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Enhanced stability of a naringenin/2,6-dimethyl β-cyclodextrin inclusion complex: Molecular dynamics and free energy calculations based on MM- and QM-PBSA/GBSA

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ABSTRACT

The structure, dynamic behavior and binding affinity of the inclusion complexes between naringenin and the two cyclodextrins (CDs), β-CD and its 2,6-dimethyl derivative (DM-β-CD), were theoretically studied by multiple molecular dynamics simulations and free energy calculations. Naringenin most likely prefers to bind with CDs through the phenyl ring. Although a lower hydrogen bond formation of naringenin with the 3-hydroxyl group of DM-β-CD (relative to β-CD) was observed, the higher cavity could encapsulate almost the whole naringenin molecule. In contrast for the naringenin/β-CD complex, the phenyl ring feasibly passed through the primary rim resulting in the chromone ring binding inside instead. MM-PBSA/GBSA and QM-PBSA/GBSA binding free energies strongly suggested a greater stability of the naringenin/DM-β-CD inclusion complex. Van der Waals force played an important role as the key guest–host interaction for the complexation between naringenin and each cyclodextrin.

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1. Introduction

The polyphenols, and in particular flavonoids, are natural products found in many vegetables and fruits. Based on the variations in their polyphenolic structure, flavonoids can be divided into the different classes of flavonols, flavones, flavanones, catechins, anthocyanidins, isoflavones, dihydroflavonols and chalcones. Their broad pharmacological profiles include anti-lipoperoxidant and anti-inflammatory properties [1] and the ability to exert anticancer and chemopreventive activities [2]. Naringenin (5,7,4-trihydroxyflavanone or 5,7-dihydroxy-2-(4-hydroxyphenyl) chroman-4-one in Fig. 1A) belongs to the flavanones class of flavonoids. It is abundant in citrus fruits, such as grapefruit (*Citrus paradise*) and orange (*Citrus sinensis*). It exerts a variety of pharmacological effects [3] including antioxidant effects, blood lipid-lowering effects (Borradaile et al., 1999; Santos et al., 1999), anti-inflammatory activity through inhibition of the enzymes involved in arachidonate metabolism [4–6], drug inhibition against cytochrome P-450 [7] and anti-carcinogenic effects [8,9]. In the cancer case, naringenin was reported to induce apoptosis in various cancer cell lines with no effect on normal cells [10]. Additionally, it has an insulin-like effect to decrease apoliprotein B (Apo B) secretion in hepatocytes and to lower blood glucose levels in healthy male wistar rats [11]. From this point of view, there is a growing interest in applying naringenin in food products to enhance their health functions as well as its use in developing nutraceutical and pharmaceutical products. Unfortunately, a common limiting factor in the use of flavonoids in many applications is their low water solubility and stability. The formation of an inclusion complex with cyclodextrin (CD) is one effective way to solve this problem.

The cyclodextrins (CDs) are a group of cyclic oligosaccharides that consist of six (α-cyclodextrin or α-CD), seven (β-cyclodextrin or β-CD) or eight (γ-cyclodextrin or γ-CD) glucopyranose units linked by α-(1, 4) glycosidic bonds. From their geometry, the internal cavity is highly hydrophobic, whilst the external hydroxyl face establishes a hydrophilic character. In the recent years, CD complexation has been successfully used to improve the solubility, stability toward light and oxidative degradation, dissolution rate, and bioavailability of poorly water soluble drugs [12–15]

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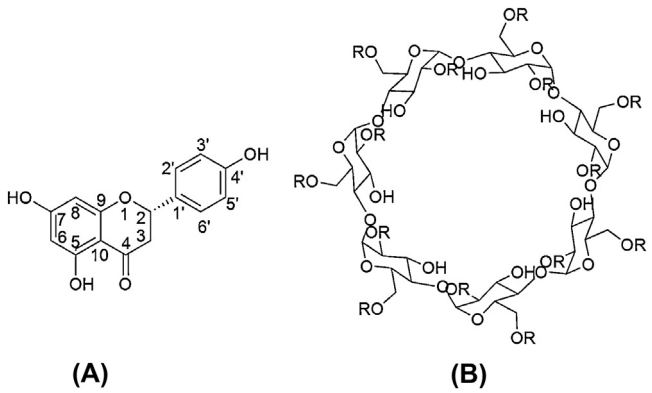

Fig. 1. Chemical structures of (A) naringenin and (B) the two CDs, β-CD and DM-β-CD, where –R is H– and $–CH_3$, respectively.

such as nimbin [16], crassicauline A [17] and alpinetin [18]. Since the application of β-CD in pharmaceutical fields is limited by its rather low aqueous solubility, more soluble derivatives of β-CD are presently of interest [12,13]. The amorphous CD, 2,6-dimethyl-β-cyclodextrin (DM-β-CD, Fig. 1B), is a chemically modified cyclomaltoheptaose (β-CD) derivative obtained by methylation of the 2- and 6-hydroxyl groups. Compared to the native β-CD, DM-β-CD exhibits an increased solubility in water and organic solvents [15] which enable its use as a carrier for poorly soluble molecules in water or hydrophobic solvents [19,20]. In addition, DM-β-CD was found to be an effective absorption promoter for nasal glucagon in rabbit [19] and has been reported in a European patent application for oral or parenteral administration [21]. To date, the solubility enhancement of naringenin by natural CD has been reported on from experimentally and theoretically derived studies, but only a few studies on the DM-β-CD derivative are available.

In the present work, the stability of naringenin was theoretically achieved by complexation with natural β-CD and DM-β-CD using multiple molecular dynamic (MD) simulations and free energy calculations. We aimed to obtain a better understanding of the structure and dynamic properties of naringenin inside the CD cavity. These results constitute new and valuable information on the naringenin binding strength, the key guest–host interaction and the binding free energy of complex formation.

2. Methods of computation

The starting configuration of naringenin was created and fully optimized with the *ab initio* calculation using the HF/6-31G* basis set in the Gaussian09 program [22], The geometry of β-CD was taken from a systematic investigation on the structure of β-CD [23], and the structure of DM-β-CD was obtained by adding methyl groups to β-CD and subsequent geometry optimization with B3LYP/6-31G**. Prediction of a naringenin inclusion complex with these two CDs was performed *via* a docking procedure with 500 independent runs using the CDOCKER module of Accelrys Discovery Studio 2.5 (Accelrys, Inc.). The three docked inclusion complexes with the best ranked interaction energy and hydrogen bond (H-bond) formation between naringenin and each CD were then chosen for the MD study. The following system preparation and MD simulations on all inclusion complexes were performed with the Amber 12 software package [24]. The Glycam-06 bimolecular force field [25] was applied for the β-CD and DM-β-CD. In case of naringenin, the atomic charges and parameters were developed according to standard procedures [26–28]. The electrostatic potential (ESP) charges around the optimized naringenin molecule were evaluated by the HF/6-31G* calculation using Gaussian09. The restrained electrostatic potential (RESP) charges of naringenin were then obtained by a charge fitting procedure using the antechamber module implemented in the Amber 12, while its parameters were obtained using the parmchk module. The hydrogen atoms of each inclusion complex were minimized with the 1000 steps of steepest descents (SD) followed by 3000 steps of conjugated gradients (CG) to relax the structure and release bad contacts. The complex was solvated by SPC water molecules with a spacing distance of 12 Å around the system surface. The naringenin/β-CD and naringenin/DM-β-CD complexes consisted of 1480 ± 10 and 1750 ± 3 water molecules in the $41\,Å \times 41\,Å \times 41\,Å$ and $44.0\,Å \times 44.0\,Å \times 44.0\,Å$ truncated octahedron periodic boxes, respectively. The water molecules alone were minimized with the SD (1000 steps) and CG (3000 steps) and then minimization with the same process was applied on the whole system. In the next step, the MD simulation with periodic boundary condition using the NPT ensemble and a time step of 2 fs. The electrostatic interactions were taken into account by the particle mesh Ewald approach [29] with a cutoff distance of 12 Å. The SHAKE algorithm was used to constrain all bonds with hydrogen atoms. Each system was heated up to 298 K with a relaxation time of 100 ps and then simulated at the same temperature for 80 ns. The coordinates were recorded every 500 steps for analysis. The root means square displacement (RMSD), distance between the centers of gravity of the naringenin ring and CD (d ($Cg_{chromone/phenyl\ ring}$–$Cg_{CD}$)) along the simulation time were analyzed by the ptraj module. The 30 MD trajectories of inclusion complex extracted from simulation at equilibrium (discussed later) were used for the binding free energy prediction. MM-PBSA and MM-GBSA approaches, the acceptable methods for predicting the absolute binding free energy of molecules in solution [30] were adopted for calculating the free energy of naringenin binding to β-CD and DM-β-CD. The methodology details of both methods have been described elsewhere [27,31–33]. To correct the MM energy, single point M06-2X/6-31+G** calculations were applied to the structures of the inclusion complex, CD and naringenin. Note that the DFT M06-2X functional energy includes the empirical dispersion correction energy [34], which is an important factor in the guest–host interaction.

3. Results and discussion

3.1. Naringenin/CD inclusion complex

From the 500 independent docking runs, the conformation, interaction energy and H-bond formation of naringenin inside the hydrophobic cavity of the CDs are given in Table 1.

Note that the interaction energy of inclusion complex was calculated by the energy difference between inclusion complex, cyclodextrin and naringenin using the CHARMm-based docking algorithm [35]. It can be clearly seen that the phenyl ring of naringenin molecule (Fig. 1A) preferentially dipped to β-CD (99% docked conformation) and DM-β-CD (100%) with a location close to the primary rim. The obtained information was in good agreement with the recent ^{1}H and 2D NMR study of naringenin in complex with β-CD and DM-β-CD [36] and the theoretical studies by 6-ns MD simulation [37] as well as the semi-empirical AM1 method [38] on naringenin/β-CD complex.

Based on docked interaction energy and H-bond between naringenin and cyclodextrin, the best formed inclusion complex with β-CD and DM-β-CD were depicted in Fig. 2. It is worth noting that the DM-β-CD encapsulates this flavanones molecule better than the native β-CD by 2 kcal/mol in the gas phase. For naringenin/β-CD complex (Fig. 2A), the hydroxyl oxygen (O7) on its chromone ring formed a H-bond with the 3-OH group located in the interior of β-CD (1.9 Å). Differentially, a weaker H-bond was detected in the naringenin/DM-β-CD complex (2.5 Å) between the O1 atom and

Table 1
Percentage of docked conformation, interaction energy (kcal/mol) and number of H-bond formation of naringenin in the interior of β-CD and DM-β-CD.

Inclusion complex	% Docked conformation	Interaction energy (kcal/mol)	# H-bond (distance)
Naringenin/β-CD	99% phenyl ring inserted	−26.70	1 (1.9 Å)
	1% chromone ring inserted	−25.00	–
Naringenin/DM-β-CD	100% phenyl ring inserted	−28.76	1 (2.5 Å)

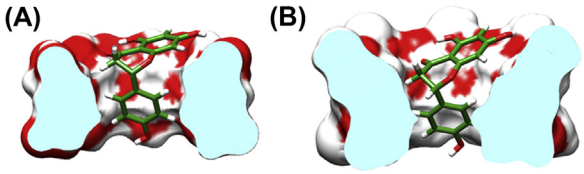

Fig. 2. Cutaway views of the CD hydrophobic cavity showing naringenin occupied in (A) β-CD and (B) DM-β-CD from the docked structures.

the 3-OH group. The decreased H-bond strength in the DM-β-CD is due to the larger and deeper cavity (Fig. 2B), as previously discussed [38,39]. By the two mentioned criteria, the top three ranked conformations of each inclusion complex from the docking results were chosen for further study on dynamics behaviors of complex in aqueous solution.

3.2. Stability of the simulated system

The system stability of the simulated inclusion complex in solution was monitored using the RMSD calculation. Fig. 3 shows the RMSD plots for all atoms of the inclusion complex (black), CD (dark gray) and naringenin (light gray) relative to those of the docked structure for the three different conformations of naringenin/β-CD (A1–A3) and naringenin/DM-β-CD (B1–B3) along the simulation time. The RMSD plots of the six simulated inclusion complexes (black) suggested that all systems had reached equilibrium at 25 ns and so the obtained results from the last 55 ns were mainly discussed. Comparing the RMSD values of the inclusion complex with the two CDs (black) during the 25–80 ns of simulation, the decreased fluctuation of the naringenin/DM-β-CD complex (1.8–3.4 Å in B1; 1.4–3.6 Å in B2 and B3) implied that naringenin might form a better inclusion complex with DM-β-CD than with native β-CD (1.25–4.0 Å in A1–A3). Interestingly, for the DM-β-CD host molecule, the methyl substitutions on the C2 and C6 positions of each D-glucopyranose did not affect the RMSD value (~2.0 Å, comparable to that of β-CD, dark gray). The RMSD value of naringenin (light gray) in the cavity of both CDs was enhanced from ~0.5 Å to ~2.0 Å, but its fluctuation was considerably larger in the DM-β-CD based complex (except for the B1 system). This is probably because the increased height of the DM-β-CD's cavity (Fig. 2B) may allow for a higher conformational flexibility of naringenin.

3.3. Ligand binding inside the CD cavity

To understand the binding mode and dynamics behavior of naringenin in the interior of the two CDs, the distance measured from the center of gravity of each naringenin ring ($Cg_{chromone/phenyl\ ring}$) to the center of gravity of CD (Cg_{CD}) was determined along the simulation time. The results (Fig. 4) reveal that the approximated positions of the primary and secondary rims of β-CD (the horizontal dashed lines) ranged from −3.95 Å to 3.95 Å and so represent a β-CD height of 7.9 Å as previously reported [39–41].The representative MD structures of the two inclusion complexes are shown in Fig. 5.

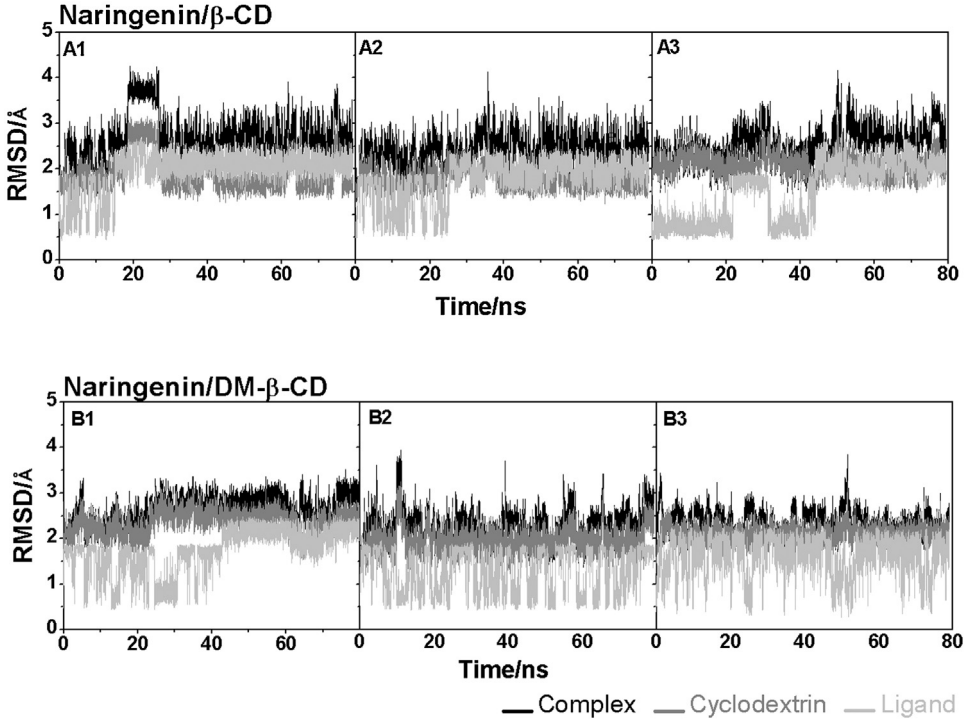

Fig. 3. RMSD plots for the simulated systems of naringenin complexes with β-CD and DM-β-CD from the three different (best) docked conformations for (A1–A3) naringenin/β-CD and (B1–B3) naringenin/DM-β-CD.

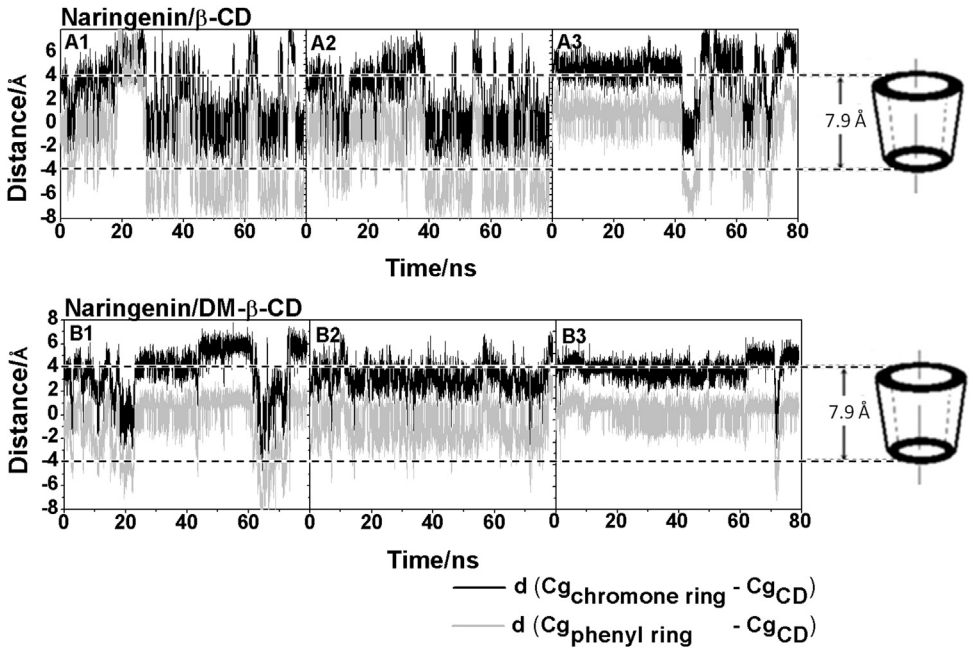

Fig. 4. Distance from the center of gravity of each naringenin ring (Cgchromone ring or Cgphenyl ring) to the center of gravity of CD (CgCD) for (A1–A3) naringenin/β-CD and (B1–B3) naringenin/DM-β-CD inclusion complexes. Dash line represents the primary and secondary rims and so the cavity height of β-CD.

Although the simulations of each naringenin/CD complex were initiated from three different structures obtained from the docking procedure, a relatively similar mobility of naringenin in the CD cavity was observed in each case. For the naringenin/β-CD complex, the phenyl ring (gray, Fig. 4) mostly stayed at the β-CD center (∼0.0 ± 1.8 Å in the A1 and A2 simulations, and ∼1.0 ± 1.0 Å in A3) while the chromone ring (black) was likely to be located nearby the secondary rim (∼3.5 ± 1.0 Å and ∼2.5 ± 1.0 Å, respectively) in the first 30 ns (A1) or 40 ns (A2 and A3) of simulation (see also Fig. 5A, left). Afterwards, the phenyl ring moved deeper and feasibly passed through the primary rim (∼−6.0 ± 2.0 Å) with a result that the chromone ring occupied inside the cavity instead (∼0.0 ± 2.0 Å) in the A1 and A2 simulations (Fig. 5B, right). However, the phenyl ring was able to move back into the cavity as well, which was found in all three simulations but in particular in A3. Since an increased height of the cavity (>7.9 Å) with a narrower primary and wider secondary rim (Fig. 2B) was established in the DM-β-CD, different dynamic behavior of naringenin binding was expected for the naringenin/DM-β-CD inclusion complex. All three simulations (B1–B3) suggested that the phenyl ring mainly occupied and moved within the interior of DM-β-CD in a range of −3.5 to 2.0 Å, while the chromone ring structure was supported by the methyl groups at the secondary rim (Fig. 5B, left). Among the three simulations (B1–B3), there was a low possibility of the phenyl ring moving down to the primary rim or staying outside the cavity of DM-β-CD (Fig. 5B, right), as seen in the B1 simulation at the early stage and again at ∼62–73 ns and shortly in the B3 simulation at ∼73 ns. Therefore, it can be presumed that naringenin significantly better fitted in the cavity of DM-β-CD to form a more stable naringenin/DM-β-CD complex.

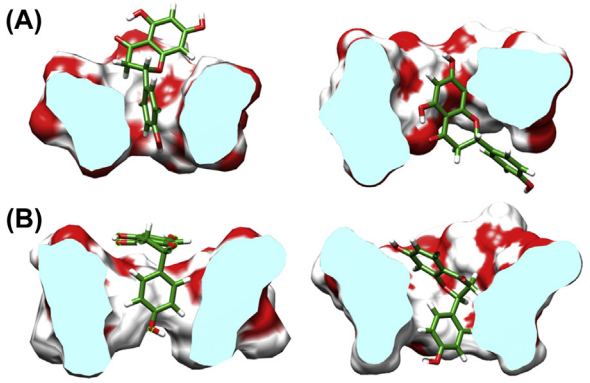

Fig. 5. Cutaway views on the MD structures of the (A) naringenin/β-CD and (B) naringenin/DM-β-CD complexes showing the possible orientations of naringenin in the inner surface of the CD.

3.4. Binding free energy

The molecular mechanics with two different continuum solvation methods, PBSA and GBSA, was applied to estimate the absolute binding free energies of the naringenin/β-CD and naringenin/DM-β-CD inclusion complexes. The binding free energies ($\Delta G_{MM/PBSA}$ and $\Delta G_{MM/GBSA}$) and their energetic components, including the gas phase energy (ΔE_{MM}) from a summation of ΔE_{ele} and ΔE_{vdW}, solvation free energies (ΔG_{PBSA} and ΔG_{GBSA}) and entropic term ($T\Delta S$) are summarized in Table 2.

In the gas phase, the contribution of the attractive electrostatic interaction was almost equal in the naringenin/β-CD

Table 2
Binding free energy (kcal/mol) and its calculated energy components of the each complex in comparison to experimental values.

Energy (kcal/mol)	Naringenin/β-CD	Naringenin/DM-β-CD
ΔE_{ele}	−4.09 ± 2.89	−4.73 ± 3.65
ΔE_{vdw}	−25.69 ± 2.85	−29.71 ± 2.61
ΔE_{MM}	−29.78 ± 4.32	−34.43 ± 3.54
ΔE_{QM}	−23.51 ± 0.01	−27.05 ± 0.03
$T\Delta S$	−11.70 ± 1.31	−14.1 ± 5.82
$\Delta G_{Sol(PBSA)}$	11.65 ± 2.12	11.64 ± 1.97
$\Delta G_{Sol(GBSA)}$	10.64 ± 2.19	9.28 ± 1.63
$\Delta G_{MM/PBSA}$	−5.89 ± 1.25	−8.70 ± 2.57
$\Delta G_{MM/GBSA}$	−7.44 ± 1.46	−11.06 ± 2.69
$\Delta G_{QM/PBSA}$	−0.16 ± 0.08	−1.31 ± 1.42
$\Delta G_{QM/GBSA}$	−1.17 ± 0.04	−3.67 ± 1.75
$\Delta G_{experiment}$	−3.45	N/A

and naringenin/DM-β-CD complexes (ΔE_{ele} of −4.09 and −4.73 kcal/mol, respectively). The van der Waals (vdW) energy was some six-fold greater than the ΔE_{ele} in both of the naringenin/CD complexes (ΔE_{vdW} of −25.53 and −27.22 kcal/mol), which implied that the vdW interaction played an important role in forming/stabilizing the inclusion complex. The obtained information was in good agreement with the previous studies in which the hydrophobic interaction was found to be the main driving force for flavanones-CD inclusion complexes [42]. From the two interaction energies, the MM energy (ΔE_{MM}) suggested a better binding of naringenin in the cavity of DM-β-CD than in that of β-CD by ∼4.6 kcal/mol. However, the absolute MM energy can overestimate the binding interaction, and so QM calculations with the DFT M06-2X/6-31+g(d,p) level of theory was applied on the same set of MD trajectories. With energy correction, the QM energy also indicated a more stable complexation of naringenin/DM-β-CD than naringenin/β-CD (∼3.5 kcal/mol). By including the solvation free energy and entropic terms, all four approaches (MM/PBSA, MM/GBSA, QM/PBSA and QM/GBSA) predicted the same trend of absolute binding free energy of naringenin/DM-β-CD ≫ naringenin/β-CD, and so strongly suggest that the DM-β-CD derivative could better encapsulate naringenin with an enhanced complex stability. In addition, the calculated ΔG values of the naringenin/β-CD complex were somewhat close to the previously reported experimental ΔG value (−3.45 kcal/mol) [43].

4. Conclusions

In the present work, the stability of inclusion complexes between naringenin and β-CD or DM-β-CD was investigated theoretically using molecular docking, multiple MD simulations and four different free energy calculations. The results revealed that the phenyl ring of naringenin preferentially dipped to both CDs. The increased width and height of the DM-β-CD cavity compared to that of the β-CD resulted in a weaker H-bond of naringenin with the 3-OH group located at the interior of DM-β-CD and a higher conformational change of naringenin within the hydrophobic inner cavity. Both chromone and phenyl rings of naringenin were located well inside the cavity of DM-β-CD, whilst a dramatically higher mobility of naringenin was observed in the complex with β-CD. A more stable complexation of naringenin/DM-β-CD complex was supported by MM-PBSA/GBSA and QM-PBSA/GBSA binding free energy calculations. Importantly, vdW interactions were found to be the key guest–host interaction for naringenin binding inside the CDs.

Acknowledgments

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