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In Silico Analysis of Pinocembrin Inclusion Complexes with β-Cyclodextrin and Hydroxypropyl-β-Cyclodextrin Using DFT and Molecular Docking

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Abstract. Pinocembrin is a naturally occurring flavanone found in medicinal plants, particularly *Boesenbergia rotunda*, with promising pharmacological activities; however, its poor aqueous solubility limits its pharmaceutical application. Cyclodextrin inclusion complexation represents a potential strategy to improve the solubility characteristics of poorly water-soluble compounds. This study aimed to investigate the molecular characteristics and inclusion behavior of pinocembrin with β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HPβ-CD) using an in silico approach combining ADME prediction, Density Functional Theory (DFT), and molecular docking analysis. The physicochemical properties, drug-likeness, and pharmacokinetic profiles of pinocembrin were evaluated using SwissADME and pkCSM. Geometry optimization and electronic properties were analyzed using DFT at the B3LYP/6-311G(d,p) level of theory. Molecular docking simulations were performed using AutoDock Vina to evaluate binding orientations, binding affinities, and intermolecular interactions between pinocembrin and cyclodextrin cavities. The ADME analysis indicated that pinocembrin exhibited favorable drug-like properties and pharmacokinetic characteristics, although low aqueous solubility remained a critical challenge. DFT analysis revealed a stable optimized structure with an energy gap of 5.08 eV and a dipole moment of 2.8912 Debye. Molecular docking demonstrated that pinocembrin could be accommodated within both β-CD and HPβ-CD cavities through different inclusion orientations. The A-form orientation showed the most favorable interaction, with the pinocembrin–HPβ-CD complex exhibiting a slightly more favorable predicted binding affinity (−5.9 kcal/mol) than pinocembrin–β-CD (−5.6 kcal/mol); However, the 0.3 kcal/mol difference is small and within the expected uncertainty of molecular docking. These findings provide molecular insights into pinocembrin–cyclodextrin inclusion complexes and suggest the potential application of HPβ-CD as a carrier for improving the solubility characteristics of pinocembrin.

Keywords: *Pinocembrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, density functional theory, molecular docking*

Abstrak. Pinocembrin merupakan flavanon alami yang ditemukan pada tanaman obat, khususnya *Boesenbergia rotunda*, dengan aktivitas farmakologis yang menjanjikan; namun, kelarutannya yang rendah dalam air membatasi aplikasinya dalam bidang farmasi. Kompleksasi inklusi siklodekstrin merupakan salah satu strategi potensial untuk meningkatkan karakteristik kelarutan senyawa yang sukar larut dalam air. Penelitian ini bertujuan untuk mengkaji karakteristik molekuler dan perilaku inklusi pinocembrin dengan β-siklodekstrin (β-CD) dan hidroksipropil-β-siklodekstrin (HPβ-CD) menggunakan pendekatan in silico yang mengombinasikan prediksi ADME, *Density Functional Theory* (DFT), dan analisis molecular docking. Sifat fisikokimia, drug-likeness, dan profil farmakokinetik pinocembrin dievaluasi menggunakan SwissADME dan pkCSM. Optimasi geometri dan sifat elektronik dianalisis menggunakan DFT pada tingkat teori B3LYP/6-311G(d,p). Simulasi molecular docking dilakukan menggunakan *AutoDock Vina* untuk mengevaluasi orientasi ikatan, afinitas pengikatan, dan interaksi antarmolekul antara pinocembrin dan rongga siklodekstrin. Analisis ADME menunjukkan bahwa pinocembrin memiliki sifat menyerupai obat dan karakteristik farmakokinetik yang baik, meskipun kelarutan dalam air yang rendah masih menjadi tantangan utama. Analisis DFT menunjukkan struktur teroptimasi yang stabil dengan energy gap sebesar 5,08 eV dan momen dipol sebesar 2,8912 Debye. Molecular docking menunjukkan bahwa pinocembrin dapat terakomodasi di dalam rongga β-CD dan HPβ-CD melalui berbagai orientasi inklusi. Orientasi A-form menunjukkan interaksi yang paling menguntungkan, dengan kompleks pinocembrin–HPβ-CD memiliki afinitas pengikatan prediktif yang sedikit lebih menguntungkan (−5,9 kcal/mol) dibandingkan pinocembrin–β-CD (−5,6 kcal/mol), Namun, perbedaan sebesar 0,3 kkal/mol relatif kecil dan masih berada dalam kisaran ketidakpastian yang diharapkan dalam *molecular docking.* Temuan ini memberikan wawasan molekuler mengenai kompleks inklusi pinocembrin–siklodekstrin dan menunjukkan potensi penggunaan HPβ-CD sebagai pembawa untuk meningkatkan karakteristik kelarutan pinocembrin.

Kata kunci: *Pinosembrin, β-siklodekstrin, hidroksipropil-β-siklodekstrin, density functional theory, molecular docking*

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INTRODUCTION

Natural products are an important source of bioactive compounds for pharmaceutical development because they contain diverse secondary metabolites with various biological activities. Indonesia, as a megabiodiverse country, provides a rich source of plant-derived bioactive compounds, particularly flavonoids with diverse chemical structures and biological activities (Faramayuda et al., 2025). Flavonoids have been widely investigated because of their potential antioxidant, anti-inflammatory, antimicrobial, antiviral, and anticancer activities. One notable medicinal species native to Southeast Asia is *Boesenbergia rotunda*, commonly known as temu kunci. This plant belongs to the Zingiberaceae family and contains several biologically active flavonoids, including pinocembrin (Wang et al., 2025).

Pinocembrin (5,7-dihydroxyflavanone) is a naturally occurring flavanone found in medicinal plants, particularly *Boesenbergia rotunda*. As members of the plant secondary-metabolite group, flavonoids contribute to numerous biological effects, particularly antioxidant activity (Ngibad et al., 2023). Previous investigations have reported that pinocembrin possesses a broad range of pharmacological properties, such as antioxidant, anti-inflammatory, antimicrobial, neuroprotective, antimutagenic, and anticancer activities (Elbatreek et al., 2023; González et al., 2022). In addition, pinocembrin has shown a favorable safety profile, highlighting its potential as a promising pharmaceutical compound.

Despite its broad biological potential, the development of pinocembrin as a pharmaceutical ingredient is hindered by its very low solubility in water. This property can slow the dissolution process, restrict absorption, and ultimately decrease its bioavailability (Muharrami et al., 2024). Limited water solubility is a frequent obstacle in drug development because the amount of compound that dissolves can directly influence its absorption performance (S. Belsarkar et al., 2022). Therefore, enhancing pinocembrin's water solubility is crucial for realizing its full potential in pharmaceutical applications.

Cyclodextrin inclusion complexation is one of the most widely used strategies for improving the solubility of hydrophobic compounds because it can enhance aqueous solubility, dissolution rate, and physicochemical stability without altering the chemical structure of the guest molecule (Alfei & Zuccari, 2024; Aminah et al., 2025). Cyclodextrins are ring-shaped oligosaccharides built from glucopyranose units, with a water-attracting exterior and a comparatively nonpolar internal cavity. This structural arrangement enables them to host lipophilic compounds through weak intermolecular forces, including hydrogen bonding, van der Waals forces, and hydrophobic interactions (Xu et al., 2021). β-cyclodextrin (β-CD) is widely used due to its suitable cavity size for flavonoid compounds (Sarabia-Vallejo et al., 2023). Hydroxypropyl-β-cyclodextrin (HPβ-CD), as a β-CD derivative, exhibits higher aqueous solubility, improved complexation ability, and better physicochemical properties compared with native β-CD (Musuc, 2024). The improved solubility characteristics of HPβ-CD further support its application as a carrier for poorly water-soluble compounds (Neaz et al., 2024).

Although the inclusion complexation of pinocembrin with cyclodextrins has been experimentally investigated, including its complexation with β-CD and HPβ-CD, previous

studies have primarily focused on the characterization, solubilization, and stability of the resulting inclusion complexes (Zhou et al., 2014). However, the molecular-level aspects of pinocembrin inclusion, particularly the preferred binding orientation, binding affinity, and specific intermolecular interactions within β-CD and HPβ-CD cavities, remain insufficiently characterized. Molecular-level information regarding host–guest interactions is important for understanding the factors influencing complex stability and for evaluating the potential of different cyclodextrin carriers. Molecular docking is a computational technique commonly applied to estimate host–guest binding orientations, interaction strengths, and intermolecular contacts, thereby providing insights into the molecular basis of inclusion complex formation. (Abdjan, Aminah, Kristanti, Siswanto, Saputra, et al., 2023; Agu et al., 2023).

Computational methods, including Density Functional Theory (DFT) and molecular docking, are useful for examining molecular properties and estimating interactions between host and guest molecules. DFT analysis can provide information regarding molecular optimization and electronic properties based on quantum mechanical calculations. Molecular docking can predict binding orientation, affinity, and interaction patterns between guest and host molecules, providing insights into host–guest interactions (Abdjan, Aminah, Kristanti, Siswanto, Saputra, et al., 2023; Belhocine, Rahali, Allal, Assaba, Ghoniem, & Ali, 2021). Previous studies have demonstrated that molecular docking is an efficient computational approach for predicting binding orientation, binding affinity, and intermolecular interactions, providing valuable insights into molecular recognition prior to experimental validation (Gaspersz et al., 2024).

Therefore, this study was designed to examine the inclusion complexes of pinocembrin with β-cyclodextrin and hydroxypropyl-β-cyclodextrin using an in silico approach. DFT calculations were used to determine the optimized geometry and electronic characteristics of pinocembrin, whereas molecular docking was applied to estimate binding strength, preferred inclusion mode, and intermolecular contacts inside the cyclodextrin cavities. This study offers a molecular-level explanation of how pinocembrin interacts with cyclodextrins and suggests that β-CD and HPβ-CD could function as carriers to enhance its aqueous solubility.

MATERIAL AND METHODS

Molecular Structure Preparation of Pinocembrin, β-Cyclodextrin, and Hydroxypropyl-β-Cyclodextrin.

The molecular structure of pinocembrin was retrieved from the PubChem database (PubChem, 2022) and converted from a two-dimensional (2D) structure into a three-dimensional (3D) structure using Chem3D software. The initial energy minimization process was performed to obtain a stable molecular conformation before further computational analysis. The prepared structure of pinocembrin is shown in Figure 1.

The three-dimensional models of β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HPβ-CD) were constructed using UCSF Chimera. Both compounds were chosen as host molecules because they can accommodate hydrophobic guest compounds within inclusion complexes stabilized by noncovalent forces (Esteso & Romero, 2024). HPβ-CD, as a β-CD derivative, exhibits

improved aqueous solubility and complexation characteristics compared with native β-CD (Musuc, 2024). Structural preparation included hydrogen addition, charge assignment, and structural refinement to obtain suitable host molecules for molecular docking analysis. The prepared structures of pinocembrin, β-CD, and HPβ-CD were then employed as the starting molecular models for the docking simulations.

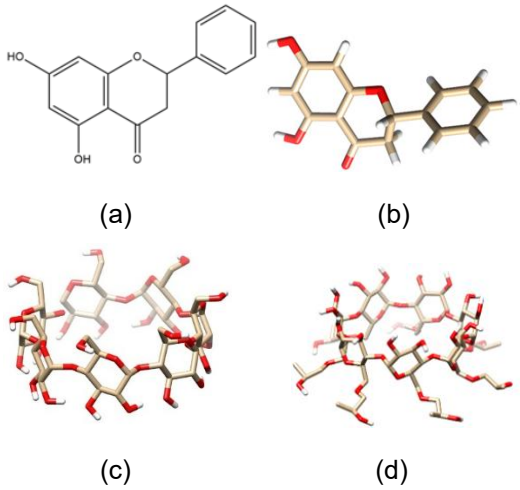

Figure 1. Two-dimensional and three-dimensional molecular structures of (a) pinocembrin, (b) three-dimensional pinocembrin structure, (c) β-cyclodextrin (β-CD), and (d) hydroxypropyl-β-cyclodextrin (HPβ-CD).

Density Functional Theory (DFT) Calculation

Pinocembrin geometry was optimized through Density Functional Theory (DFT) calculations using the B3LYP functional combined with the 6-311G(d,p) basis set in Gaussian 09 under gas-phase conditions. No implicit solvation model was applied during the geometry optimization. DFT calculation was applied to obtain the optimized molecular structure in its lowest-energy conformation and evaluate the electronic characteristics of the molecule (Abdjan, Aminah, Kristanti, Siswanto, Saputra, et al., 2023). The geometry optimization was performed in the gas phase without applying an implicit solvation model such as PCM or SMD.

The electronic characteristics were examined using frontier molecular orbital analysis, covering the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO), the HOMO–LUMO energy gap, molecular electrostatic potential (MEP), and dipole moment. The optimized geometry of pinocembrin was then employed as the starting structure for molecular docking calculations.

Molecular Docking Simulation

Molecular docking simulations were carried out with AutoDockTools and AutoDock Vina to examine the interactions of pinocembrin with β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HPβ-CD). This method was used to estimate the possible inclusion modes and binding interactions between the guest molecule and the cyclodextrin hosts. (Agu et al., 2023). Previous studies have demonstrated that molecular docking is an efficient computational approach for evaluating molecular recognition and estimating binding affinity prior to experimental validation (Gaspersz et al., 2024). The optimized structure of pinocembrin obtained from DFT calculations and the prepared cyclodextrin structures were converted into PDBQT format prior to docking analysis. Hydrogen atoms were incorporated into the molecular models, followed by the assignment of partial atomic charges.

The docking grid box was defined to cover the cyclodextrin cavity. For β-CD, the grid center was set at (0.000, 0.000, 0.000) with grid dimensions of 60 × 60 × 60 points. For HPβ-CD, the grid center was set at (6.500, 3.000, 3.000) with grid dimensions of 60 × 60 × 60 points. A

maximum of 20 binding modes (num_modes = 20) was generated for each docking calculation. Docking was performed separately for β-CD and HPβ-CD, with the random seed automatically generated by AutoDock Vina. The random seeds recorded in the docking log files were −380433344 for β-CD and 1118957728 for HPβ-CD.

The generated docking poses were ranked based on binding affinity values, and the most favorable complexes were selected for further molecular interaction analysis (Khatimah et al., 2025). The docking poses were classified into two inclusion orientations according to the rim of the cyclodextrin cavity through which pinocembrin entered. The A-form was defined as the orientation in which pinocembrin entered through the secondary rim, whereas the B-form was defined as the orientation in which pinocembrin entered through the primary rim. Representative A-form and B-form poses were subsequently selected for further interaction analysis.

Docking protocol validation by redocking was not performed because a suitable experimentally resolved three-dimensional reference structure of the pinocembrin–β-CD or pinocembrin–HPβ-CD complex was not available within the computational workflow for direct RMSD-based comparison. Therefore, the docking results were interpreted as predicted inclusion orientations and binding affinities rather than experimentally validated binding modes.

Molecular Interaction Analysis

The selected docked complexes were further assessed based on their intermolecular interactions. Pinocembrin was accommodated within the cyclodextrin cavity through several noncovalent forces, including hydrogen bonds, hydrophobic contacts, and van der Waals interactions. Together, these interactions may promote guest insertion into the cavity and support the formation of the inclusion complex.

RESULT AND DISCUSSION

ADME and Pharmacokinetic Characteristics of Pinocembrin

The physicochemical characteristics, drug-likeness profile, and pharmacokinetic characteristics of pinocembrin were evaluated using in silico ADME prediction. These evaluations were conducted to examine the molecular characteristics related to its pharmaceutical potential, including solubility, bioavailability, absorption, distribution, metabolism, and toxicity profiles. The predicted physicochemical properties and drug-likeness parameters of pinocembrin are summarized in Table 1. These parameters were estimated using SwissADME, a commonly used platform for the preliminary assessment of drug-like behavior and pharmacokinetic properties of bioactive molecules (Daina et al., 2017).

Table 1. Physicochemical properties and drug-likeness parameters of pinocembrin

Parameters	Pinocembrin
Molecular Weight (g/mol)	256.25
LogP (Lipophilicity)	1.27
Topological Polar Surface Area (Å²)	66.76
Hydrogen Bond Donor (HBD)	2
Hydrogen Bond Acceptor (HBA)	4
Lipinski Violation	0

According to Lipinski's rule of five, pinocembrin showed a favorable drug-likeness profile without any detected violations. Its

molecular weight, lipophilicity, and numbers of hydrogen-bond donors and acceptors remained within the recommended limits, suggesting appropriate physicochemical characteristics for further drug development. According to Lipinski's criteria, compounds with no violation of these parameters are considered to possess favorable drug-likeness characteristics for oral drug candidates (Lipinski et al., 2001). The TPSA value suggested an appropriate balance between polarity and molecular permeability. Similar findings have been reported in previous in silico studies, where compounds with favorable drug-likeness characteristics still exhibited limitations in aqueous solubility, emphasizing the importance of further molecular evaluation through computational approaches (Suri & Suryani, 2026). However, despite these favorable drug-like properties, pinocembrin showed limited aqueous solubility, which may represent a major challenge for its pharmaceutical application. The predicted solubility-related parameters are presented in Table 2.

Table 2. Solubility and bioavailability of pinocembrin

Parameters	Pinocembrin
LogS (ESOL)	-3.64
Solubility (mg/mL)	0.08
Bioavailability score	0.55

The ESOL prediction indicated poor aqueous solubility of pinocembrin, with a logS value of −3,64 and a predicted solubility of 0,08 mg/mL. The negative logS value indicates limited aqueous solubility, which is consistent with the ESOL model developed by Delaney for estimating aqueous solubility based on molecular properties (Delaney, 2004). Although pinocembrin exhibited a moderate predicted bioavailability score (0,55), its low aqueous solubility may limit dissolution performance and oral absorption. Therefore, cyclodextrin inclusion complex formation offers a promising approach for enhancing the solubility characteristics of pinocembrin.

The pharmacokinetic and toxicological profiles of pinocembrin were further evaluated using SwissADME and pkCSM predictions to assess its absorption, distribution, metabolism, and safety characteristics. The predicted ADMET profile is summarized in Table 3.

Table 3. In silico pharmacokinetic and ADMET profile of pinocembrin predicted by SwissADME and pkCSM

Parameters	Pinocembrin
Absorption	
GI absorption	High
Caco-^{2} permeability (log Papp, cm/s)	1.152
Distribution	
BBB permeant	Yes
Metabolism	
CYP1A2 Inhibitor	Yes
CYP2C19 Inhibitor	Yes
CYP2C9 Inhibitor	No
CYP2D6 Inhibitor	No
CYP3A4 Inhibitor	No
Toxicity	
AMES toxicity	No
Hepatotoxicity	No

The predicted ADMET profile indicated that pinocembrin exhibited favorable pharmacokinetic characteristics, including high gastrointestinal absorption and acceptable toxicity profiles. No AMES toxicity or hepatotoxicity was predicted, suggesting a favorable safety profile. However, the low aqueous solubility remains a major limitation, supporting the potential application of cyclodextrin inclusion complexation for solubility enhancement. Overall, these

findings suggest that pinocembrin possesses promising pharmaceutical potential, while molecular-level investigations are required to further understand its structural and interaction characteristics. Similar integration of ADMET prediction and molecular docking has also been applied in previous in silico studies to support the early-stage evaluation of potential drug candidates (Suri & Suryani, 2026).

DFT Analysis of Pinocembrin

A density functional theory (DFT) calculation was conducted to examine the optimized geometry and electronic characteristics of pinocembrin. Structural optimization at the B3LYP/6-311G(d,p) level of theory resulted in a stable molecular conformation with minimum energy. The optimized structure was subsequently analyzed through frontier orbital analysis, molecular electrostatic potential (MEP) mapping, and other electronic descriptors to clarify the molecular characteristics of pinocembrin (Abdjan, Aminah, Kristanti, Siswanto, Ilham, et al., 2023).

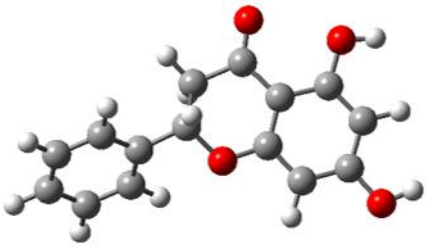

Figure 2. Optimized geometry molecular structure of pinocembrin obtained from DFT calculation.

The optimized structure of pinocembrin exhibited a minimum total energy of −879.93 Hartree. The obtained geometry retained the characteristic flavanone framework consisting of two aromatic rings connected through a heterocyclic ring. The optimized geometry was then used as the starting molecular model for docking studies with β-cyclodextrin and hydroxypropyl-β-cyclodextrin.

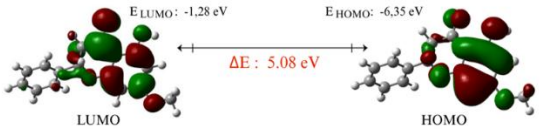

Figure 3. HOMO and LUMO orbital distributions of pinocembrin obtained from DFT calculation.

The frontier molecular orbitals of pinocembrin were analyzed to evaluate its electronic distribution and reactivity characteristics. The HOMO and LUMO energy levels were determined to be −6,35 eV and −1,28 eV, respectively, resulting in a HOMO–LUMO gap of 5,08 eV. The HOMO corresponds to the region capable of donating electrons, while the LUMO represents the electron-accepting region. This energy-gap value indicates that pinocembrin has a relatively stable electronic structure (Aman et al., 2023).

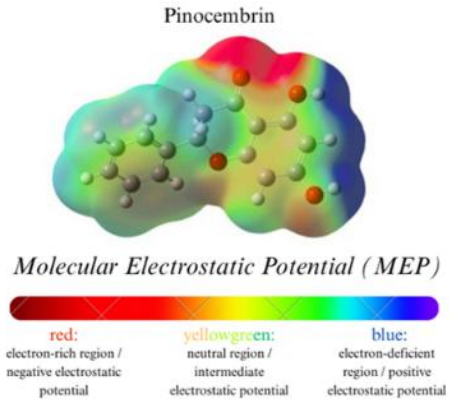

Figure 4. Molecular electrostatic potential (MEP) surface of pinocembrin generated from DFT calculations.

The MEP surface was examined to visualize the distribution of electron density across the pinocembrin molecule. Red-colored regions correspond to electron-rich sites with negative electrostatic potential, whereas blue-colored regions indicate electron-poor sites characterized by positive electrostatic potential. The observed electrostatic distribution

highlights potential interaction sites of pinocembrin that may contribute to noncovalent interactions during inclusion complex formation with cyclodextrins (Aman et al., 2023).

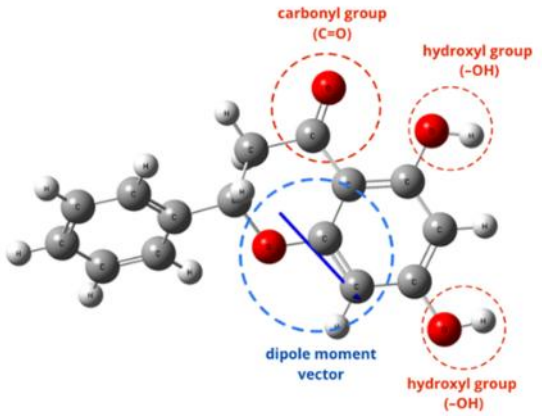

Figure 5. Dipole moment vector of pinocembrin obtained from DFT calculation.

The dipole moment analysis was conducted to assess the molecular polarity and charge distribution of pinocembrin. The calculated dipole moment of pinocembrin was 2,8912 Debye, indicating the presence of molecular polarity derived from the uneven distribution of electronic charge. The dipole vector was mainly influenced by polar moieties, particularly hydroxyl (–OH) and carbonyl (C=O) groups. This polarity may contribute to intermolecular interactions between pinocembrin and cyclodextrin molecules during inclusion complex formation (Aman et al., 2023).

The global reactivity descriptors of pinocembrin were further evaluated to investigate its electronic stability and reactivity characteristics. The computed descriptors—ionization energy, electron affinity, electronegativity, chemical potential, hardness, softness, and electrophilicity index are presented in Table 4 (Chakraborty & Chattaraj, 2021).

Table 4. Global reactivity descriptors of pinocembrin obtained from DFT calculation

Parameters	Pinocembrin
EHOMO	-6.35
ELUMO	-1.28
Energy gap, ΔE (eV)	5.08
Ionization potential, I (eV)	6.35
Electron affinity, A (eV)	1.28
Electronegativity, χ (eV)	3.815
Chemical potential, μ (eV)	-3.815
Chemical hardness, η (eV)	2.54
Chemical softness, S (eV^{-1})	0.197
Electrophilicity index, ω (eV)	2.87

The calculated global reactivity descriptors provide further insight into the electronic characteristics of pinocembrin. The energy gap value of 5,08 eV indicates a relatively stable electronic structure, while the electronegativity and chemical potential values reflect its electron-accepting tendency. The chemical hardness and softness parameters describe the molecular stability and reactivity of pinocembrin, which may influence its interaction behavior with cyclodextrin molecules during inclusion complex formation.

Molecular docking analysis of Pinocembrin-β-CD and Pinocembrin-HPβ-CD complexes

Molecular docking was conducted to examine how pinocembrin is accommodated within the cavities of β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HPβ-CD). The docking simulation was used to evaluate the preferred binding orientation and interaction affinity of pinocembrin toward both cyclodextrin hosts (Agu et al., 2023).

The cyclodextrin structure contains a hydrophobic inner cavity surrounded by hydrophilic hydroxyl rims. This cavity provides a suitable environment for accommodating the hydrophobic flavanone structure of pinocembrin through noncovalent interactions. The

orientation of pinocembrin within the cyclodextrin cavity may affect the predicted binding affinity and interaction pattern of the resulting inclusion complex (Abdjan, Aminah, Kristanti, Siswanto, Ilham, et al., 2023).

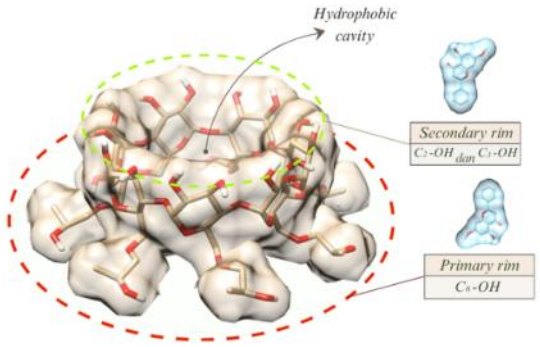

Figure 6. Structural representation of cyclodextrin cavity regions and possible inclusion orientations of pinocembrin

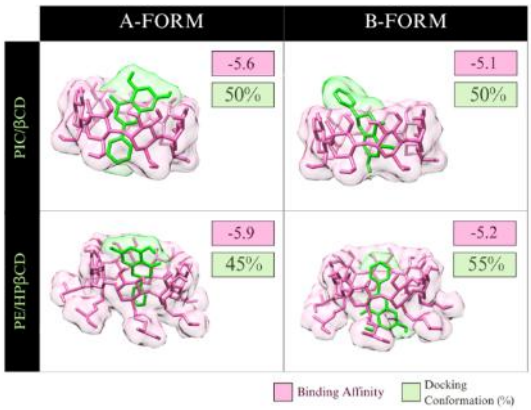

Figure 7. Docking poses and binding affinity comparison of pinocembrin inclusion systems involving β-CD and HPβ-CD

The docking results revealed two major inclusion orientations, namely A-form (secondary rim insertion) and B-form (primary rim insertion), for pinocembrin within β-CD and HPβ-CD cavities. Among these orientations, the A-form exhibited a more favorable predicted binding affinity than the B-form for both cyclodextrin hosts, suggesting that this orientation provides a more favorable predicted interaction with the cyclodextrin cavity. The pinocembrin–HPβ-CD complex in the A-form orientation exhibited the most favorable predicted interaction, with a binding affinity of −5,9 kcal/mol, followed by the pinocembrin–β-CD complex with −5,6 kcal/mol.

However, the difference in predicted binding affinity between the two complexes was only 0,3 kcal/mol. This relatively small difference should be interpreted cautiously, as it may fall within the expected uncertainty of molecular docking scoring. Therefore, the results indicate a slightly more favorable predicted binding affinity for HPβ-CD, rather than definitive evidence of a substantially stronger binding preference. The slightly more favorable predicted affinity may be related to differences in steric accessibility and molecular complementarity between the guest molecule and the cyclodextrin cavity. The A-form configuration was chosen as the representative inclusion model for subsequent analysis of intermolecular interactions. (Abdjan et al., 2025).

The selection of docking poses was based on binding affinity values, which represent the strength of interaction between guest and host molecules (Khatimah et al., 2025). The selected docked complexes were further assessed based on their intermolecular interactions. The inclusion of pinocembrin within the cyclodextrin cavity was mainly supported by noncovalent interactions, including hydrogen bonds, hydrophobic contacts, and van der Waals interactions. Collectively, these interactions may facilitate the accommodation of pinocembrin within the cyclodextrin cavity and promote the development of stable inclusion complexes (Abdjan, Aminah, Kristanti, Siswanto, Saputra, et al., 2023). The analysis of binding affinity together with intermolecular

interactions is widely employed in molecular docking to evaluate the stability of molecular complexes and identify favorable binding conformations, as demonstrated in previous computational studies (Gazpersz et al., 2024).

CONCLUSION

This study demonstrated that pinocembrin can form inclusion complexes involving β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HPβ-CD), examined through an in silico approach integrating DFT calculations and molecular docking. DFT results revealed the stable electronic characteristics of pinocembrin and identified potential regions involved in molecular interactions. Molecular docking showed that pinocembrin could be accommodated within both cyclodextrin cavities through different inclusion orientations, with the A-form exhibiting the most favorable binding affinity, particularly in the HPβ-CD complex. These results clarify, at the molecular level, how pinocembrin interacts with cyclodextrins and indicate that HPβ-CD may serve as an appropriate carrier for enhancing the aqueous solubility of pinocembrin. As these findings are based on computational predictions, experimental validation through approaches such as phase-solubility studies and DSC/FTIR characterization is needed to confirm the formation and physicochemical characteristics of the inclusion complexes.

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