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Inclusion complexation of pinostrobin with various cyclodextrin derivatives

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ABSTRACT

Pinostrobin (PNS) is one of the important flavonoids and can be abundantly found in the rhizomes of fingerroot (*Boesenbergia rotrunda*) and galangal (*Alpinia galangal* and *Alpinia officinarum*), the herbal basis of Southeast Asian cooking. Similar to other flavonoids, PNS exhibits anti-oxidative, anti-inflammatory and anti-cancer properties. However, this compound has an extremely low water solubility that limits its use in pharmaceutical applications. Beta-cyclodextrin (βCD) and its derivatives, 2,6-dimethyl-βCD (2,6-DMβCD) and the three hydroxypropyl-βCDs (2-HPβCD, 6-HPβCD and 2,6-DHPβCD), have unique properties that enhance the stability and solubility of such low-soluble guest molecules. In the present study, molecular dynamics simulations were applied to investigate the dynamics and stability of PNS inclusion complexes with βCD and its derivatives (2,6-DMβCD, 2,6-DHPβCD, 2-HPβCD and 6-HPβCD). PNS was able to form complexes with βCD and all four of its derivatives by either the chromone (*C*-PNS) or phenyl (*P*-PNS) ring dipping toward the cavity. According to the molecular mechanics-generalized Born surface area binding free energy values, the stability of the different PNS/βCD complexes was ranked as 2,6-DHPβCD > 2,6-DMβCD > 2-HPβCD > 6-HPβCD > βCD. These theoretical results were in good agreement with the stability constants that had been determined by the solubility method.

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1. Introduction

Flavonoids are a large group of heterocyclic compounds that are commonly found in fruits, vegetables and herbs as plant secondary metabolites [1,2]. A fairly diversified range of bioactivities, such as anti-bacterial, anti-allergic and anti-oxidative activities, have been reported for flavonoids [3,4]. They are widely used as drug and dietary supplements due to their potential pharmacological properties and their rather low toxicity. Pinostrobin (PNS) belongs to the flavanone subclass of flavonoids (Fig. 1A) and can be extracted from the rhizomes of Thai galangal (*Alpinia rotundra* and *Alpinia officinarum*) and Chinese ginger (*Boesenbergia rotunda*). It has several important biological activities, such as an anti-inflammatory role on the cyclooxygenase activity [5], anti-aromatase activity [6], decreased growth rate of the MCF-7 breast cancer cell line [6] and inhibition of HIV-1 protease [7]. Furthermore, the activity of the β-amyloid peptide related to Alzheimer's disease can be inhibited by PNS through reducing the oxidative damage and calcium overload as well as suppressing the mitochondrial pathway that is involved in the cellular apoptosis [8]. Similar to many flavonoids, PNS exhibits a relatively low water solubility leading to a significant limitation in its use in pharmaceutical applications. Consequently, suitable drug delivery carriers are of interest to solve this problem.

Cyclodextrins (CDs) are macrocyclic oligosaccharides of α-1,4 linked D-(+)-glucopyranose produced from starch by cyclodextrin glycosyl transferase catalysis [9]. CD structures have a trun-

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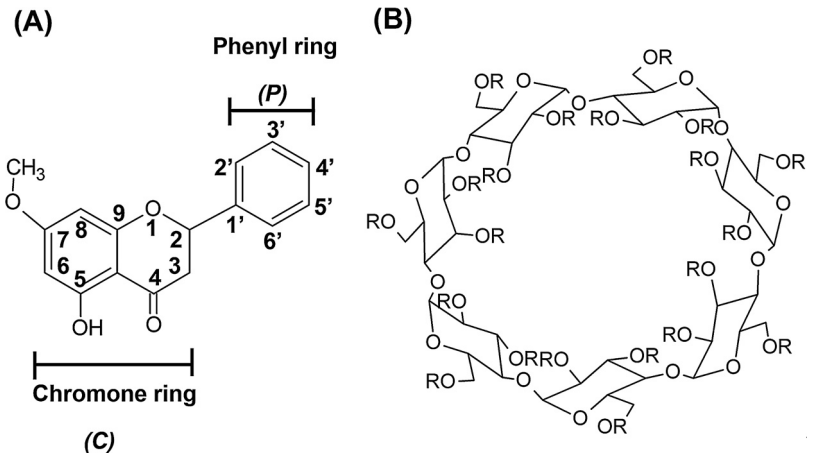

Fig. 1. Two dimensional structures of (A) pinostrobin (PNS) and (B) β-cyclodextrin (βCD) and its derivatives, where —R is —H, —CH_3 and —C_3H_7O for βCD, 2,6-DMβCD and 2,6-DHPβCD, respectively.

cated cone shape with a relatively hydrophilic outer surface and a hydrophobic inner cavity. The wider rim of βCD consists of hydroxyl groups at the 2- and 3-position of each glucose subunit, while the other narrower rim contains hydroxyl groups at the 6-position of each glucose subunit.

The inclusion of poorly water-soluble drugs into βCD can be used to enhance the solubility, stability and bioavailability of these drugs [10–12], where the hydrophobic drugs prefer to insert their hydrophobic motif(s) inside the CD cavity [13]. Naturally, there are three major types of small-ring CDs; namely αCD, βCD (Fig. 1B) and γCD that are composed of six, seven and eight glucose subunits, respectively [14]. Due to the high yield synthesis and low price of βCD it has been the main form used in the pharmaceutical, food and cosmetic industries [15]. Albeit, βCD shows a relatively lower water solubility (18.5 mg/mL) than other CDs [16,17], which limits its applications. Derivatives of βCD, for example 2,6-dimethyl βCD (2,6-DMβCD) and 2-hydroxypropyl βCD (HPβCD) that have a higher water solubility (570 and >600 mg/mL, respectively) [18,19], have been shown to improve the bioavailability and bioactivity of the encapsulated molecule in a much more efficient way [20–22].

Experimental studies to determine the stability and phase solubility of inclusion complexes between CDs and flavonoids have been reported [23,24], and have shown that a higher solubility of the CD derivatives and better affinities between host and guest molecules are advantages for pharmaceutical applications. For example, phase solubility studies on rutin forming 1:1 molar ratio complexes with HPαCD, HPβCD and HPγCD revealed that the complex stability constants with HPβCD and HPγCD were significantly increased [25]. Accordingly, the solubility of artesunate, a low water soluble antimalarial drug, can be improved by a 1:1 molar ratio formation with methyl-βCD more than with HPβCD or βCD [26].

In addition to experimental investigations, computational tools are useful to determine the preferable binding mode of drugs, such as flavonoids, and for the prediction of guest-host interactions as well as the stability of inclusion complexes at a molecular level [27]. For example, the molecular dynamics simulations (MDs) of quercetin and myricetin complexed with different CD derivatives provided the host-guest orientation in a good agreement with the ^{1}H NMR results [28]. In addition, although there are various possible inclusion geometries of fisetin/βCD complexes, it was found by molecular simulations that the insertion of the phenyl ring inside the cavity of βCD was more favorable [29]. Moreover, the molecular mechanics-Poissan–Boltzmann surface area/-generalized Born surface area (MM-PBSA/GBSA) and quantum mechanics (QM)-PBSA/GBSA binding free energy calculations predicted that naringenin would bind to 2,6-DMβCD better than to natural βCD [30].

To date, theoretical and experimental studies of PNS in inclusion complexes with various βCDs have not been reported. Thus, the main aim of this study was to predict computationally the most suitable βCD derivative for PNS encapsulation, and then the PNS/βCD complexes were formed experimentally for further pharmaceutical applications. In addition, the molecular details of the PNS binding mode and orientation, stability and solvation in the inclusion complex with βCD and its derivatives, 2,6-DMβCD and the three HPβCDs (2- and 6-HPβCD and 2,6-DHPβCD), were discussed and compared.

2. Methods

2.1. Computation

2.1.1. System preparation

The optimized structures of βCD and 2,6-DMβCD were taken from our previous studies [31]. For the three HPβCD derivatives, the structures of 2-HPβCD, 6-HPβCD and 2,6-DHPβCD were prepared by 2-hydroxylpropyl substitutions on all 2-, 6- and both 2- and 6-hydroxyl positions of the natural βCD, respectively. The PNS geometry was built and then optimized by the HF/6-31(d) level of theory using the Gaussian09 program to obtain well-adjusted bond lengths and angles [32]. The inclusion complex between PNS and each respective (modified or not) βCD was constructed by the CDOCKER module in the Discovery Studio 2.5 (Accelrys, Inc.) with 500 independent docking runs. The complex with the best ranked interaction energy and highest hydrogen bond (H-bond) formation at each PNS binding mode, chromone (*C*-PNS) or phenyl ring (*P*-PNS) dipping into the βCD cavity, was chosen as the representative structure. Where only one binding orientation was obtained by the docking procedure, another was manually generated for comparison. In total, there were 15 systems for further MD studies; five free CDs (βCD, 2,6-DMβCD, 2,6-DHPβCD, 2-HPβCD and 6-HPβCD) plus these five different CDs complexed with either P-PNS or C-PNS. Note that the docking manner was used to determine the starting position of PNS in βCDs. Hence, the molecular dynamics (MD) simulation was performed to clarify the importance of solvent effects in the forming inclusion complexes.

2.1.2. Molecular dynamics (MD) simulation

The structure of βCD and its dimethyl and hydroxypropyl derivatives alone and complexed with PNS in aqueous solution were simulated with three different initial velocities using the

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