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Original Article

Host-Guest Interactions of α–Mangostin with (α,β,γ)–Cyclodextrins: Semi-Empirical Quantum Mechanical Methods of PM6 and PM7

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ABSTRACT

Objective: This study aimed to investigate the molecular interactions, geometrical properties, encapsulation process and calculated energy of the inclusion complexes system between α–mangostin (guest) with α–cyclodextrin, β–cyclodextrin and γ-cyclodextrin (hosts) in an aqueous environment using the semi-empirical quantum mechanical methods of PM6 and PM7. **Materials and Methods:** Molecular docking simulation and semi-empirical quantum mechanical calculations of PM6 and PM7 were employed to identify the molecular interactions between α–mangostin and three types of cyclodextrin. **Results:** The inclusion complex formation energy values of all α–mangostin/cyclodextrin that obtained by the semi-empirical PM7 method were significantly lower than complexation energy obtained by the semi-empirical PM6 method. **Conclusion:** The inclusion complex of α–mangostin/γ–cyclodextrin is the most favorable pathway of inclusion complex formation of α–mangostin with cyclodextrin because it has the highest negative value of free binding energy (Δ*G*) and complexation energy (Δ*E*) compared to α–mangostin/α–cyclodextrin and α–mangostin/β–cyclodextrin.

Key words: Alpha mangostin, Cyclodextrin, Host-guest interactions, PM6, PM7.

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INTRODUCTION

Molecular design and modeling based on computational simulation methods are widely employed in pharmaceutical and chemistry sciences to obtain the information about the mechanism of molecular reactions among compounds. The equations and algorithms of calculation can predict the experimental results when the system conditions prior to laboratory trials. Semi–empirical quantum mechanical calculations have some approximated parameters to the experimental data and can simplify the calculations.

Parameterization Method (PM) 6 and 7 (PM 6 and PM7) are widely used to identify the molecular and electronic structure properties of large molecules. PM7, the improved parameterization method was constructed using over 9,000 compounds that obtained from experimental and *ab initio* data. PM7 provides the improvement of some parameters including spatial aspects of reaction barrier, molecular formation heat, then integrate these parameters to dispersion and hydrogen interactions in the final parameterization. Therefore, this method can identify the non-covalent interactions properly.[1,2] This research focused on molecular interactions of α–mangostin inclusion complex with α–cyclodextrin (α–CD), β–cyclodextrin (β–CD) and γ–cyclodextrin (γ–CD). The inclusion complex is mainly formed by non-covalent interactions such as van der Waals interaction (hydrophobic interaction), dipole-dipole interaction and hydrogen interaction.[3] Because of this condition so the PM7 is the most suitable method to identify molecular inclusion complex formation between α–mangostin and cyclodextrin. The obtained results were also compared to PM6 as the previous method.

α–mangostin (*1,3,6-Trihydroxy-7-methoxy-2,8-bis(3-methylbut-2-enyl)-9H-xanthen-9-one)* is the main xanthone derivative obtained from mangosteen pericarp extract. α–mangostin (AM) has anti-microbial, anti-cancer, anti-inflammation, anti-oxidant and anti-allergic activities.[4,5] There are few reports showed that β–CD can form an inclusion complex with α–mangostin to increase its solubility.[6] Meanwhile, there is no experimental data using α–CD and γ-CD as the host of α–mangostin.

Cyclodextrin (CD) is cyclic oligosaccharide with three main types of structure including α–CD, β–CD and γ-CD, consisting of 6, 7 and 8 glycopyranose units, respectively and can be modified for many pharmaceutical drug delivery systems.[7] The basic structure of CD containing a hydrophilic shell and a hydrophobic core with hydroxyl groups that are lined to the exterior and the glucose residues are lined to interior.[8] CDs have been used as excipients of pharmaceutical dosages especially for lipophilic drugs sin order to enhance the solubility, stability and bioavailability due to their non-toxic and low immunogenicity properties.[9,10]

US-FDA approved CD in various dosage forms including α–CD as powder for injection, β–CD for oral and topical delivery and γ–CD for intravenous injection as solution.[11] CD can make a complex with both organic and inorganic lipophile molecules so it has been widely used as functional material in pharmaceutical dosage based drug delivery system. CD has an advantage properties in drug delivery system because it has a shaped cavity that protects the drug form degradation and minimizes the irritation at the administration site. The improvement of solubility and bioavailability can be achieved when the CD is used because the weak bonds

of the complex allow the drug molecules temporarily placed inside the cavity of CD.[12]

The aims of this study are to investigate the molecular interactions, geometrical properties, encapsulation process and calculated energy of the complexes system between α–mangostin with α–cyclodextrin, β–cyclodextrin and γ-cyclodextrin in aqueous environment using the semi-empirical quantum mechanical methods of PM6 and PM7.

MATERIALS AND METHODS

Molecular Structures Construction

The structure of α-mangostin as guest molecule was obtained and optimized by ChemOffice 2010 and ChemDraw Ultra 12.0 (PerkinElmer Inc.) (**Figure 1**). The molecular structures of α–CD, β–CD and γ-CD as hosts were obtained from Cambridge Crystallographic Data Centre[13] with the Cambridge Structural Database (CSD) entry: BANXUJ,[14] BCDEXD03[15] and CIWMIE10,[16] respectively (**Figure 2**). Hydrogen atoms were added into the structures by BIOVIA Discovery Studio 2017 R2 Client and then fully optimized by the semi-empirical quantum mechanical PM6 and PM7 methods using Molecular Orbital PACkage (MOPAC) 2016 and Avogadro 1.2 software.

Molecular Docking Simulation

The α–mangostin (guest), α–CD, β–CD and γ-CD (hosts) were prepared for docking simulation using AutoDock Tools 1.5.6. The guest and hosts were protonated. The grid parameter files were according to the grid boxes that comprised of 40×40×40 points with 0.375Å space and were centered on the center site of host molecules. The box has x × y × z dimensions of (10.674 Å × 4.481 Å × 3.231 Å); (15.282 Å × 1.22 Å × 1.105 Å) and (−1.577 Å × 2.765 Å × 5.737 Å) for α–CD, β–CD and γ-CD, respectively. AutoDock 4.2.6 (The Scripps Research Institute) was employed to do the molecular docking simulations. The docking parameter files were according to Lamarckian Genetic Algorithm (LGA) with: 100 number of runs, 150 population sizes and 2.500.000 energy evaluations. The conformation results from the docking simulation were clustered using a root mean square deviation (RMSD) with tolerance of 2.0 Å.[17] The guest-host conformation with the lowest Gibbs free binding energy (ΔG) was chosen from the most favored cluster. The guest-host complexes from docking simulation were visualized using Jmol Molecular Viewer 14.29 and BIOVIA Discovery Studio Visualizer 2017.

Complexation Energy Calculation

The selected docked conformation of α–mangostin/α–CD, α–mangostin/β–CD and α–mangostin/γ-CD inclusion complexes were then geometry optimized by the semi-empirical quantum mechanical PM6 and PM7 methods. The most stable conformation of the inclusion complexes were selected by based on the complexation energy (Δ*E*) that defined as the difference between the heat of complex formation and the heat of involved free molecules formation represented by formula:

$$\Delta E = E_{(AM/CD)} - (E_{AM} + E_{CD})^{18}$$

where *EAM/CD*, *EAM* and *ECD* represent the heat of formation of the inclusion complex, isolated α–mangostin molecule and isolated cyclodextrin molecule, respectively.

RESULTS

Molecular Structures Construction

The energy of α-mangostin **(Figure 1),** α–CD, β–CD and γ-CD **(Figure 2)** were minimized to obtain the optimal geometrical structures. The molecular properties of α–CD, β–CD and γ-CD were also determined (**Table 1**).

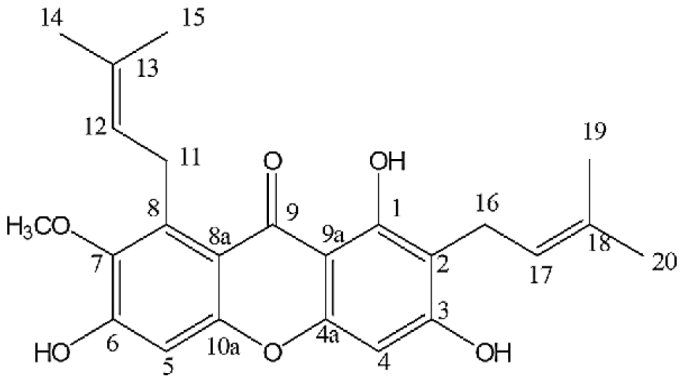

Figure 1: The structure of α–mangostin.

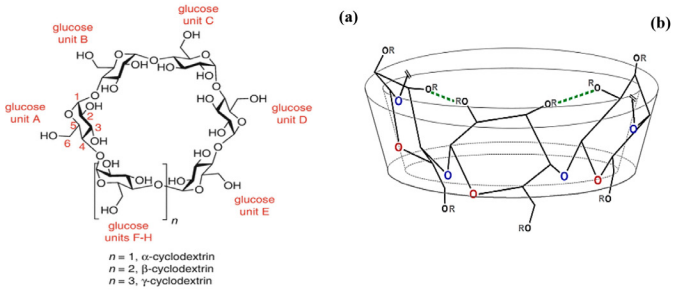

Figure 2: (a) Top prospect and (b) front side of basic structure of cyclodextrin.

Table 1: Molecular properties of α–Cyclodextrin, β–Cyclodextrin and γ–Cyclodextrin.

No	Properties	α–Cyclodextrin	β–Cyclodextrin	γ–Cyclodextrin
1	Number of pyranose units	6	7	8
2	Radicals (R)	–H	–H	–H
3	Molecular weight (g/mol)	973	1153	1297
4	Diameter of internal cavity (Å)	5	6	8
5	Diameter of external cavity (Å)	14	15	17
6	Cavity volume (Å)	175	261	428
7	ΔG of dissolution (kJ/mol)	15	20	14

Molecular Docking Simulation

Molecular docking simulations were employed to calculate the free binding energy (ΔG) and the best conformation between α–mangostin (as guest) molecule complex with α–CD, β–CD and γ-CD (as host) by optimizing the structure of host molecule and allowing the guest molecule to be placed in the determined grid box of host molecule. The starting geometrical structure of the host and guest molecules were calculated by the semi-empirical quantum mechanical methods of PM6 and PM7. The results of molecular docking simulation can be seen in (Table 2 and Table 3).

Molecular docking simulation results showed that the lowest free binding energy (ΔG) of α–mangostin/CD complex was α–mangostin/γ–CD

Table 2: The results of molecular docking simulations at 298.15 K. The starting geometrical structures of the host and guest were calculated by the semi-empirical quantum mechanical methods of PM6.

No	Guest/Host	RMSD	Cluster	ΔG (kcal/mol)	
				Lowest	Average
1	α–mangostin/α–CD	1.05	16	−5.91	−4.89
2	α–mangostin/β–CD	0.58	10	−5.62	−4.95
3	α–mangostin/γ–CD	0.52	12	−5.72	−5.29

Table 3: The results of molecular docking simulations at 298.15 K. The starting geometrical structures of the host and guest were calculated by the semi-empirical quantum mechanical methods of PM7.

No	Guest/Host	RMSD	Cluster	ΔG (kcal/mol)	
				Lowest	Average
1	α–mangostin/α–CD	0.95	11	−5.45	−4.76
2	α–mangostin/β–CD	1.17	16	−5.74	−5.02
3	α–mangostin/γ–CD	0.56	4	−6.03	−5.68

ranged from −5.29 kcal/mol to −6.03 kcal/mol compared to α–mangostin/α–CD (ranged from −4.76 kcal/mol to −5.91 kcal/mol) and α–mangostin/β–CD (ranged from −4.95 kcal/mol to −5.74 kcal/mol). These results indicated that α–mangostin has the highest affinity to γ–CD. However, the rigidity of CD as the host molecule in the docking calculation model need the further investigation. Thus, the further analyzes were done using semi-empirical quantum mechanical both PM6 and PM7 methods in the aqueous phase calculation model to further identify the molecular interactions between with α–mangostin and three types of CD (α–CD, β–CD and γ-CD).

Complexion Energy Calculation

The formation of the inclusion complexes of α–mangostin with three type the CD molecular systems were done using molecular docking calculation model. All system conformations were then fully optimized by the semi-empirical quantum mechanical of PM6 and PM7 methods that allowing the guest and host molecules to move flexibly in an aqueous environment. Table 4 showed the final heat of formation energy (E) and the complexation energy (ΔE) of the minimized inclusion complexes structures generated by PM6 and PM7 methods.

The minimized structure of the inclusion complexes always has lower energy (heat) of formation (E) than the sum of the heat of formation of the isolated CD (host) and α–mangostin (guest) molecule representing the formations were favorable. Based on the complexation energy (ΔE) equation, more negative value of the complexation energy (E), then the pathway mechanism of inclusion complex formation is more favorable.

The values ΔE of inclusion complex from PM7 method (ranged from −96.97 to −320.29 kcal/mol) were considerably lower than PM6 method (ranged from −29.80 to −144.53 kcal/mol) because the PM7 method includes the calculation of the hydrogen and dispersion interactions so this method is more appropriate for the noncovalent interactions in α–mangostin/CD complexes.

The distance (Å) of the intermolecular hydrogen bonds were also determined as shown in Table 5. There are two types of hydrogen bonds in inclusion complex system were most generated. Firstly, the hydrogen bonds between 1'hydroxyl group of guest molecule and ether-like anomeric oxygen atom of the host molecule ($O4_{(\alpha-CD)}\cdots H_{(1\text{-}OH-AM)}$). The second one, the hydrogen bonds between 3'hydroxyl group of guest molecule and ether-like anomeric oxygen atom of the host molecule ($O4_{(CD)}\cdots H_{(3\text{-}OH-AM)}$). The hydrogen bonds keep the guest molecule tightly as do the hydrophobic atoms of host molecule enclosing. The molecular interactions of each host–guest system in an aqueous environment are further represented in the Table 5.

Table 4: Final heat of formation energy (E) and the complexation energy (ΔE) of the minimized inclusion complexes structures from semi-empirical quantum mechanical PM6 and PM7 methods.

No	Molecule	PM6		PM7	
		E (kcal/mol)	ΔE (kcal/mol)	E (kcal/mol)	ΔE (kcal/mol)
	Isolated molecule				
1	α–mangostin	−208.04		−208.73	
2	α–CD	−1340.82		−1342.14	
3	β–CD	−1547.16		−1550.19	
4	γ–CD	−1628.27		−1631.14	
	Inclusion complex				
5	α–mangostin/α–CD	−1675.53	−126.67	−1701.18	−150.31
6	α–mangostin/β–CD	−1785.00	−29.80	−1855.89	−96.97
7	α–mangostin/γ–CD	−1980.84	−144.53	−2160.16	−320.29

Table 5: The distance of hydrogen bonds between α–mangostin as guest molecule and three types of cyclodextrin as host molecule (α–CD, β–CD, γ–CD) generated from PM6 and PM7 minimized inclusion complexes.

No	Method	Inclusion Complex	Hydrogen Bond	Distance (Å)
1	PM6	α–mangostin/α–CD	$O4_{(\alpha-CD)}\cdots H_{(1\text{-}OH-AM)}$	1.78
			$O_{(4a-O-AM)}\cdots H_{(OH-\alpha-CD)}$	2.70
			$O4_{(\alpha-CD)}\cdots H_{(3\text{-}OH-AM)}$	2.76
			$O_{(3-OH-AM)}\cdots H_{(O3H-\alpha-CD)}$	2.94
			$O_{(9=O=AM)}\cdots H_{(OH-\alpha-CD)}$	3.12
2	PM6	α–mangostin/β–CD	$O4_{(\beta-CD)}\cdots H_{(6\text{-}OH-AM)}$	2.01
			$O4_{(\gamma-CD)}\cdots H_{(1\text{-}OH-AM)}$	2.08
3	PM6	α–mangostin/γ–CD	$O4_{(\gamma-CD)}\cdots H_{(3\text{-}OH-AM)}$	2.30
			$O4_{(\gamma-CD)}\cdots H_{(6\text{-}OH-AM)}$	2.85
			$O4_{(\alpha-CD)}\cdots H_{(3\text{-}OH-AM)}$	2.04
4	PM7	α–mangostin/α–CD	$O4_{(\alpha-CD)}\cdots H_{(1\text{-}OH-AM)}$	2.76
			$O_{(9=O=AM)}\cdots H_{(OH-\alpha-CD)}$	3.27
			$O_{(4a-O-AM)}\cdots H_{(OH-\alpha-CD)}$	3.78
5	PM7	α–mangostin/β–CD	$O4_{(\beta-CD)}\cdots H_{(1\text{-}OH-AM)}$	2.08
			$O4_{(\beta-CD)}\cdots H_{(3\text{-}OH-AM)}$	2.31
			$O4_{(\beta-CD)}\cdots H_{(6\text{-}OH-AM)}$	2.85
6	PM7	α–mangostin/γ–CD	$O_{(7-CO-AM)}\cdots H_{(OH-\gamma-CD)}$	2.74
			$O_{(9=O=AM)}\cdots H_{(OH-\gamma-CD)}$	3.55

DISCUSSION

The inclusion complexes between α–mangostin and (α, β and γ)–cyclodextrins were generated and analyzed using semi empirical quantum of PM6 and PM7 methods. Each of host and guest molecules were minimized to get the best spatial structure. The important parameter of generated inclusion complexes was the hydrogen bonds that made

the interaction between the host and the guest molecules possible. The position of guest molecule (α–mangostin) in the cavity of guest molecule (cyclodextrin) was also determined based on the formed hydrogen bonds to obtain the most favorable inclusion complex conformation. These parameters were directly correlated to the value of complexation energy (Δ*E*) of the formed inclusion complexes.

The hydrogen bonds of the best docked conformation of α–mangostin/α–CD inclusion complexes formed using PM6 and PM7 methods are shown in Figure 3**.** The minimized inclusion complex of α–mangostin/α–CD conformations that obtained from the PM6 and PM7 methods were similar. However, in α–CD obtained from the PM7 calculation model, the structure of α–mangostin molecule was dipped deeper into the α–CD cavity (Å) than the α–mangostin structure that obtained from the PM6 calculation model due to the hydrogen bond between the oxygen atom of α–mangostin's oxo group at position 9 and the hydrogen atom of the hydroxyl group at O of $O_{(9=O=AM)}\cdots H_{(OH-\alpha-CD)}$, as depicted in Figure 3b.

The inclusion complex of α–mangostin/β–CD obtained from PM6 and PM7 were stabilized in a water environment as shown in Figure 4. The α–mangostin as guest molecule is located inside the β–CD's cavity with a hydrogen bond between the oxygen atom of α–mangostin's hydroxy group at position 6 and the ether-like anomeric oxygen atom of β–CD $O4_{(\beta-CD)}\cdots H_{(6\text{-}OH-AM)}$. The PM6 and PM7 calculations yield different β–CD energy-minimized structures in a water environment. In the β–CD obtained from PM6 calculation, the guest molecule is located near the wide-side of β–CD (Figure 4a), meanwhile the guest molecule from PM7 calculation was slightly dipped inside the β–CD's cavity due to the hydrogen bond between the oxygen atom of α–mangostin's hydroxyl group at position 9 and the ether-like anomeric oxygen atom of $O4_{(\beta-CD)}\cdots H_{(1\text{-}OH-AM)}$ (Figure 4b).

The inclusion complexes of α–mangostin and γ–CD obtained from PM6 and PM7 calculations were stabilized in a water environment, as shown in **Figures 5**. The energy minimized structures of α–mangostin/γ–CD from the PM6 and PM7 methods were slightly similar. The host molecule is located near the wide-side of the γ–CD molecule in all complex conformations, as shown in **Figures 5a and 5b** based on the existence of methyl groups at the primary hydroxyl group of all glucose units (C6 position) of CD. In the structure of γ–CD molecule, all of methoxy groups at the C6 position can be accommodated based on the absence of steric hindrance from the guest molecule. After an insertion of guest molecule (α–mangostin) into the cavity of γ–CD, two of the methoxy groups at the C6 position of γ–CD move away from the cavity due to the existence of the two methyl groups of α–mangostin molecule at position 14 and 15, located at the narrow-side of γ–CD. Based on the electronic and steric hindrances, the guest molecule should entrance into γ–CD at the wide side to form the obtained inclusion complexes.

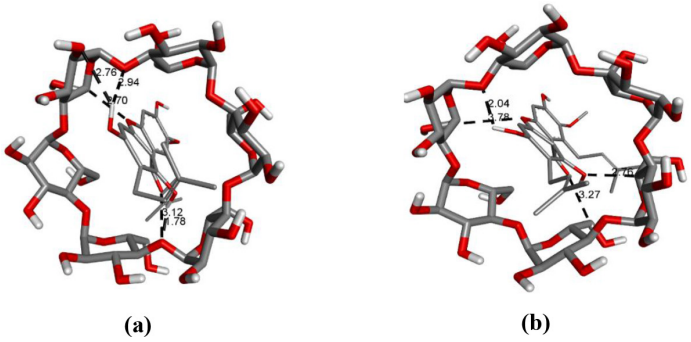

Figure 3: Hydrogen bonds in 1:1 α–mangostin/α–CD inclusion complex. (a) α–mangostin/α–CD obtained from semi-empirical quantum mechanical PM6 method, (b) α–mangostin/α–CD obtained from semi-empirical quantum mechanical PM7 method.

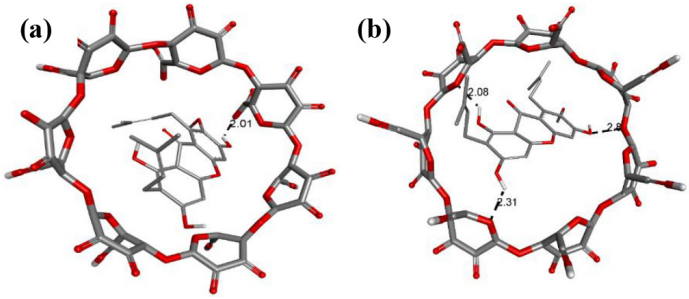

Figure 4: Hydrogen bonds in 1:1 α–mangostin/β–CD inclusion complex. (a) α–mangostin/β–CD obtained from semi-empirical quantum mechanical PM6 method, (b) α–mangostin/β–CD obtained from semi-empirical quantum mechanical PM7 method.

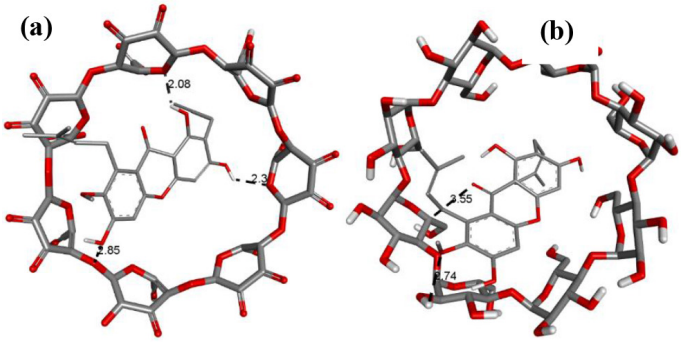

Figure 5: Hydrogen bonds in 1:1 α–mangostin/γ–CD inclusion complex. (a) α–mangostin/γ–CD obtained from semi-empirical quantum mechanical PM6 method, (b) α–mangostin/γ–CD obtained from semi-empirical quantum mechanical PM7 method.

Thus, the α–mangostin could not gone deeper inside the γ–CD's cavity, resulting α–mangostin/γ–CD obtained from semi-empirical method of PM7 as the preferable complex with a lower complexation energy (Δ*E*) by −320.29 kcal/mol compared to α–mangostin/γ–CD obtained from semi-empirical method of PM6 (−144.53 kcal/mol). The methyl part of the hydroxypropyl group substituent falls into the CD's cavity (from PM7 method) and pushes the α–mangostin molecule deeper inside the cavity due to presence of the hydrophobic interaction.

CONCLUSION

The inclusion complex formation energy values of all α–mangostin/CD that obtained by the semi-empirical PM7 method are significantly lower than complexation energy obtained by the semi-empirical PM6 method. The effort to increase the solubility and reduce the toxicity of the α–mangostin can be done either using α–CD, β–CD or γ–CD based on the results of molecular docking simulations and PM calculations. The inclusion complex of α–mangostin/γ–CD is the most favorable pathway of inclusion complex formation of α–mangostin with CD because it has the highest negative value of free binding energy (Δ*G*) and complexation energy (Δ*E*). Molecular interactions between α–mangostin and three types of cyclodextrin were done using molecular docking simulation and semi-empirical quantum mechanical calculations of PM6 and PM7. The inclusion complex of α–mangostin/γ–cyclodextrin is the most favorable pathway of inclusion complex formation of α–mangostin with cyclodextrin because it has the lowest complexation energy (Δ*E*).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

AM: alpha mangostin; **CD:** Cyclodextrin; **α–CD:** Alpha cyclodextrin; **β–CD:** Beta cyclodextrin; **γ–CD:** Gamma cyclodextrin; **PM:** Parameterization Method**;** Δ***E*:** complexation energy; Δ***G*:** Gibbs free binding energy.

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