

STUDIES ON THE ANTIOXIDANT ACTIVITY OF APIGENIN, LUTEOLIN AND NEVADENSIN USING DFT[#]

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Abstract. The molecular properties of apigenin, luteolin and nevadensin which are three naturally flavonoid compounds have been studied theoretically by DFT method at 6-311++G(d,p) level. All FMO analysis, mechanism, and kinetics studied suggested that compound luteolin (**3**) was a promising antioxidant agent. The results indicated that HAT is thermodynamically preferred in the gas phase, and SPLET is the thermodynamically favorable pathway in methanol and water.

Keywords: DFT, flavonoids, HAT, SET-PT, SPLET, antioxidant.

Classification numbers: 1.1.3, 1.2.1.

1. INTRODUCTION

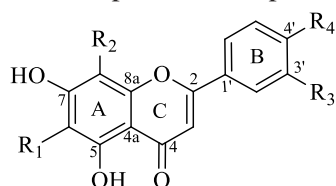
Free radicals such as hydroxy, superoxide anion, alkoxy and peroxy are harmful compounds in living organisms. They can attack biomolecules such as proteins, lipids, carbohydrates and nucleic acid and cause damages to tissues, cell membranes and DNA [1 - 3]. Consequently, these oxidative damages can result in various diseases such as asthma, cardiovascular disease, cancer, and aging [4 - 6].

Flavonoids are naturally occurring compounds and classified as polyphenolic chemicals, including two benzene rings and a pyrene ring. These compounds are widely distributed in foods such as fruits, vegetables, cereals, teas, wines, honey, and bee pollen and thus are important constituents of the human diet [7]. This class of organic compounds possesses various biological activities such as antibacterial, antiviral, anti-inflammatory and anti-ischemic activities [8 - 11].

[#] This paper is dedicated to the 40th anniversary of Institute for Tropical Technology if accepted for publication

But their most important biological activity is antioxidant potential. This activity involves free radical scavenging or free radical trapping processes [12 - 14].

Apigenin, luteolin, and nevadensin are the representatives among flavonoids. The structures of studied compounds with atom numbering are shown in Figure 1. Apigenin is a natural flavonoid found in many plants such as parsley, celery, celeriac, and chamomile tea. The antioxidant activity of this compound and its chelation has been well reported [15 - 17]. The flavonoid luteolin can be served for human diets from celery, broccoli, green pepper, parsley, thyme, dandelion, perilla, chamomile tea, carrots, olive oil, peppermint, rosemary, navel oranges, and oregano [17 - 18]. This compound exhibits potential antioxidant activities by scavenging free radicals as well as inducing the upregulation of the ARE-dependent phase [19]. Nevadensin is a natural flavonoid distributed in many plants and possesses various biological activities such as hypotensive, anti-inflammatory, antitubercular, antitumor, anticancer, and antimicrobial activities [20]. The *in vitro* nitric oxide, superoxide, and hydroxyl radical scavenging activity of this compound was reported by Narsu *et al.* [21].



Nevadensin (1) $R_1 = R_2 = R_4 = \text{OCH}_3$; $R_3 = \text{H}$
Apigenin (2) $R_1 = R_2 = R_3 = \text{H}$; $R_4 = \text{OH}$
Luteolin (3) $R_1 = R_2 = \text{H}$; $R_3 = R_4 = \text{OH}$

Figure 1. General structures of studied compounds with atom numbering.

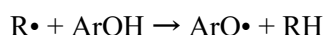
Despite the fact that apigenin, luteolin, and nevadensin are very popular and they play important role in human's diet, their antioxidant mechanism has not been fully revealed. This limitation mainly originates from the experimental conditions, and the theoretical aspects. There have been a number of studies on the structure, IR, Raman, NMR, UV spectrum as well as the antioxidant mechanism of these compounds [22 - 24]. However, there has not been a complete study of the relationship between antioxidant structure, antioxidant mechanisms, kinetics with the radical scavenging agents. The purpose of this study is to gain a better understanding of the antioxidant activity of these three flavonoids by using DFT model chemistry. We will compute and analyze in detail structural features, conformations and electronic properties of these compounds in three media, namely, gas, water, and methanol. The kinetic reaction between these compounds with DPPH and HOO radicals were computed using DFT calculations to discover the dynamic pathway for the radical scavenging treatment.

2. METHODOLOGY

All calculations are employed using the Gaussian 09 software package [25]. The B3LYP/6-311++G(d,p) was used to optimize the structures of studied compounds in the gaseous phase (dielectric constant, $\epsilon = 1.00$) and in the solvents water ($\epsilon = 78.35$), methanol ($\epsilon = 32.61$). To correct the zero-point energy (ZPE) and to confirm the presence of ground states lacking imaginary frequencies, vibrational frequencies were calculated at the same level of theory. The

integral equation formalism polarizable continuum model (IEF-PCM) has been employed for estimating solvent effects [26, 27].

Mechanistic studies have suggested three pathways for radicals scavenging property: HAT (H atom transfer), SET-PT (single electron transfer-proton transfer), and SPLET (Sequential Proton Loss Electron Transfer) [26-29]. The first mechanism, HAT, involves an H-atom transfer process, in which a hydrogen atom is removed from a flavonoid antioxidant compound to a free radical ($R\bullet$), which is illustrated as follows:



HAT mechanism can be characterized by the homolytic bond dissociation enthalpy (BDE) (1).

$$BDE = H(ArO\bullet) + H(H\bullet) - H(ArOH) \quad (1)$$

The second mechanism, SET-PT, undergoes an electron transfer process, in which the antioxidant donates an electron to the free radical.



In this mechanism, the ionization potential (IP) is found to be an essential factor to estimate the radical scavenging activity (2).

$$IP = H(ArOH^{+\bullet}) + H(e) - H(ArOH) \quad (2)$$

In the third mechanism, SPLET, flavonoids is deprotonated to form a typical anion, and subsequent electron transfer from this anion occurs.



Proton affinity (PA) and electron transfer enthalpy (ETE) are two key parameters that correspond to deprotonation and electron transfer (3).

$$PA = H(ArO^-) + H(H^+) - H(ArOH) \quad (3)$$

In these equations, $H(ArOH)$, $H(ArO\bullet)$, (ArO^-) , $H(ArOH^{+\bullet})$, $H(H\bullet)$, $H(H^+)$, $H(e)$ are the enthalpies of parent compound, radical $ArO\bullet$, anion ArO^- , radical cation $ArOH^{+\bullet}$, hydrogen radical atom, proton and electron, respectively. The calculated gaseous-phase enthalpy values of $H(e)$ and $H(H^+)$ are $0.75 \text{ kcal mol}^{-1}$ and $1.48 \text{ kcal mol}^{-1}$, respectively. The IEF-PCM model gave values of $25.08 \text{ kcal mol}^{-1}$ and $244.15 \text{ kcal mol}^{-1}$ in water, $20.54 \text{ kcal mol}^{-1}$ and $247.97 \text{ kcal mol}^{-1}$ in methanol, respectively [29].

The rate constant k in the radical reactions with DPPH and $HOO\bullet$ agents was calculated based on the conventional transition state theory, which can be described as follows:

$$k(T) = \kappa \frac{T \cdot k_B}{h} e^{\frac{-\Delta G^\ddagger}{RT}}$$

where κ , T , k_B and h are the Wigner coefficient, temperature, Boltzmann constant and Planck constants, respectively. The Gibbs activation energy ΔG^\ddagger was obtained at 298.15 K and demonstrated the differential energy between reactant and transition states.

3. RESULT AND DISCUSSION

3.1 Geometrical and FMO analysis

To determine all possible conformers of all studied compounds, we perform the potential energy surface (PES) scans around dihedral C3-C2-C1'-C2' by changing the torsion angle from -

180° to 180° in the step of 10° at the B3LYP/6-311G(d,p) level. The results show that the minimization procedure for all the studied compounds is found at around 15°. The same results between these compounds can be explained by the similarities of the structures. All compounds do not have any methyl and OH groups and at positions C3 and C2'. The interaction between C and B rings is done through conjugation for all compounds. The barrier between the maximum and minimum energy are found to be 4.5 kcal/mol at around 100° for all compounds, indicating that the stability at this angle is least for all studied compounds.

The optimized parameters of all studied compounds are calculated in the gas, methanol and water medium by using the minimum conformal as the initial input at the B3LYP/6-311++G(d,p) level.

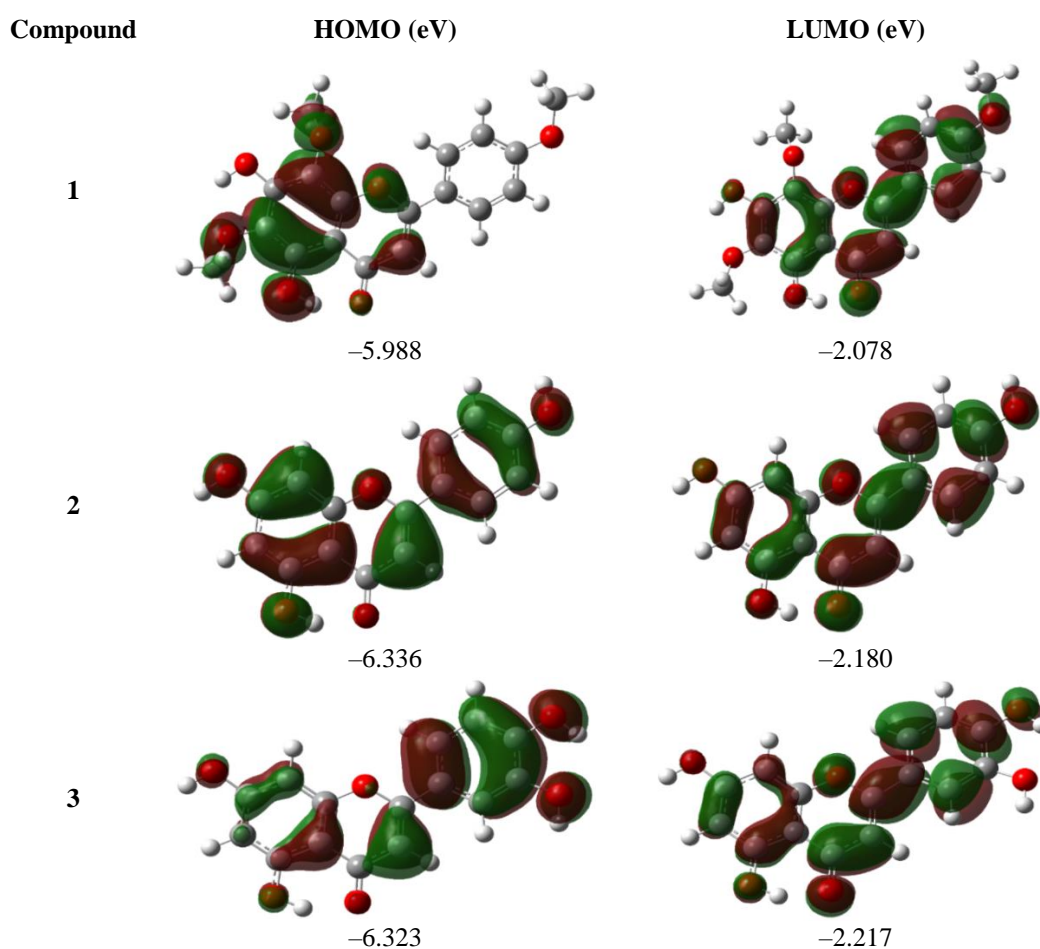


Figure 2. Neutral HOMO, LUMO images and its value of studied compounds in gas medium.

The stabilization of neutrals and radicals after proton abstraction depends on π -electron delocalization. Considering the frontier molecular orbital distribution would not only help to explain the relationship between neutral and radical forms in terms of the electron contribution but also support the identification of donor-acceptor reactive sites [29]. The energy HOMO orbital level plays an essential role in describing the free radical scavenging activities of studied compounds. The higher energy of the HOMO orbital (more positive), the stronger electron-

donating ability [27 - 29]. HOMO and LUMO of neutral images and frontier orbital energies of **1-3** are shown in Figure 2. The computed HOMO energy level for compounds **1, 2, 3** are -5.99 ; -6.23 ; -6.24 in gas, respectively. This clearly confirms that compound **1** has the strongest electron-donating capability among the studied compounds. The neutral HOMO and LUMO show that the electrons delocalized over the whole of each compound, except for the HOMO of **1**. It can be explained by the lacking of the OH group on ring B of this compound. Although compound **3** has two OH groups on ring B and the same on ring A, the HOMO orbitals are mainly localized on ring B. These results indicate that the OH groups on ring B are responsible for the free radical activities. The low energy of the LUMO in flavonoid compounds indicates that the compounds to be more powerful inhibitors of mutagenesis indicate that they can behave as soft electrophiles.

3.2. Antioxidant mechanism

3.2.1. HAT mechanism

Table 1. Studied phases reaction enthalpies for radical of compounds **1, 2, 3** at B3LYP/6-311++G(d,p) (in kcal.mol⁻¹).

Compound	Bonds	Solvent	HAT	SET-PT		SPLET	
			BDE	IP	PDE	PA	ETE
1	5-OH	Gas	91	155	252	346	60
		Water	84	106	26	52	80
		Methanol	87	111	22	49	83
	7-OH	Gas	83	155	244	330	69
		Water	80	106	22	42	85
		Methanol	82	111	17	39	89
2	4'-OH	Gas	83	177	222	323	76
		Water	82	117	13	42	88
		Methanol	84	122	8	38	92
	5-OH	Gas	106	177	245	347	74
		Water	92	117	23	52	87
		Methanol	95	122	19	50	91
	7-OH	Gas	87	177	226	329	74
		Water	86	117	17	41	92
		Methanol	88	122	12	39	96
3	3'-OH	Gas	76	176	216	321	71
		Water	76	115	9	40	83
		Methanol	79	120	4	37	87
	4'-OH	Gas	83	176	223	326	73
		Water	79	115	12	43	84
		Methanol	81	120	7	38	89
	5-OH	Gas	99	176	239	347	68
		Water	92	115	25	52	87
		Methanol	94	120	20	49	91
	7-OH	Gas	88	176	228	329	74
		Water	86	115	18	41	92
		Methanol	88	120	14	38	96

To determine the activity of an antioxidant via hydrogen donating mechanism, the O-H homolytic BDEs that relate to the ability to donate hydrogen atom and form radical species, are taken into account. The lowest BDE value is indicated for O-H's relevant position where the easiest hydrogen for free radical scavenging reaction can occur [30, 31].

The computed values of $BDE < IP < PA$ showed in Table 1 indicated that these compounds can easily transfer the H-atom in the gas phase than non-polar solvents (methanol and water). In the gas phase, BDE values (83 – 91 kcal.mol⁻¹) are significantly lower than those of IP (155 kcal.mol⁻¹) and PA (330 – 346 kcal.mol⁻¹) for compound **1**. This behavior is also similarly established from the remainder like **2** – **3**. In the other way, the HAT mechanism gets more favor in the gas phase for all studied compounds. **3** – 3'-OH radical has the smallest enthalpy BDE value of 76 kcal.mol⁻¹, the next rank belongs to **3** – 4'-OH, **2** – 4'OH and **1** – 7-OH (83 kcal.mol⁻¹). The smallest BDE value of **3**-3'OH is related to the fact that a hydrogen bond exists between a hydrogen atom in C4'-OH group and the oxygen atom in C3'-OH group leading the O-H to become more polarized and easily break. The largest enthalpy BDE values are found in 5-OH for all compounds by 91, 106, 99 76 kcal.mol⁻¹ for **1**, **2**, **3**, respectively, indicating that 5OH sites should not be the suitable sites for radical scavenging. The largest enthalpy BDE value of 5-OH can be explained by the influence of intramolecular hydrogen bonds between 5-OH and 4-CO. It can be seen that ring B of isoflavones is an active center in antioxidant activity due to the small BDE values of 3'-OH and 4'-OH. It is in accordance with various research on flavonoids that phenyl unit ring B is a suitable site for the radicals forming more than A-ring [27 - 31].

3.2.2. SET-PT and SPLET mechanism

It is well known that SET-PT and SPLET mechanisms may act as the key role in the free radical scavenging reaction of flavonoid derivatives [28, 34]. The SETPT mechanism, which is characterized by the IP and the PDE, is also considered to evaluate the antioxidant properties of the studied compounds and compare it to the order obtained based on the HAT mechanism. According to the SETPT mechanism, ionization of the molecule, which is the first step, plays an important role, so the IP is used to describe the electron donor ability. The lower the IP value, the easier the electron transfer and the higher the antioxidant activity. The potential for the SPLET mechanism, which is defined by the PA and ETE, was also determined. The SPLET mechanism starts with the dissociation of the acidic moiety, which can be characterized by the PA. Lower PA is characteristic of higher antioxidant capacity *via* this mechanism. On the basis of inspection of data from Table 1, it is clear that the SPLET mechanism is dominant in both methanol and water phases because the PA values are significantly lower than corresponding IP and BDE values. From the data in Table 1, it is observed that the IP value of compound **1** is significantly lower than those of **2**, **3** in both gas and solvents. This behavior shows a good agreement with the analysis of FMO above. The calculated PA values for studied compounds in methanol and water are near the same with the maximum difference of only 5 kcal.mol⁻¹. The computed PA values in the gas phase for all studied compounds range from 321 - 347 kcal.mol⁻¹. In the meantime, in the polar solvent (methanol and water), one observed a dramatic decrease in PAs by comparison with the values calculated in the gas phase. The calculated PA values in the water and methanol solvents for all compounds are found from 37 to 52 kcal.mol⁻¹. This phenomenon can be explained by the higher solvation enthalpy of proton in water and methanol compared to that in the gas phase, and also it is in good agreement with the results obtained in previous researches [28 - 29, 32 - 34]. In other words, the deprotonation process of an antioxidant is favored in polar solvents. Once again, the **3**-4'-OH site has not only the smallest

BDE but also the smallest PA values. It indicates that this site is the most active for the antioxidant reaction.

Regarding the ETE which determine the electron-donating ability of anion formed, it can be seen that the ETE values are relatively lower than IP values for all sites of all studied compound. It indicates that the electron transfer from anion is more suitable than that from the neutral one.

Overall, among the three mechanisms, HAT is thermodynamically preferred in the gas phase, and SPLET is the thermodynamically favorable pathway in methanol and water. These results were in good agreement with other related previous studies [22 - 24].

3.3. The kinetic reaction of the radical scavenging

DPPH radicals are familiar agents in experiment laboratories to determine the efficacies of natural products in antioxidant targets. Besides, hydrogen peroxide ($\text{HOO}\cdot$) is generated from the various chemical reactions of our organism. The kinetic reaction between **1**, **2**, **3**, and these agents are computed using DFT calculations to discover the dynamic pathway for the radical scavenging treatment (Figure 3 and Table 2).

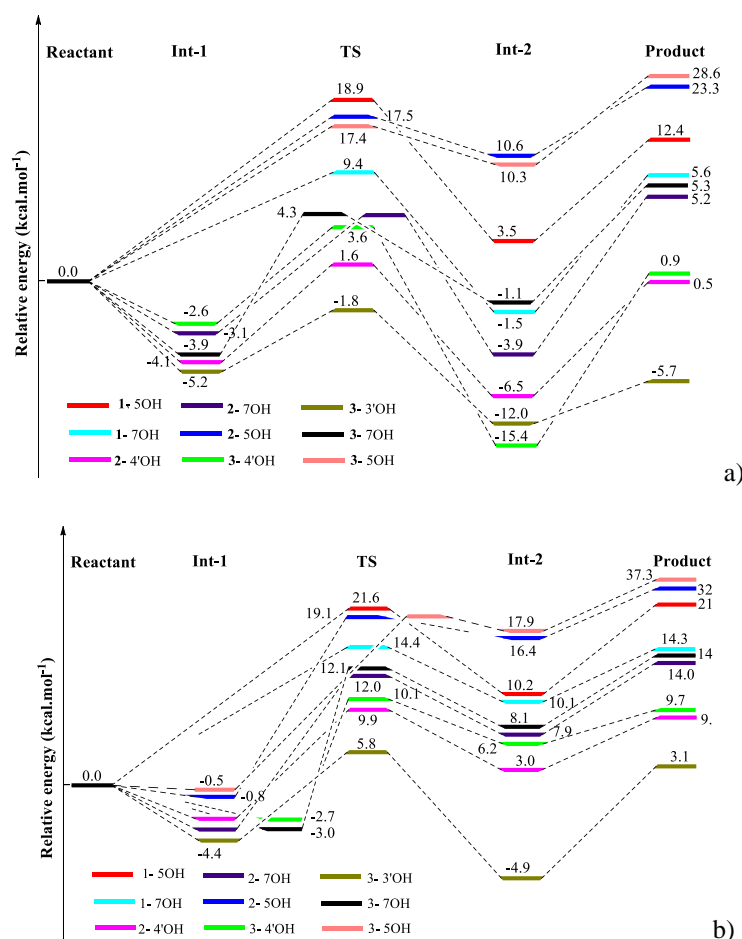


Figure 3. Energy diagram for the reaction of $\text{HOO}\cdot$ (a) and DPPH radical attack to the studied compounds at B3LYP/6-311G(d,p)//6-311++G(d,p).

Table 2. The calculated $\Delta G^\ddagger_{(\text{barier})}$ and k in the gaseous phase at B3LYP/6-311G(d,p)//6-311++G(d,p).

Compound	Bonds	HOO•		DPPH	
		$\Delta G^\ddagger_{(\text{barier})}$	k	$\Delta G^\ddagger_{(\text{barier})}$	k
1	5-OH	18.9	1.57×10^4	21.6	9.58×10^2
	7-OH	9.4	4.09×10^8	14.4	1.81×10^6
2	4'-OH	5.7	2.01×10^{10}	12.6	1.28×10^7
	5-OH	17.5	7.69×10^4	19.1	1.04×10^4
	7-OH	7.4	3.33×10^9	15.0	8.55×10^5
3	3'-OH	3.4	2.41×10^{11}	10.2	1.61×10^8
	4'-OH	6.3	1.11×10^{10}	12.7	1.10×10^7
	5-OH	17.4	8.30×10^4	19.1	1.03×10^4
	7-OH	8.2	1.44×10^9	15.1	8.05×10^5

In agreement with the highest BDE enthalpies, 5-OH of all compounds exhibited not only the highest ΔG^\ddagger but also the lowest k in both reactions with DPPH and HOO• radicals. The calculated ΔG^\ddagger of 5-OH for **1**, **2**, **3** are 18.9; 17.5; 17.4 kcal.mol⁻¹ and 21.6; 19.1; 19.1 kcal/mol in reaction with HOO• and DPPH, respectively. The lowest k values are found at compound **1**, by 1.57×10^4 for HOO• and 9.58×10^2 for DPPH radical, thereby indicating that the interaction between the 5-OH positions of compound **1** and the radical was not facilities. It is interesting to note that the OH radicals in ring B (4'-OH of compound **2**, 3'-OH and 4'-OH of compound **3**) always exhibited lower ΔG^\ddagger and higher k values in comparison with those of OH radical on ring A and C. The highest k values are found at 3'-OH of compound **3**, by 2.41×10^{11} and 1.61×10^8 for HOO• and DPPH radical, respectively. It is in agreement with the FMO analysis above when the HOMO orbitals are mainly localized on ring B for all compounds.

4. CONCLUSION

The antioxidant ability of three flavonoid compounds has successfully been investigated by DFT method. The results indicated that the HAT pathway was most favorable in the antioxidant of these compounds in the gaseous phase but the SPLET model was preferentially closely in methanol and water solvents. All FMO analysis, mechanism, and kinetics studied suggested that compound **3** (at position 4'-OH) was a promising antioxidant agent. Our results provide necessary guidelines for future researches.

Abbreviations: DFT: Density functional theory, HOMO: Highest occupied molecular orbital, LUMO: Lowest unoccupied molecular orbital, BDE: Homolytic bond dissociation enthalpy, PDE: Heterolytic bond dissociation enthalpy, IP: Ionization potential, PA: Proton affinity, ETE: Electron transfer enthalpy, HAT: Hydrogen atom transfer, SET-PT: Single-electron transfer-proton transfer, SPLET: Sequential proton loss electron transfer.

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Authors contributions: Nguyen Trung Huy: Methodology. Nguyen Van Trang: Investigation. Nguyen Thi Xuyen: Formal analysis. Cao Thi Hong: Formal analysis. Vo Thi Kieu Anh: Formal analysis. Vu Quoc Thai: Formal analysis. Bui Van Cuong: Funding acquisition. Tran Thi Thanh Van: Formal analysis. Tran Dai Lam: Supervision. Nguyen Thi Hoan: Formal analysis. Phan Thi Thuy: Formal analysis. Trinh Quang Dung: Formal analysis.

Declaration of competing interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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