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Molecular Docking Insights into the Interaction of Cyclodextrin-Based Systems with Bioactive Monoterpenes of Biotechnological Interest

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ABSTRACT: Cyclodextrin-based systems are promising carriers for improving the stability and bioavailability of hydrophobic bioactive compounds. Monoterpenes, the major constituents of medicinal plant essential oils, exhibit significant pharmacological potential but are limited by poor aqueous solubility, high volatility, and chemical instability. This study investigated the structural and energetic interactions of sulfobutylether-β-cyclodextrin (SBE-β-CD) with the major bioactive constituents of essential oil of *Alpinia zerumbet* (EOAz), through molecular docking simulations. OEAz was obtained by hydrodistillation and complexed with SBE-β-CD (1:1 molar ratio) using the co-precipitation method. The resulting host–guest inclusion complexes, formed between SBE-β-CD and terpinen-4-ol or 1,8-cineole, were evaluated by molecular docking simulations. These compounds were selected based on their established status as major constituents of EOAz. Computational analyses were performed using HEX 8.0.0 software, followed by structural inspection in PyMOL. The docking results revealed energetically favorable interaction clusters, indicating high affinity and structural stability between the evaluated molecules. The most stable conformations demonstrated significant spatial complementarity and multiple intermolecular interactions, including hydrophobic contacts and hydrogen-bond-associated stabilization. Energetic analyses showed negative binding energies compatible with stable molecular association, supporting the formation of persistent host–guest complexes. Furthermore, the predicted host–guest interactions indicate that cyclodextrin complexation may favor the preservation of monoterpene integrity and bioavailability, factors that could contribute to enhanced or more consistent biological activity. Overall, these findings demonstrate the usefulness of molecular docking for investigating cyclodextrin-based systems and provide preliminar structural evidence for future studies exploring the therapeutic and biotechnological applications of monoterpene inclusion complexes.

KEYWORDS: molecular docking; SBE-β-CD; 1,8-cineole; terpinen-4-ol; host–guest interaction; computational biochemistry; bioactive monoterpenes; structural bioinformatics.

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides derived from enzymatic degradation of starch that have a truncated shape with a hydrophilic surface and a hydrophobic cavity. CDs have been extensively investigated as molecular carriers due to their ability to form inclusion host-guest complexes with many hydrophobic compounds, improving solubility, chemical stability, and biological availability (Musuc, 2024).

Among CDs derivates, sulfobutylether–β-cyclodextrin (SBE-β-CD) has emerged as a promising platform for pharmaceutical and biotechnological applications owing to its high aqueous solubility, stability, biocompatibility and low toxicity. SBE-β-CD is a polyanionic cyclic oligosaccharide having 7 α-D-glucopyranose units with torus ring-like structure (Figure 1). Compared with native β-cyclodextrin, it exhibits more than 50-fold greater water solubility, making it an attractive carrier for drug delivery of a wide range of therapeutic compounds (Pardeshi *et al.*, 2023).

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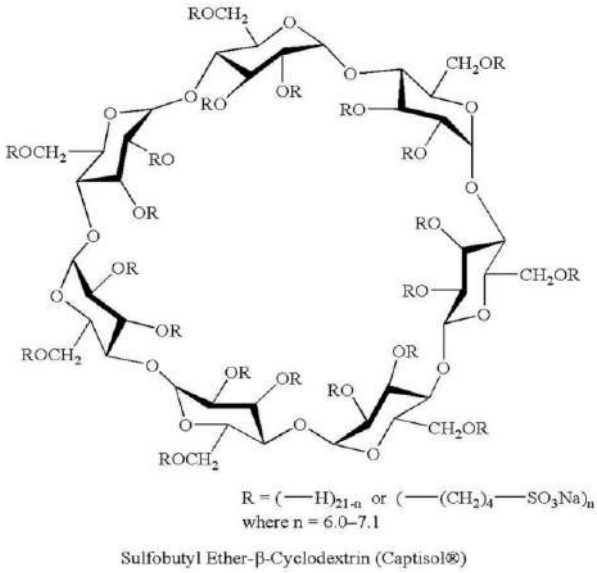
Figure 1. 2D-chemical structure of a representative species of Sulfobutylether–cyclodextrin (SBE-β-CD)



Source: http://www.chemspider.com/Chemical-Structure.25940133.html

Natural products, including medicinal plants and their secondary metabolites, such as essential oils (EO - complex mixtures of volatile compounds) represent a promising source for the development of new therapeutic agents. In this context, the essential oil of *Alpinia zerumbet* (EOAz) has attracted considerable attention due to its broad spectrum of biological activities, including antimicrobial, antioxidant, anti-inflammatory, vasorelaxant, antihypertensive, antinociceptive, anxiolytic, antiparasitic, and anti-aging effects, thereby supporting its traditional use and highlighting its potential for pharmaceutical and biotechnological applications (Nishidono & Tanaka, 2024).

These activities have been largely attributed to the predominance of oxygenated monoterpenes, particularly 1,8-cineole and terpinen-4-ol, which are consistently reported as major constituents of EOAz and are considered key contributors to its pharmacological properties, although their volatility and hydrophobicity may limit their technological application. Thus, computational molecular docking represents an important strategy for evaluating host–guest interactions and predicting the structural stability of cyclodextrin-based complexes.

Therefore, the present study investigated, through *in silico* molecular docking analyses, the structural and energetic interactions between SBE-β-CD and two major bioactive monoterpenes (1,8-cineole and terpinen-4-o) from EOAz and promising compounds for biotechnological applications, aiming to assess the formation and stability of host–guest inclusion complexes.

MATERIALS AND METHODS

Extraction of the essential oil of *Alpinia zerumbet* (EOAz) by hydrodistillation

EOAz was obtained by hydrodistillation using a Clevenger-type apparatus from 1000 g of freshly collected leaves. The leaves were cut, mixed with distilled water, and subjected to boiling for 2 h. After extraction, the essential oil was separated from the aqueous phase, dried over anhydrous sodium sulfate and stored at −20 °C.

Preparation of the EOAz:SBE-β-CD inclusion complexes by co-precipitation

The preparation of the inclusion complexes (ICs) between the EOAz and SBE-β-CD was performed by co-precipitation method. All samples were prepared in a 1:1 stoichiometric molar ratio. The SBE-β-CD (300 mg) was previously solubilized in 15 ml of ethanol:water (1:2) solution heated at 55 °C for 30 min (150 rpm), 200 µl aliquot of EOAz was solubilized in ethanol PA (1300 µl) and added to the cyclodextrin solution stirred at 150 rpm for 24 h at 25 °C. The suspension was then removed from the stirring and cooled to 4 °C for 12 h and the precipitate was submitted to freeze-drying. The samples were stored in a glass desiccator at room temperature.

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Molecular docking assay

The three-dimensional molecular structures of sulfobutylether–β-cyclodextrin (SBE-β-CD), 1,8-cineole, and terpinen-4-ol were obtained from publicly available chemical databases, including PubChem and ChemSpider. Molecular structures were inspected and standardized prior to computational analysis in order to ensure geometric consistency and appropriate atom typing for docking simulations. The selected monoterpenes, 1,8-cineole and terpinen-4-ol, were chosen due to their recognized biological and biotechnological relevance, including previously reported antimicrobial, anti-inflammatory, and bioactive modulation properties.

Molecular docking analyses were performed to evaluate the structural affinity and interaction profile between SBE-β-CD and the selected bioactive monoterpenes. Docking simulations were conducted using HEX 8.0.0 software, an FFT-based molecular docking platform widely employed for the prediction of intermolecular interactions and energetically favorable conformations (Macindoe *et al.*, 2010).

The docking protocol consisted of automated molecular fitting between the cyclodextrin derivative and each ligand, aiming to identify the most energetically stable interaction clusters. A total of 50,000 docking solutions were generated for each simulation, from which the highest-ranked conformational clusters were selected according to total interaction energy (E_{total}). The computational parameters adopted during the docking procedures were: correlation type set to shape-only mode; FFT mode configured as 3D fast lite; grid dimension of 0.6; receptor rotational range of 180°; ligand rotational range of 180°; twist range of 360°; and distance range of 40 Å. Calculations were performed using GPU acceleration to optimize computational performance.

The conformational clusters generated during docking simulations were analyzed using PyMOL Molecular Graphics System version 1.4.7 (Delano, 2002). Structural inspection focused on the spatial orientation of the ligands within the interaction region, the identification of intermolecular contacts, and the evaluation of steric complementarity between host and guest molecules.

Special attention was directed toward the characterization of hydrophobic interactions, hydrogen bond-associated contacts, and the overall conformational stability of the predicted complexes. The spatial occupation of the ligands within the interaction environment was also evaluated to infer potential stabilization effects associated with molecular inclusion and host–guest recognition.

The energetic stability of the predicted molecular complexes was evaluated based on the total interaction energy (Etotal, kcal/mol) generated by HEX docking simulations. The most energetically favorable conformations were selected for detailed structural analysis. Negative interaction energy values were interpreted as indicative of favorable intermolecular association and structural stabilization between SBE-β-CD and the evaluated monoterpenes. Comparative analysis among the highest-ranked clusters was performed to identify recurrent conformational patterns and the most stable interaction profiles.

RESULTS AND DISCUSSION

EOAz extracted showed a strong characteristic odor, yellow color, density of 0.82 g/cm3 and yield of 0.29 % (w/w) in relation to the mass of fresh leaves collected. The yield obtained was low, which is characteristic in the isolation of essential oils. The yield value found is among the values described by Mendes et al. (2015).

The co-precipitation method successfully produced EOAz:SBE-β-CD inclusion complexes as a white, homogeneous powder after freeze-drying. The marked reduction in the characteristic odor of the essential oil suggests effective encapsulation of volatile constituents within the SBE-β-CD cavity, consistent with the formation of stable host–guest complexes. Similar effects have been widely reported for cyclodextrin-based inclusion systems of essential oils, where co-precipitation promotes efficient complex formation under mild conditions, improving stability and reducing volatility. These findings are further supported by the molecular docking results, which indicate favorable binding interactions between the major EOAz constituents and SBE-β-CD, corroborating the stability of the experimentally obtained inclusion complexes (Fonseca *et al.*, 2019).

Molecular docking simulations revealed favorable interaction profiles between SBE-β-CD and the evaluated monoterpenes, 1,8-cineole and terpinen-4-ol. The generated conformational clusters demonstrated stable molecular arrangements, with negative total interaction energies (Etotal), indicating energetically favorable host–guest association and structural stabilization of the predicted complexes.

The energetic parameters obtained from the docking simulations are summarized in Table 1. Both monoterpenes presented negative interaction energy values, supporting the existence of stable intermolecular affinity with the cyclodextrin derivative. The

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observed energetic profile suggests that hydrophobic interactions and Van der Waals forces play a central role in maintaining the conformational stability of the complexes.

Table 1. Energetic parameters obtained from molecular docking simulations between sulfobutylether–β-cyclodextrin (SBE-β-CD) and the evaluated monoterpenes. Total interaction energy values (Etotal) were obtained from HEX 8.0.0 docking simulations and used to identify the most energetically favorable conformational clusters. Negative energy values indicate favorable intermolecular association and structural stabilization of the predicted host–guest complexes.

Clusters	**1,8-Cineol x SBE-β-CD E_{total} (Kcal/mol)**	**Terpinen-4-ol x SBE- β-CD E_{total} (Kcal/mol)**
01	-97.20	-120.46
02	-96.82	-119.22
03	-93.93	-116.52
04	-93.27	-113.36
05	-93.01	-113.05
06	-92.54	-112.39
07	-91.27	-112.10
08	-91.07	-111.46
09	-90.91	-111.19
10	-90.43	-110.64

Source: Authors.

Figure 2 illustrates the three-dimensional interaction profile between SBE-β-CD and 1,8-cineole. The docking analysis demonstrated favorable spatial accommodation of the monoterpene within the interaction region, with evident steric complementarity between the guest molecule and the cyclodextrin cavity. The compact cyclic structure of 1,8-cineole contributed to stable molecular fitting and favorable conformational organization.

Figure 2. Three-dimensional molecular docking interaction between sulfobutylether–β-cyclodextrin (SBE-β-CD) and 1,8-cineole. Note(s): The figure illustrates the spatial accommodation and conformational organization of 1,8-cineole within the interaction region of the cyclodextrin derivative, highlighting steric complementarity and predicted host–guest stabilization.

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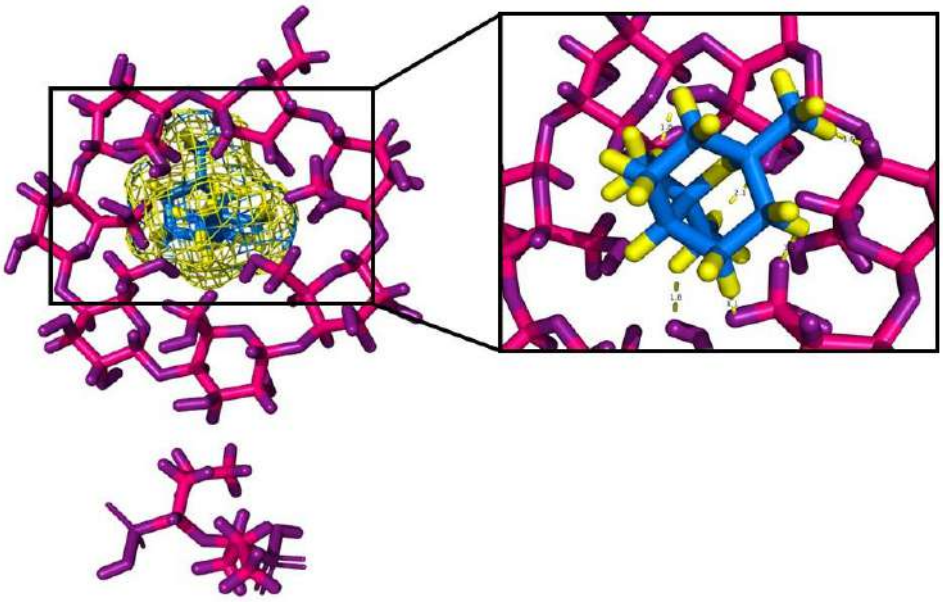
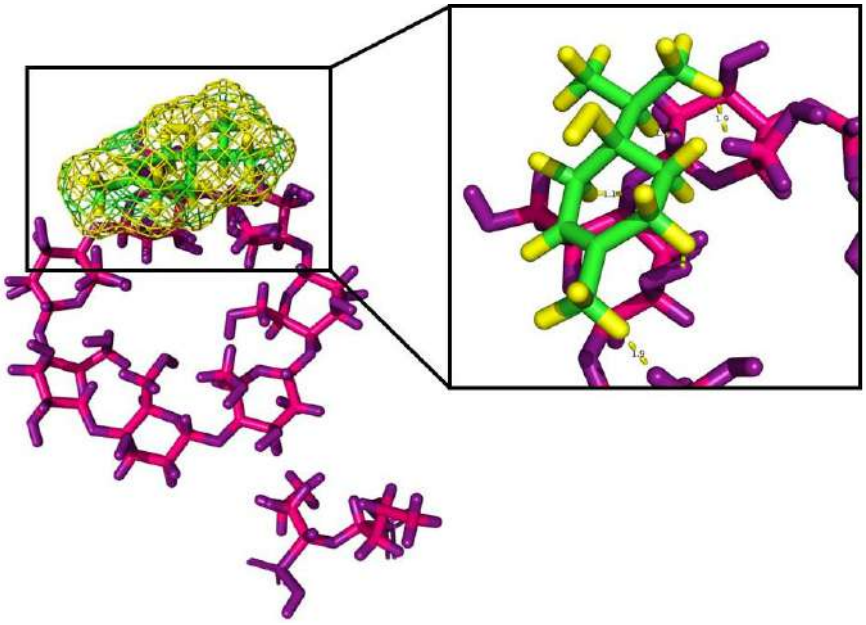


Source: Authors

Similarly, the interaction between SBE-β-CD and terpinen-4-ol demonstrated stable energetic and structural characteristics, as shown in Figure 3. The molecular arrangement revealed consistent spatial organization and favorable accommodation within the cyclodextrin system. In addition to hydrophobic stabilization, the hydroxyl group present in terpinen-4-ol may contribute to additional intermolecular stabilization through hydrogen bond-associated interactions.

Figure 3. Three-dimensional molecular docking interaction between sulfobutylether–β-cyclodextrin (SBE-β-CD) and terpinen-4-ol.
Note(s): The figure demonstrates the predicted conformational arrangement and intermolecular interaction profile between terpinen-4-ol and SBE-β-CD, indicating favorable spatial organization and potential stabilization through non-covalent interactions.



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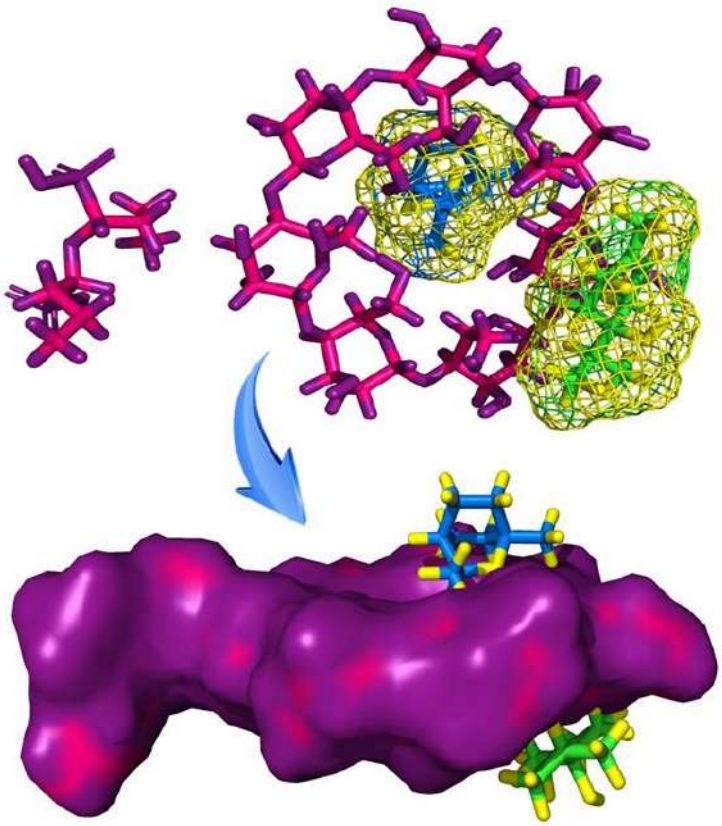
Comparative analysis of the docking conformations demonstrated that both monoterpenes established stable host–guest interaction profiles with SBE-β-CD (Figure 4), although subtle differences in molecular geometry and polarity may influence their conformational orientation within the interaction environment. The recurrent conformational clusters observed during the simulations reinforce the structural consistency and energetic stability of the predicted complexes.

Figure 4. Predicted host–guest complexes formed between SBE-β-cyclodextrin and the investigated monoterpenes. Upper figure show the optimized docking conformations, highlighting the structural arrangement of the guest molecules within the cyclodextrin cavity. Lower figure present the corresponding molecular surface representations, illustrating the three-dimensional inclusion pattern and evidencing the favorable accommodation and spatial complementarity of the ligands within the SBE-β-CD cavity.



Source: author.

Overall, the computational findings suggest that SBE-β-CD may act as a promising molecular carrier for volatile bioactive monoterpenes, potentially contributing to enhanced molecular stabilization and improved physicochemical properties. These results reinforce the applicability of molecular docking approaches for the rational design and optimization of cyclodextrin-based inclusion systems with potential biotechnological and pharmaceutical relevance.

CONCLUSIONS

The present *in silico* investigation demonstrated that SBE-β-CD establishes energetically favorable interactions with the bioactive monoterpenes 1,8-cineole and terpinen-4-ol, leading to the formation of stable host–guest inclusion complexes supported by hydrophobic interactions, structural complementarity, and negative binding energies. Molecular docking analyses further revealed conformational stability and significant spatial accommodation of both monoterpenes within the cyclodextrin cavity, indicating the potential formation of persistent cyclodextrin-based delivery systems. The formation of these inclusion complexes may improve the stability, solubility, and potential bioavailability of 1,8-cineole and terpinen-4-ol, overcoming key limitations associated with these monoterpenes.

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These findings contribute to the understanding of cyclodextrin-based molecular interactions but also highlight the potential of SBE-β-CD as a versatile carrier for the development of innovative pharmaceutical and medicinal formulations. Furthermore, the study reinforces the value of computational approaches as effective tools for the rational design and optimization of cyclodextrin-based inclusion systems aimed at biotechnological applications.

REFERENCES

1. Choisnard, L., Gèze, A., Putaux, J.-L., Wong, Y.-S., Wouessidjewe, D., 2006. Nanoparticles of β-cyclodextrin esters obtained by self-assembling of biotransesterified β-cyclodextrins. Biomacromolecules 7(2), 515–520. https://doi.org/10.1021/bm0507655
2. Delano, W. L. (2002) The PyMOL Molecular Graphics System, DeLano Scientific, Palo Alto, CA, USA
3. Fonseca, L.B., de Sá Barreto, L.C.L., da Silva, F.G., de Sousa, J.M.C., de Morais, S.M., de Paula Cavalcante, C.S., 2019. Characterization of inclusion complex of Croton zehntneri essential oil and β-cyclodextrin prepared by spray drying and freeze drying. Rev. Virtual Quim. 11, 560–573.
4. Hou, J., Gong, H., Gong, Z., Qin, X., Nie, J., Zhu, H., & Zhong, S. (2023). Chemical composition and potential antimicrobial and anti-inflammatory activities of essential oil from fruits of Alpinia zerumbet (Pers.) B.L.Burtt & R.M.Sm. Chemistry & Biodiversity, 20(12), e202301269. https://doi.org/10.1002/cbdv.202301269
5. Macindoe, G., Mavridis, L., Venkatraman, V., Devignes, M.-D., Ritchie, D.W., 2010. HexServer: An FFT-based protein docking server powered by graphics processors. Nucleic Acids Res. 38(Suppl. 2), W445–W449. https://doi.org/10.1093/nar/gkq311
6. Mendes, F. R. S., Silva, F. G. E., Sousa, E. O., Rodrigues, F. F. G., Costa, J. G. M., Monte, F. J. Q., Lemos, T. L. G., & Assunção, J. C. C. (2015). Essential oil of Alpinia zerumbet (Pers.) B.L. Burtt & R.M. Sm. (Zingiberaceae): Chemical composition and modulation of the activity of aminoglycoside antibiotics. Journal of Essential Oil Research, 27(3), 259–263. https://doi.org/10.1080/10412905.2014.982876
7. Musuc AM. Cyclodextrins: Advances in Chemistry, Toxicology, and Multifaceted Applications. Molecules. 2024 Nov 12;29(22):5319. DOI: 10.3390/molecules29225319. PMID: 39598708; PMCID: PMC11596893.
8. Nishidono, Y., & Tanaka, K. (2024). Phytochemicals of Alpinia zerumbet: A review. Molecules, 29(12), 2845. https://doi.org/10.3390/molecules29122845
9. Pardeshi, C. V., Kothawade, R. V., Markad, A. R., Pardeshi, S. R., Kulkarni, A. D., Chaudhari, P. J., Longhi, M. R., Dhas, N., Naik, J. B., Surana, S. J., & García, M. C. (2023). Sulfobutylether-β-cyclodextrin: A functional biopolymer for drug delivery applications. Carbohydrate Polymers, 301, 120347. https://doi.org/10.1016/j.carbpol.2022.120347
10. Tu, P. T. B., & Tawata, S. (2015). Anti-Oxidant, Anti-Aging, and Anti-Melanogenic Properties of the Essential Oils from Two Varieties of Alpinia zerumbet. Molecules, 20(9), 16723–16740. https://doi.org/10.3390/molecules200916723

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