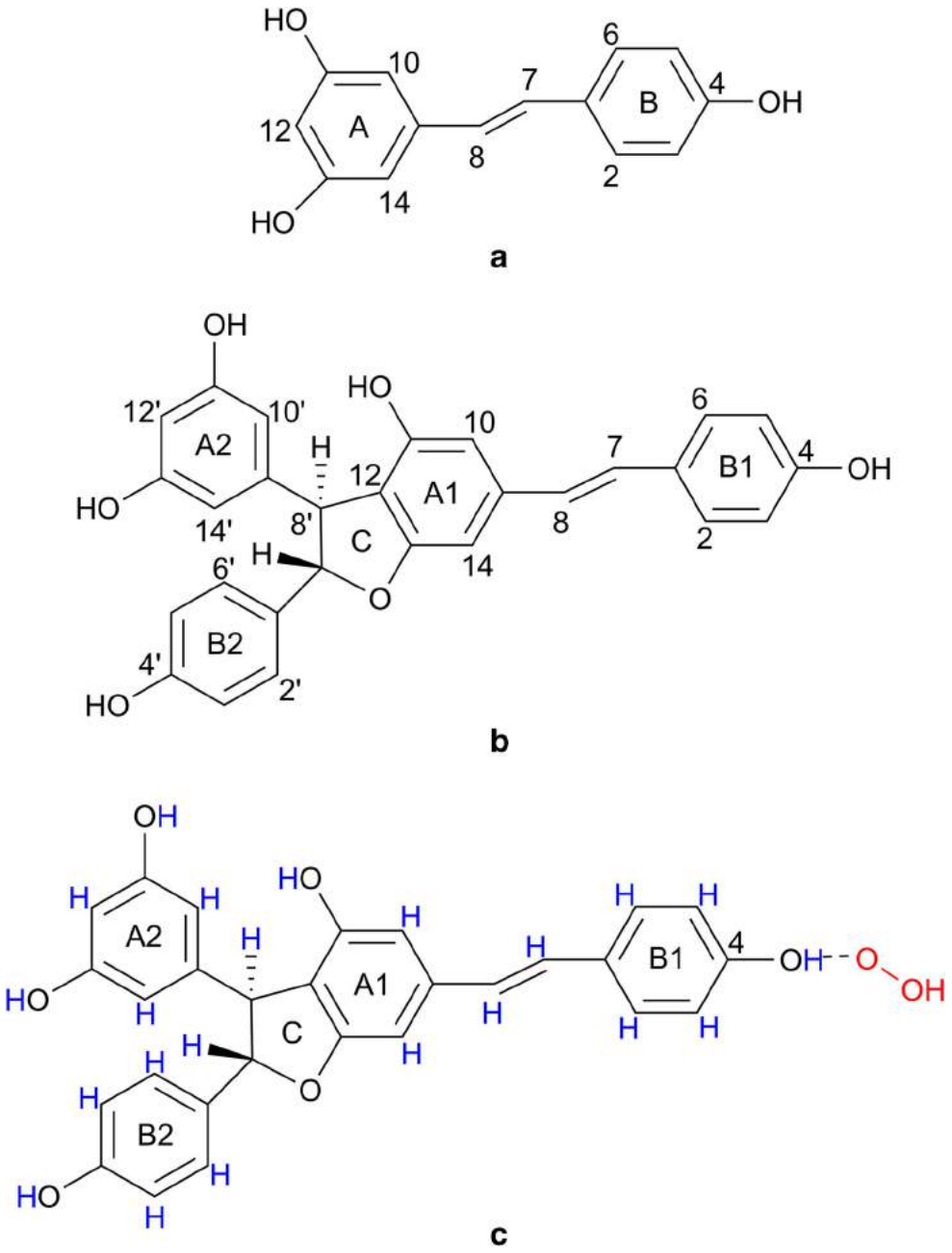

Fig. 1 Molecular model for **a** trans-resveratrol, **b** gnetin C, and **c** activated complex of gnetin C and •OOH for 4-OH site. The nomenclature is used throughout manuscript. A, B, C, are resorcinol, phenol, and furan rings in resveratrol system respectively. Red atom and blue atom labels indicate •OOH and the 22 possible scavenging sites respectively

Result and Discussion

The Bond Dissociation Energy

Figure 2 shows the optimized geometry for trans-resveratrol and gnetin C, while Table S1 (Supplementary Materials) 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).

Table 1 shows the ΔBDE* in all possible sites of trans-resveratrol and gnetin C based on Fig. 1. Overall, ΔBDE* in the O-H site is less than that in the C-H site in both molecules. Interestingly, 7′-CH and 8′-CH sites of gnetin C have comparable ΔBDE* with the O-H sites. The lower ΔBDE* in 7′-CH and 8′-CH sites is explained by the contribution of sp^n hybrid in their bonding orbital (as shown in Table S2, Supplementary Materials). The C-H bond in these sites has n≈3, instead of n≈2 as the other C-H bonds in gnetin C. It suggests that the weaker sp^3 bonding than sp^2 bonding is the reason of the lower ΔBDE* in 7′-CH and 8′-CH sites. Therefore, we consider 7′-CH and 8′-CH

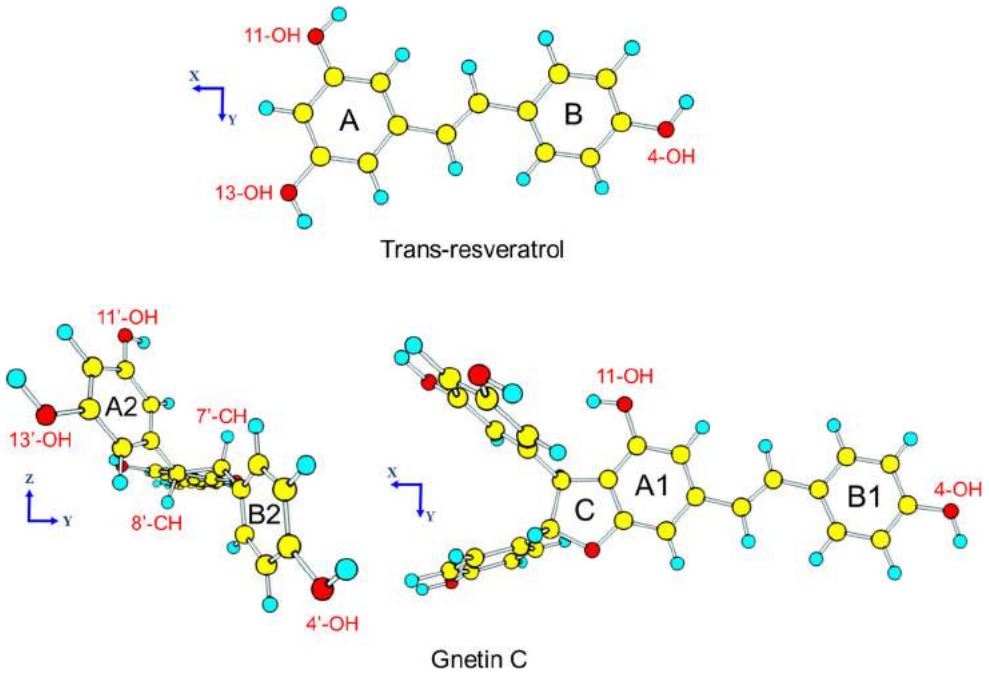

Fig. 2 Optimized structure of trans-resveratrol and gnetin C in water environment. Blue, red, and yellow atoms represent H, O, and C atom. Red marker indicates scavenging site

for the scavenging sites of gnetin C in addition to the OH sites.

The spin density plots in Fig. 3 shows the stability of gnetin C radical. The most stable radical is 8′-C gnetin C radical since the spin density covers two resorcinol and one furan ring. The stability of the radical reduces as the number of rings covered decreases. The second and third most stable radicals are 4′-O and 7′-C gnetin C radical. The former has two rings covered, while the latter has one and a half rings covered. The stability of 8′-C, 4′-O, and 7′-C radicals are inversely proportional to the ΔBDE* at site 8′-CH, 4′-OH, and 7′-CH. Therefore, the stability of gnetin C radical

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

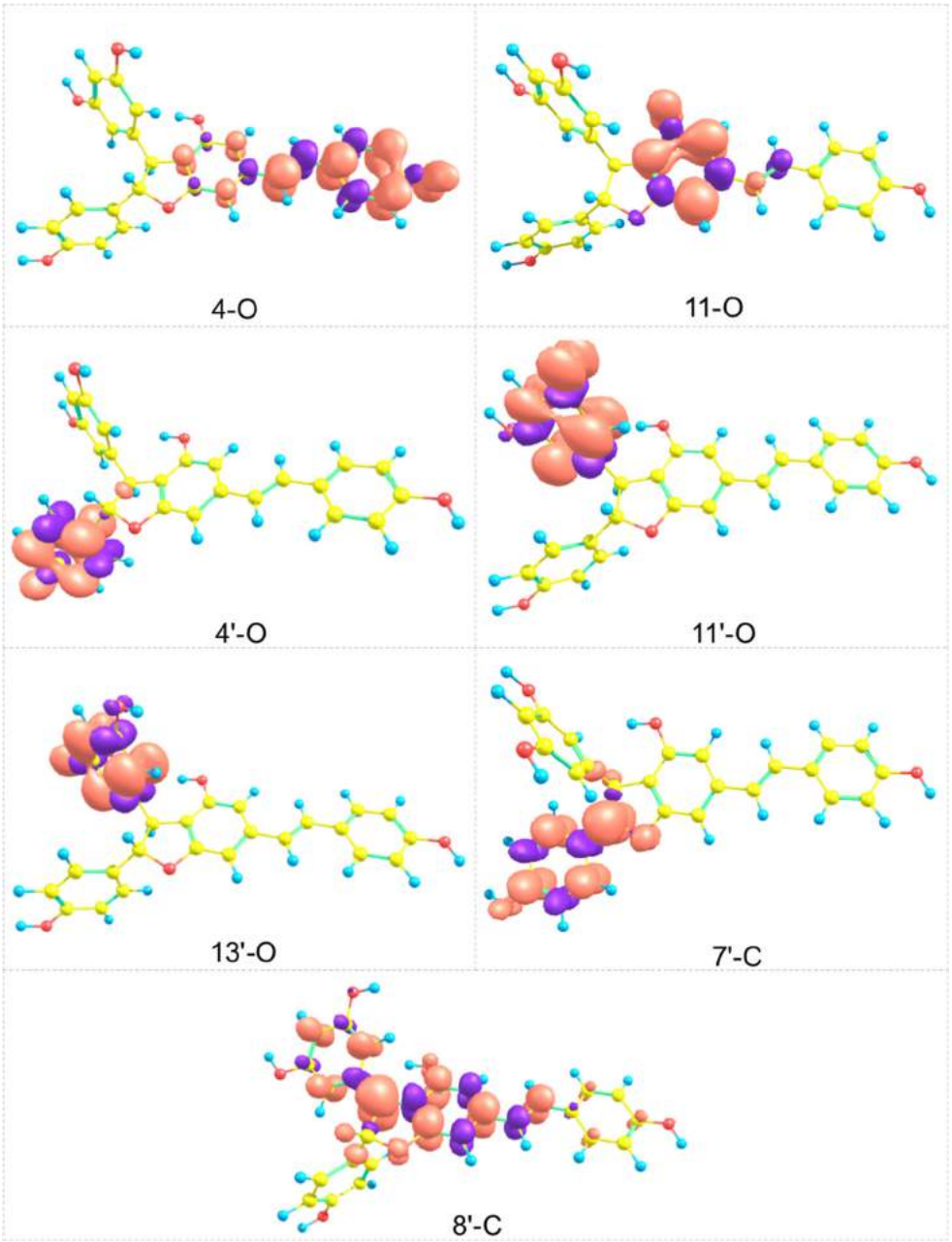

Fig. 3 The spin density distribution of gnetin C radical with isovalue 0.003. Orange and purple colors indicate α and β densities are dominant, respectively

supports the hydrogen atom transfer process in site 8′-CH, 4′-OH, and 7′-CH.

The Standard Gibbs Energy of Reaction

Table 2 provides the $\Delta_r G^0$ 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 on the identical system, employing the same exchange-correlation functional but 6-311++G(d,p) and solvation model based on density, concluded the same result [23]. It supports the recommendation by Zhao et al. [32, 33] that M05-2X is reliable for studying the scavenging reaction energetically.

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 are 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 later. These results support the experimental findings which reported that gnetin C has better antioxidant capacity than trans-resveratrol in ORAC assay [40]. Furthermore, by considering the ring in gnetin C, ring C provides more scavenging sites than other rings

Table 2 The calculation results of the standard Gibbs free energy of reaction ($\Delta_r G^0$, in kcal/mol) and activation ($\Delta^{\ddagger} G^0$, in kcal/mol) for the $^{\bullet}$OOH scavenging reaction based on Eq. (1)

Molecule	Reaction site	$\Delta_r G^{0a}$	$\Delta^{\ddagger} G^{0a}$	$\Delta^{\ddagger} G^{0b}$
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	n/a[c]
	11-OH	2.69	21.55	n/a
	4′-OH	0.86	19.86	n/a
	11′-OH	4.03	21.29	n/a
	13′-OH	3.07	21.72	n/a
	7′-CH	-2.43	22.14	n/a
	8′-CH	-5.02	20.85	n/a

The values in column 3 and 4 are obtained from our calculations. The values from Iuga's calculations [24] in column 5 are used as benchmark for $\Delta^{\ddagger} G^0$

[a]Using M05-2X/6-31++G(d,p), this work.

[b]Using M05-2X/6-311++G(d,p), reported by Iuga et al. [24].

[c]n/a means not available value.

(A, phenol, and B, resorcin ring). It indicates that furan ring plays a more important role than other rings in the scavenging capacity of melinjo resveratrol.

Overall, ring A always provides the lowest $\Delta_r G^0$ value for OH site. It is valid for both trans-resveratrol and gnetin C. It implies, there is a relation between the position of the OH site and the $\Delta_r G^0$. Queiroz et al. [41] also reported this relation.

The Standard Gibbs Energy of Activation

We validate our work on reaction kinetics based on the trans-resveratrol case. Our predictions of $\Delta^{\ddagger} G^0$ are comparable with a theoretical work reported by Iuga et al. [24] (see Table 2), which computed the rate constants at room temperature with the basis of transition-state theory, whose results are comparable with the experimental results by Zinatullina et al. [42]. Consequently, our density-functional calculations on Eq. (1) is adequate to study $^{\bullet}$OOH scavenging by resveratrol system such as gnetin C.

Regarding gnetin C, Figure 4 shows the TS of $^{\bullet}$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 shown in the optimized structure in Fig. S1 (Supplementary Materials). It is also noteworthy that the distance between the H-atom of gnetin C and its scavenging site elongates to 0.16 $\AA$ 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.

The $\Delta^{\ddagger} G^0$ values of gnetin C in Table 2 show that the lowest $\Delta^{\ddagger} G^0$ is at site 4-OH. The site 4-OH in trans-resveratrol also has the lowest activation energy. These results agree with the previous experimental findings reporting that site 4-OH is the most reactive one in trans-resveratrol and its derivatives [43]. However, $\Delta^{\ddagger} G^0$ 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 $^{\bullet}$OOH than its monomer form.

As for $\Delta_r G^0$, the $\Delta^{\ddagger} G^0$ values at OH-group also has a relation with its location. Both site 4-OH and 4′-OH have the lowest $\Delta^{\ddagger} G^0$ 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 the scavenging reactivity of an OH site.

Considering the $\Delta_r G^0$ 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 that of at 4-OH site due to their higher value of $\Delta^{\ddagger} G^0$. The high barrier is expected since geometrically ring A2 and B2 hinder $^{\bullet}$OOH to reach site 7′ and 8′. The various value of $\Delta^{\ddagger} G^0$ make the three sites scavenge three $^{\bullet}$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 gradual increase in scavenging activity was observed in the

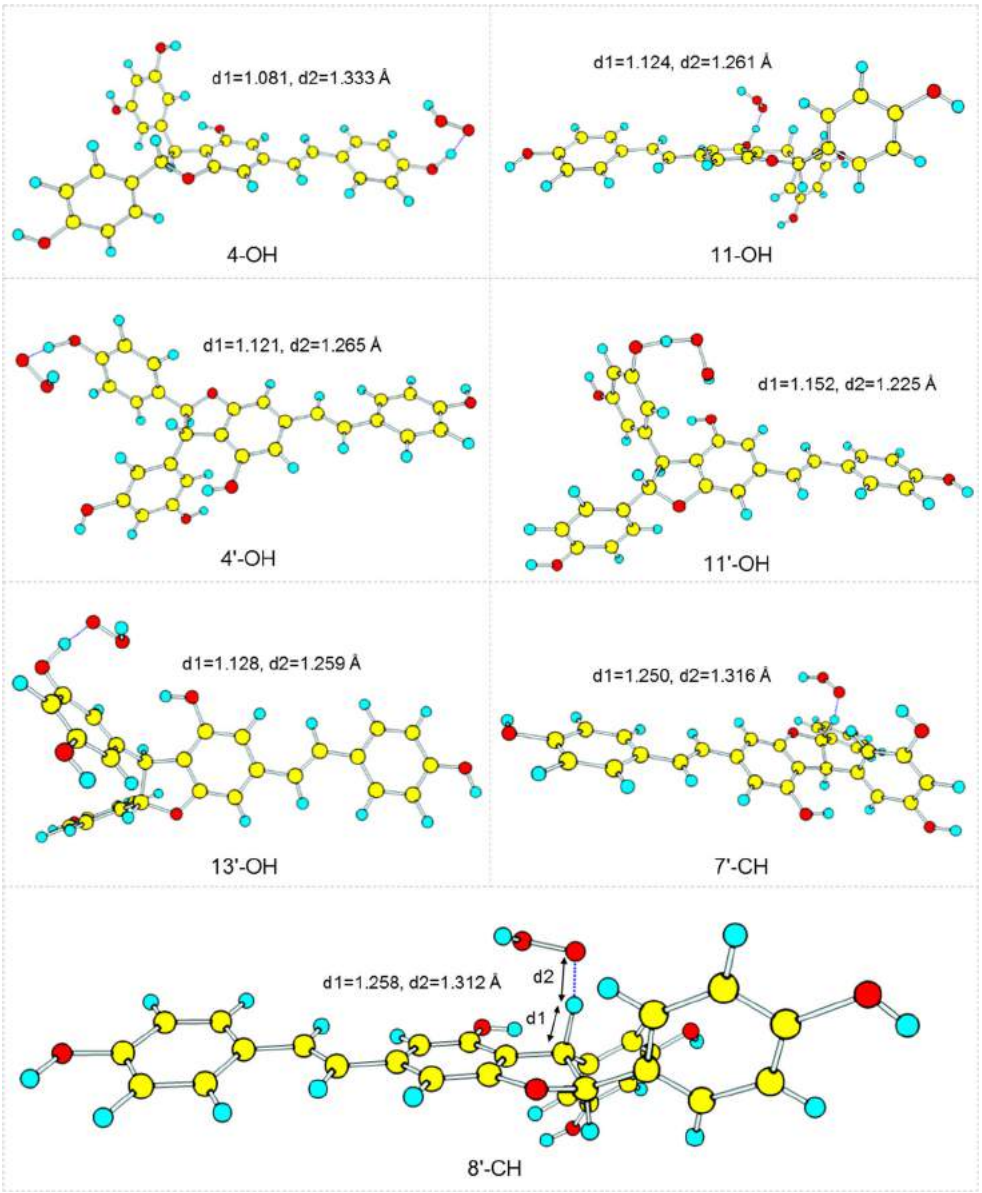

Fig. 4 TS structure for •OOH scavenging reaction by gnetin C on each site. Markers d1 is bond length of scavenging site, while d2 is the distance between O atom of •OOH with the nearest scavenging site

experiment done by Kato et al.[1]. However, this finding is contrary to their speculation proposing 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 (Supplementary Materials). 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 another [30]. It implies that the •OOH scavenging at the three sites of gnetin C through the reaction in Eq. (1) is a hydrogen atom transfer.

Conclusion

We have demonstrated the use of a density-functional calculations 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 as the one playing a crucial role in the scavenging activity of melinjo resveratrol, not the resorcin ring as has been speculated in the experimental study. Finally, this work demonstrates that density-functional calculations are a prospective approach for studying the system in question.

Supplementary Information The online version contains supplementary material available at 10.1007/s11483-021-09666-y.

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Author Contributions Conceptualization: Febdian Rusydi; Methodology: Febdian Rusydi and Vera Khoirunisa; Formal analysis: Vera Khoirunisa, Lusia S. P. Boli; Investigation: Vera Khoirunisa; Writing - original draft preparation: Vera Khoirunisa; Writing - review and editing: Febdian Rusydi, Adhitya G. Saputro, Heni Rachmawati and Hermawan K. Dipojono; Resources: Hideaki Kasai and Hiroshi Nakanishi.

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