ORIGINAL ARTICLE

Encapsulation mechanism of α-mangostin by β-cyclodextrin: Methods of molecular docking and molecular dynamics

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ABSTRACT

The study aimed to investigate the interaction of host-guest between α-mangostin and β-cyclodextrin (βCD) and also to calculate the energy of the complex system between α-mangostin with βCD for drug delivery using methods of 15 molecular dynamics and molecular docking. Simulation of molecular docking and molecular dynamics was utilized to determine molecular interactions and the complex system's bond energy. The docking simulation results showed that α-mangostin-βCD complex has a Gibbs energy value (ΔG) of −6.69 kcal/mol. The Gibbs energy value (ΔG) of molecular dynamics simulation from MMGBSA calculation showed the binding energy of α-mangostin-βCD – 11.73 kcal/mol.

Keywords: Inclusive complex, molecular docking, molecular dynamics, α-mangostin, β-cyclodextrin

INTRODUCTION

The fundamental xanthone compound in the pericarp of the mangosteen is α-mangostin. The mangosteen fruit has attracted a lot of attentions from researchers due to its various pharmacological activities such as antimicrobial, anti-inflammatory, antiviral, anticancer, and antifungal.[1-4] However, the solubility of α-mangostin in water is only 0.2 μg/ml and it has largely restricted its bioavailability.[5]

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Cyclodextrins are cyclic oligosaccharide which contains 6, 7, and 8 glucopyranose units within and are also related to α-cyclodextrin, β-cyclodextrin (βCD), and γ-cyclodextrin, respectively.[6] Cyclodextrins are commonly used in the pharmaceutical field because it has a unique hollow structure.[7,8] The inclusion complexation cyclodextrin is a technique that is common in enhancing the solubility of poorly water-soluble drugs. Compared to other natural cyclodextrins such as α-cyclodextrin and γ-cyclodextrin, βCD is often used because it can be easily synthesized and the price is cheaper. Cyclodextrins have the ability to form inclusive complexes with various compounds and thus it can help to improve the physicochemical properties of the complex compound. By forming an inclusive complex, the complex will dissolve in the solute and achieve dynamic equilibrium quickly.[9]

βCD is one of the practical cyclodextrins. However, the powerful intramolecular hydrogen bonds of βCD cause its low solubility level in the water, which is only 1.85 g/100 mL at

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25°C.[10] According to the studies conducted by Das *et al*. in 2011 and Zhao *et al*. in 2012, the formation of inclusive complex between resveratrol and oxyresveratrol with cyclodextrin can increase the solubility of the complex in the water, especially when it is complexed with 2-hydroxypropyl-βCD (HPβCD), which is a derivative of βCD.[11,12]

This study aimed to inspect molecular interactions, as well as to calculate the complex system energy between α-mangostin with βCD for drug delivery using methods of molecular dynamics and molecular docking.

MATERIALS AND METHODS

Molecular structures constructions

This study used AutoDock 4.2 (The Scripps Research Institute, La Jolla, CA, USA) to estimate the possible arrangement of complex α-mangostin-βCD and α-mangostin-HPβCD. From the Protein Data Bank (ID: 1z0n), the formation of βCD was acquired. α-mangostin structure as a guest molecule was obtained from PubChem and optimized by ChemBio3D Ultra 12.0 (PerkinElmer Inc.) The nonpolar hydrogen atoms from both receptors and guest molecule were emerged, and the Gasteiger charges were added. The grid box used was 60 × 60 × 60 points, featuring grid space of 0.375 Å. The docking parameter used was default setting from AutoDock 4.2, except docking runs, energy evaluations, and number of generations that were adjusted to 100, 2,500,000, and 250, respectively. Conformation results of the docking were grouped by root-mean-square deviation (RMSD) with a tolerance of 2.0 Å. The best docking result was visualized with BIOVIA Discovery Studio Visualizer 2017.

Molecular dynamics simulation

Particle Mesh Ewald Molecular Dynamics from package AMBER 16 was used to perform the simulation of molecular dynamic. The study used the general AMBER force field to acquire the parameters of force field for α-mangostin and βCD molecules using semi-empirical quantum calculation AM1-BCC through an antechamber program. The complexation of α-mangostin and βCD s was performed with tleap and the system was immersed in water using TIP3P water model with a periodic box size of 10 Å. In the preparation system phase, the system was minimized for 9000 steps, including the steepest descent (7000 steps) and conjugate gradient (2000 steps) with cutoff value of 9Å in constant volume periodic boundaries. Next, the system was kept hot under steady mass for 60 ps to 310 K by utilizing a Langevin thermostat with restraints of 5 kcal mol^{-1} $Å^{-2}$. Further on, the system was equilibrated under constant pressure for 500 ps with constant pressure periodic boundary. SHAKE algorithm was applied to constraint hydrogen atoms at their equilibrium distance. In the production phase, a 30ns simulation was done with constant pressure periodic boundary. Trajectory analysis was done with cpptraj module from AMBER 16. The binding energy between the βCD and α-mangostin was measured by Molecular Mechanics-Generalized Born Surface Area (MMGBSA).

RESULTS

The structure of guest molecule α-mangostin with host molecules βCD obtained is shown in Figures 1 and 2.

Molecular docking

Molecular docking was implemented to find the best position of α-mangostin inside the cavity of βCD based on the lowest binding energy in the largest cluster.

The results of molecular docking are shown in Table 1. From the table, the free binding energy of α-mangostin-βCD was −6.69.

Molecular dynamic simulation

The best docking complex from molecular docking was further studied with molecular dynamics. MMGBSA was used to measure the inclusion complexes of α-mangostin-cyclodextrin in molecular dynamic simulation. The results of molecular dynamics are shown in Table 2. From the table, the free binding energy of α-mangostin-βCD was −11.73 kcal/mol.

Table 1: The results of molecular docking of α-mangostin and β-cyclodextrins at 298.15 K in docking 176th

Type of interaction	ΔG (kcal/mol)
Final intermolecular energy	−9.08
Final total internal energy	−2.42
Torsional free energy	+2.39
Unbound system's energy	−2.42
Free energy of binding	−6.69

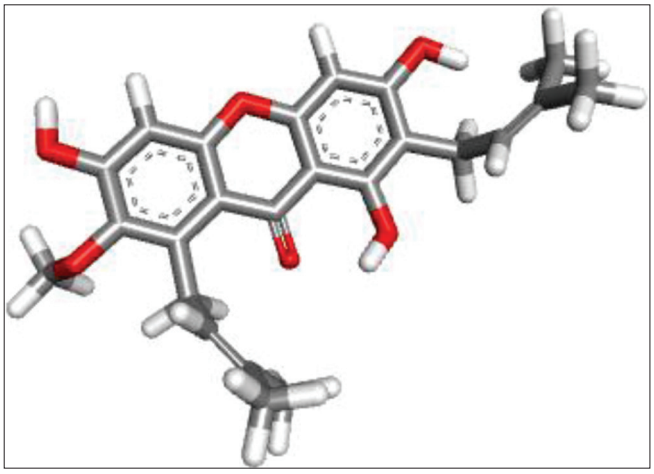

Figure 1: α-mangostin 3D structure

DISCUSSION

The docking process was repeated for 250 times. The grid coordinates for βCD was −6.686; 37.14; −7,932 (x; y; z) and HPβCD −7,214; 37.154; −6.91 (x; y; z) with grid box size of 60 × 60 × 60, to cover the entire surface of the cyclodextrin. From the docking results, no case of α-mangostin coming out of the cyclodextrin cavity during the docking process was found. This indicated that α-mangostin can establish a stable inclusive complex with βCD theoretically.[13] The 176th docking was chosen in the analysis.

The docking results of α-mangostin and βCD [Figure 3] showed that there were 2 hydrogen bonds in the complex with the distance of 2.07Å and 2.10 Å, respectively. There was also a hydrophobic effect that occurred at a distance of 3.90 Å between the aromatic group α-mangostin and C-H from βCD by Pi-Sigma. The average value of binding energy was −6.69 kcal/mol. The negative binding energy values suggested that the formation of all these inclusive complexes was a spontaneous reaction.

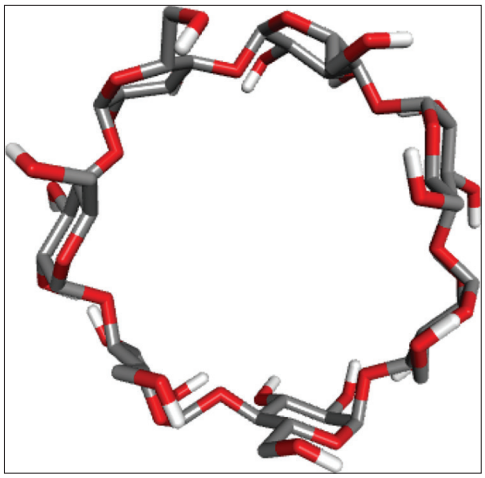

Figure 2: β-cyclodextrins three dimensional structure

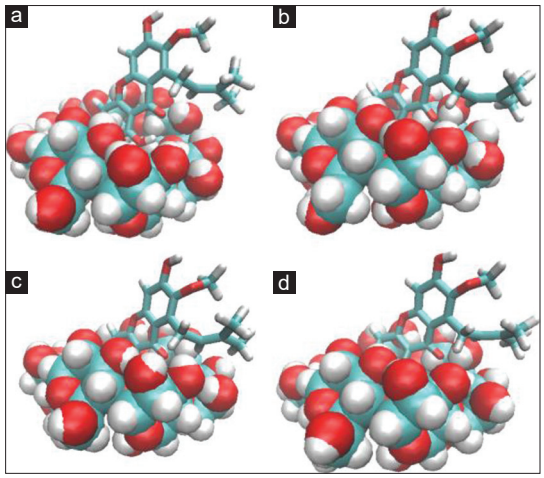

Figure 4: α-mangostin- β-cyclodextrins from front view at (a) 1 ns (b) 10 ns (c) 20 ns (d) 30 ns structure

The snapshots during 30 ns molecular dynamics simulation of α-mangostin and βCD [Figure 4]. The stability of a complex system can be known by calculating RMSD where RMSD is the average difference between atomic positions in a simulation. In the complex system of α-mangostin-βCD,

Table 2: The results of molecular dynamic simulation of α-mangostin and β-cyclodextrins at 310 K in the water model TIP3P system

Component energy (kcal/mol)	System α-mangostin-βCD	
	Average	SD
Bond	0.00	0.00
Angle	−0.00	0.00
DIHED	0.00	0.00
VDWAALS	−33.74	3.59
EEL	−5.24	4.02
EGB	31.00	5.48
ESURF	−3.74	0.35
Delta G gas	−38.98	5.79
Delta G solv	27.25	5.23
Delta total	−11.73	2.68

βCD: β-cyclodextrin, SD: Standard deviation

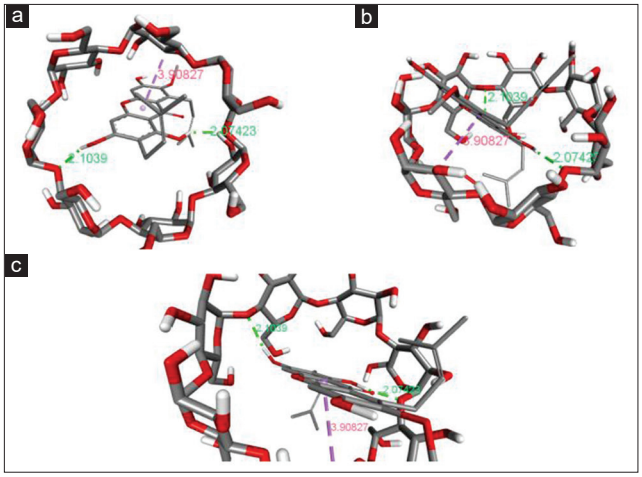

Figure 3: Interaction of α-mangostin (a) from top (b) from front (c) insight look with β-cyclodextrins. Hydrogen bond (green dotted line) and hydrophobic effect (pink dotted line) are shown above

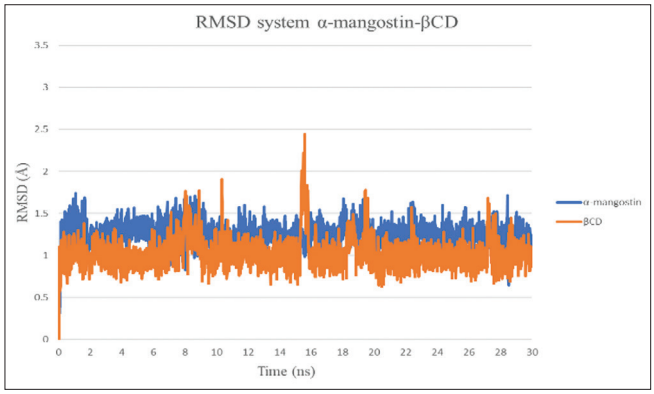

Figure 5: The root-mean-square deviation plot of backbone atoms for the simulation of α-mangostin- β-cyclodextrins

βCD and α-mangostin were stable throughout 30 ns molecular dynamics simulation [Figure 5], while in the complex system of α-mangostin-HPβCD, α-mangostin has stable RMSD graph line throughout the simulation. The system was said to be stable during this simulation.

Based on a snapshot of βCD-α-mangostin simulation system, it appeared that only methyl group entered the cavity of cyclodextrin [Figure 4]. The possible reason for this was the large methyl group caused steric hindrance in the βCD cavity. This prevented the other part of α-mangostin from entering into the cavity during the simulation.[13] In addition, the βCD structure was more or less the same throughout the simulation which was in agreement with the RMSD graph which showed that there was not much fluctuation throughout the simulation [Figure 5].

Table 2 shows the results of molecular dynamic simulation of α-mangostin and βCD at 310K in the system water model TIP3P. The study implemented MMGBSA approach to measure binding free energy. Every 100 frames out of 3000 total frames were implemented to measure binding free energy. Van der Waals force (Δ*E*VDW) made the key contribution in the formation of inclusive complex. In the βCD-α-mangostin complex, the VDW value was −33.74 kcal/mol. From the table, the low value of VDW force indicated the cavity of cyclodextrin was hydrophobic. The total value of binding energy (ΔG) in the βCD-α-mangostin system was − 11.73 kcal/mol.

CONCLUSION

In the study, two modeling methods were used to study the complexation of α-mangostin and cyclodextrins. The docking simulation results showed that α-mangostin-βCD complex has a Gibbs energy value (ΔG) of −6.69 kcal/mol. The Gibbs energy value (ΔG) of molecular dynamics simulation from MMGBSA calculation showed the binding energy of α-mangostin-βCD −11.73 kcal/mol. The results showed that α-mangostin-βCD inclusion was a stable and spontaneous process.

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Conflicts of interest

The author proclaims no conflict of interest.

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