Original Article
Food Science and Technology

ISSN 0101-2061 (Print)
ISSN 1678-457X (Online)

DOI: https://doi.org/10.1590/fst.68722



# Preparation and characterization of an oridonin and γ-cyclodextrin complex

Wei ZHOU[1*], Xiaofan LV[1], Mengran HEI[1], Yanyan ZHAO[1], Zhenkun CUI[1], Hao ZHANG[1]

**Abstract**

Oridonin, a terpenoid with various biological functions, has limited uses in the functional food and pharmaceutical industries owing to its low water solubility. Previous studies have used cyclodextrin inclusion to improve its solubility. Herein, the effects of different cyclodextrins on the inclusion of oridonin were investigated using phase solubility and molecular docking tests. The binding constants of α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin with oridonin were 22.6, 298.6, and 317.4, respectively. The corresponding binding energies were -6.49, -6.76, and -7.53 kcal/mol, respectively, suggesting that the interaction between γ-cyclodextrin and oridonin was the strongest, thereby improving the solubility of oridonin to the greatest extent. Further experiments indicated that no new unsaturated bonds formed after oridonin complexed with γ-cyclodextrin. In addition, the complexation of oridonin with γ-cyclodextrin, led to its complete dispersal in an amorphous state that was thermally stable. This study promotes the application of oridonin in food and medicines.

**Keywords:** oridonin; cyclodextrin; complex; cavity; glucose subunits.

**Practical Application:** Oridonin has a wide range of biological activities and can be used in food industry for health benefits. However, its low water solubility limits its efficient. This study sought to address this problem by increasing its solubility via cyclodextrin complexation. The results showed that oridonin complexation with γ-cyclodextrin had the best solubility, which was likely due to the number of glucose subunits that contribute to the cyclodextrin binding cavity. This study has provided a reference for the preparation of soluble oridonin for its application in food industry.

## 1 Introduction

Oridonin, the main terpenoid isolated from *Rabdosia rubescens* (Hemsl.) Hara, is widely used as a dietary supplement and therapeutic drug (Tian et al., 2017; Li et al., 2022). Studies have shown that oridonin has a wide range of pharmacological activities, including anti-inflammatory (Huang et al., 2018), anti-angiogenic (Tian et al., 2017), anticancer (Liu et al., 2021), and antidepressant activities (Liu & Du, 2020). Therefore, it has a wide application potential for functional foods and medicines. However, the poor water solubility of oridonin limits its widespread application.

The construction of active-molecule-cyclodextrin supramolecular complexes has become an important means of improving the water solubility and stability of active molecules (Jambhekar & Breen, 2016; Uekaji & Terao, 2019). Cyclodextrin (CD) is widely used as a medicinal excipient. Its three-dimensional structure presents an annular hollow cylinder with a narrow opening and a wider opening. The outer side of the cylinder is composed of hydroxyl groups, which makes the cyclodextrin cavity hydrophilic, while the inside consists of non-polar groups that form a hydrophobic cavity. The active compounds can form a stable supramolecular complex by combining with the hydrophobic groups inside cyclodextrin through hydrogen bonding or van der Waals forces. Moreover, the efficient construction of supramolecular complexes can prevent the interaction of active substances and reduce or eliminate unpleasant tastes and odors (Jambhekar & Breen, 2016). Among cyclodextrins, α-, β-, and γ-cyclodextrins have 6, 7, and 8 glucopyranose units, respectively, and are considered semi-natural compounds that are safe to use. These cyclodextrins are often used to construct supramolecular complexes (Song et al., 2009).

In this study, the effects of α-, β-, and γ-cyclodextrins on the inclusion of oridonin were investigated using phase solubility and molecular docking. Moreover, a complex consisting of oridonin and γ-cyclodextrin was prepared and characterized by ultraviolet (UV), infrared (IR), scanning electron microscopy (SEM), Thermogravimetry and differential scanning calorimetry (TG/DSC), and X-ray diffraction (XRD) analyses. These findings are beneficial for promoting the application of oridonin in the pharmaceutical and food industries.

## 2 Materials and methods

### *2.1 Materials*

Oridonin, α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin were purchased from Yuanye Biotechnology Co. Ltd. (Shanghai, China).

### *2.2 Phase solubility measurements*

Phase solubility measurements were performed according to Liu et al. (2013). Briefly, oridonin was added in excess to 10 mL of cyclodextrin (2, 4, 6, 8, or 10 mM) and shaken in a water bath at 150 rpm at 30 °C for 72 h. Next, the solution was filtered through a 0.45 μm water-based filter and the absorbance of the

*Received 25 May, 2022*
*Accepted 14 July, 2022*
[1]*School of Food Science, Henan Institute of Science and Technology, Xinxiang, China*
*Corresponding author: zhouwei1981@hist.edu.cn

sample was read at 245 nm using a Persee TU1810PC UV-Vis spectrophotometer (Beijing, China). The amount of dissolved oridonin was calculated based on a standard curve ($R^2 = 0.9994$). Using cyclodextrin concentration as the abscissa and oridonin concentration as the ordinate, the phase solubility curves of oridonin with cyclodextrins were established. The apparent stability constants ($K_s$) of oridonin and the three cyclodextrins were calculated according to the Higuchi–Connors equation (Equation 1):

$$K_S = \frac{slope}{s_0\left(1 - slope\right)} \quad (1)$$

### *2.3 Molecular docking analyses*

Molecular docking analyses of oridonin and the different cyclodextrins were performed using the Autodock 4.2 software (Hou et al., 2013; Morris et al., 2009). Molecular structure files for Cyclodextrin were obtained from the RCSB Protein Data Bank (Berman et al., 2000) and that for oridonin was from PubChem (Kim et al., 2019). After the optimization of each molecule, molecular docking of oridonin with α-, β-, and γ-cyclodextrin was performed. The Autogrid module was applied to run the grid, with the spacing of grid points set to 0.375 Å. A Lamarck genetic algorithm was used to search for possible docking sites and the simulation was set to generate 10 docking conformations, each corresponding to a binding energy calculated using a semi-empirical energy function. The binding ability of oridonin to the three cyclodextrins was evaluated based on the binding energy.

### *2.4 Preparation of an oridonin and γ-cyclodextrin complex*

Sixty milligrams of oridonin was added to 50 mL of 10 mM γ-cyclodextrin and the mixture shaken in a water bath at 150 rpm at 37 °C for 72 h. Next, the solution was centrifuged (15 min, 8000 rpm) and the supernatant was freeze-dried. Finally, the white powder, constituting a complex of oridonin and γ-cyclodextrin, was collected (Li et al., 2021).

### *2.5 Preparation of a physical mixture*

Ninety-one milligrams of oridonin and 324.5 mg of γ-cyclodextrin were ground in an agate grinder at 25 °C and collected as a physical mixture (Liu et al., 2013).

### *2.6 UV spectroscopy*

Ultraviolet spectroscopy was carried out according to Li et al. (2019) and Li et al. (2021). Briefly, 10 mg of oridonin, γ-cyclodextrin, the oridonin/γ-cyclodextrin physical mixture, and the oridonin/γ-cyclodextrin complex, were dissolved in 50 mL methanol. The diluted sample solutions were scanned using a Persee TU1810PC UV-Vis spectrophotometer with a scanning range from 220 to 400 nm.

### *2.7 IR spectroscopy*

Appropriate amounts of dried oridonin, γ-cyclodextrin, the oridonin/γ-cyclodextrin physical mixture, and the oridonin/γ-cyclodextrin complex, were mixed with potassium bromide and pressed. The IR spectra of the samples were recorded on a TENSOR 27 FT-IR spectrophotometer (Bruker, Ettlingen, Germany) with a scan range of 400-4000 $cm^{-1}$ (Li et al., 2019; Akman et al., 2022).

### *2.8 SEM observation*

The particle morphologies of oridonin, γ-cyclodextrin, the oridonin/γ-cyclodextrin physical mixture, and the oridonin/γ-cyclodextrin complex, were observed using a Quanta 200 environmental scanning electron microscope (FEI, USA). Approximately 10 mg of oridonin, γ-cyclodextrin, the oridonin/γ-cyclodextrin physical mixture, and the oridonin/γ-cyclodextrin complex, were evenly distributed on the specimen stub with double adhesive tape and coated with a thin gold layer under a vacuum. Micrographs were recorded at an accelerating potential of 20 kV under a low vacuum (Wang et al., 2022).

### *2.9 TG/DSC measurements*

Approximately 10 mg of oridonin, γ-cyclodextrin, the oridonin/γ-cyclodextrin physical mixture, and the oridonin/γ-cyclodextrin complex, were evenly spread in an alumina crucible and analyzed using a synchronous thermal analyzer (TA; Netzsch Instrument Manufacturing Co., Ltd., Germany). For TG/DSC measurements, a nitrogen environment was used with a scan rate of 20 °C/min and a temperature range of 30-400 °C (Abarca et al., 2016).

### *2.10 XRD analyses*

The XRD patterns of oridonin, γ-cyclodextrin, the oridonin/γ-cyclodextrin physical mixture, and the oridonin/γ-cyclodextrin complex, were analyzed using a Bruker D8 Advance X-ray diffractometer (Ettlingen, Germany) with Cu Kα radiation (λ = 1.54056 Å). The diffraction angle ranged from 10° to 80° (Abarca et al., 2016; Su et al., 2022).

## 3 Results and discussion

### *3.1 Cyclodextrin cavity volume corresponds to complex solubility*

The phase solubility method is widely used to evaluate the binding ability of cyclodextrins to active molecules. Here, we observed that the apparent stability constant of α-cyclodextrin was the lowest, suggesting that its effect on improving the solubility of oridonin was the poorest (Table 1, Figure 1). Conversely, γ-cyclodextrin exhibited the highest binding capacity for oridonin, which significantly improved its aqueous solubility (Table 1, Figure 1). The binding performance of the cyclodextrins was in the following order: γ-cyclodextrin > β-cyclodextrin > α-cyclodextrin. This order is consistent with the number of glucose units in

**Table 1**. Stability constants for α-, β-, and γ-cyclodextrin with oridonin.

| | α-cyclodextrin | β-cyclodextrin | γ-cyclodextrin |
|---|---|---|---|
| $K_s$ | 22.6 | 298.6 | 317.4 |
| $R^2$ | 0.9735 | 0.9830 | 0.9759 |

each cyclodextrin, with γ-, β-, and α-cyclodextrin containing 8, 7, and 6 glucose units, respectively. As the number of glucose units increases, the cavity volume increases, which increases the probability of large molecules entering the cyclodextrin cavity. Therefore, the cavity size of cyclodextrin most likely affects its binding capacity for oridonin, with larger cavities being more conducive to enhancing the aqueous solubility of oridonin (Mura, 2015). These findings are consistent with those of Li et al. (2021).

To evaluate the ability of oridonin to enter the different cyclodextrin structures, molecular docking calculations were performed (Figure 2), which can elucidate the binding mode and energy between host and guest molecules (Geng et al., 2022). We found that oridonin could enter the cavity of all three cyclodextrins; however, its orientation in the cavity varied. Oridonin can form 4, 4, and 6 hydrogen bonds with α-, β-, and γ-cyclodextrin, respectively, leading to differences in binding energy (Li et al., 2021). The binding energies of α-, β-, and γ-cyclodextrin with oridonin were -6.49, -6.76, and -7.53 kcal/mol, respectively. These results indicate that the cavity of γ-cyclodextrin was the easiest for oridonin to enter, while the cavities of α- and β-cyclodextrin were the most difficult to enter. These results are consistent with the phase solubility results.

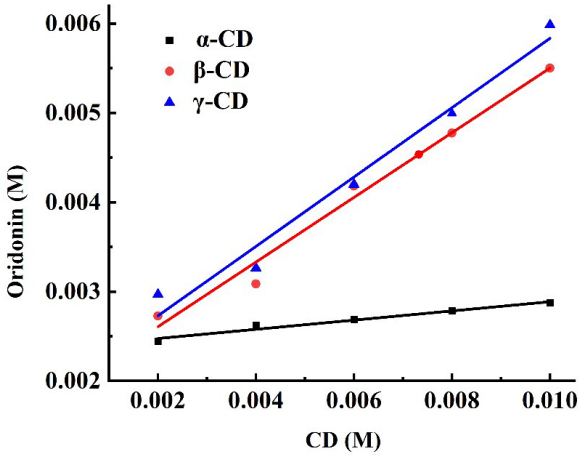


**Figure 1**. Phase solubility curves of α-, β-, and γ-cyclodextrin with oridonin.

### *3.2 Unsaturated bonds did not form during complexation*

Ultraviolet-visible spectroscopy was performed to evaluate the change in unsaturated bonds during the chemical reaction (Figure 3). Oridonin had a characteristic absorption peak at 242 nm owing to its conjugated structure of unsaturated double bonds. Conversely, γ-cyclodextrin does not have a characteristic UV absorption peak owing to a lack of unsaturated bonds. Characteristic absorption peaks appeared at 242 nm for the physical mixture of oridonin/γ-cyclodextrin and the oridonin/γ-cyclodextrin complex, indicating that no additional unsaturated bonds formed during complexation (Li et al., 2018).

Next, IR spectroscopy was used to study the molecular motion of the complex (Figure 4). Here, functional group information of compounds can be inferred from the position and shape of the absorption peak in the infrared spectrum (Liu et al., 2022). Oridonin showed the following characteristic peaks: at 3400 $cm^{-1}$ for the O-H stretching vibration of the hydroxyl group and the C-H stretching vibration of olefin; at 2929 $cm^{-1}$ for the C-H stretching vibration of methyl and methylene; at 1647 $cm^{-1}$ for the stretching vibrations of the C=C and C=O double bonds; at 1461 and 1370 $cm^{-1}$ for the methyl C-H bending vibrations; and at 1159 $cm^{-1}$ for the ether C-O-C asymmetric stretching vibration. γ-Cyclodextrin also exhibited peaks at 3400 $cm^{-1}$ (a hydroxyl O-H stretching vibration), 2929 $cm^{-1}$ (methylene, methine C-H stretching vibration), and 1159 $cm^{-1}$ (asymmetric stretching vibration of ether C-O-C). However, the IR spectra of both the oridonin/γ-cyclodextrin physical mixture and the oridonin/γ-cyclodextrin complex retained the characteristic absorption peaks of oridonin and γ-cyclodextrin, showing a simple superposition, indicating that no new chemical bonds formed during complexation (Abou-Okeil et al., 2018).

### *3.3 The oridonin/γ-cyclodextrin complex exists in an amorphous state*

To investigate the morphology of the complex, SEM was used to obtain high-resolution three-dimensional images of the sample surfaces at 1000× magnification (Figure 5). Oridonin appeared as an irregular crystal, whereas γ-cyclodextrin appeared as a cubic crystal. Oridonin and γ-cyclodextrin particles were observed

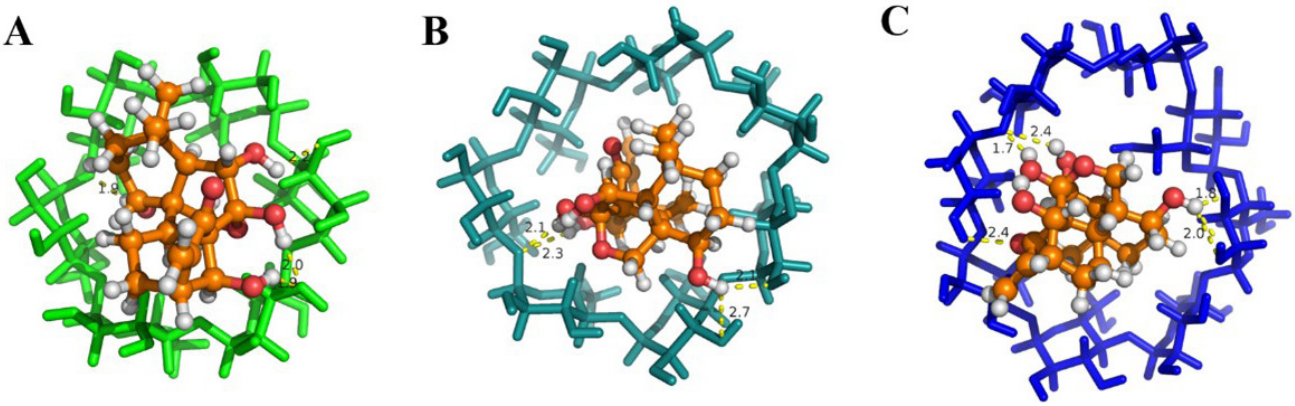


**Figure 2**. Results of the molecular docking analyses for (A) α-cyclodextrin, (B) β-cyclodextrin, and (C) γ-cyclodextrin with oridonin.

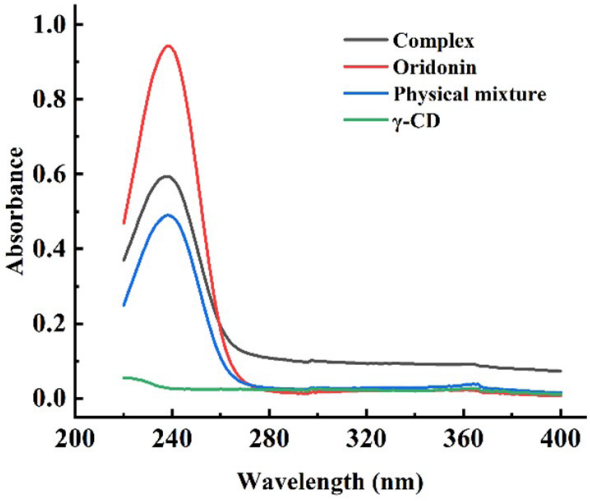


**Figure 3**. Ultraviolet visible spectra of γ-cyclodextrin (γ-CD), oridonin, the oridonin/γ-cyclodextrin physical mixture, and the oridonin/γ-cyclodextrin complex.

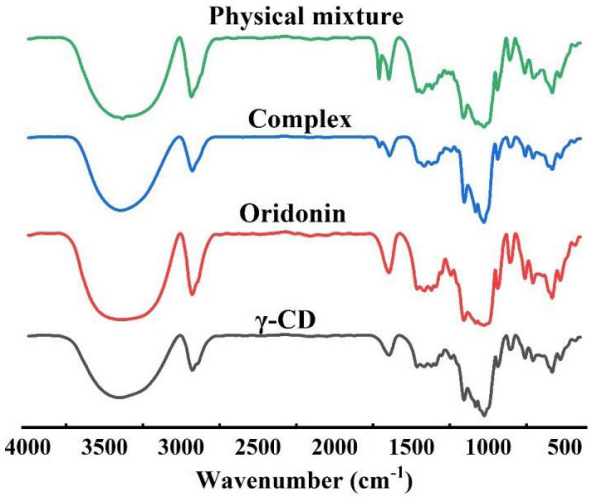


**Figure 4**. Infrared spectra of γ-cyclodextrin (γ-CD), oridonin, the oridonin/γ-cyclodextrin physical mixture, and the oridonin/γ-cyclodextrin complex.

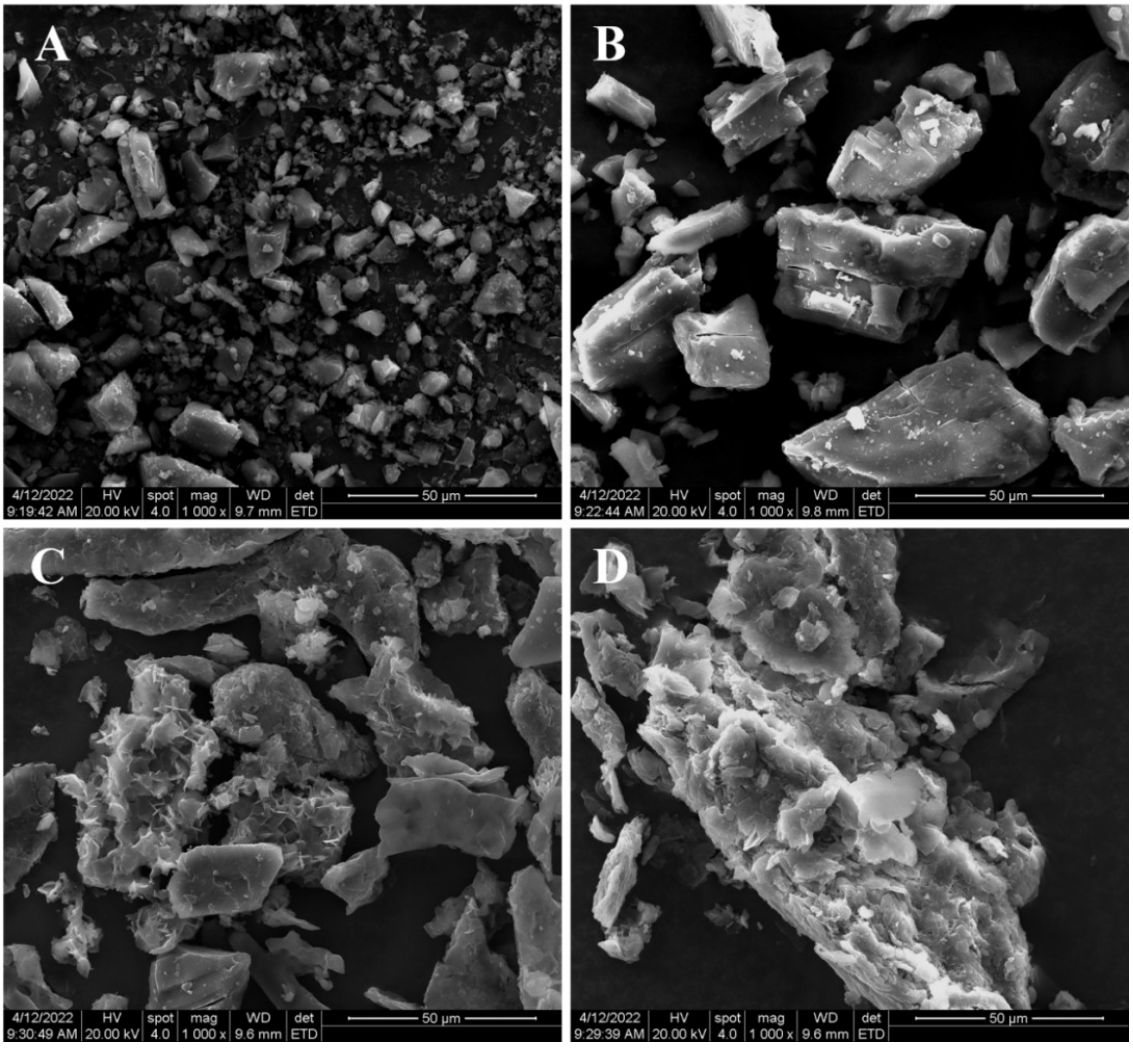


**Figure 5**. Scanning electron microscopy images of (A) oridonin, (B) γ-cyclodextrin, (C) the oridonin/γ-cyclodextrin physical mixture, and (D) the oridonin/γ-cyclodextrin complex.

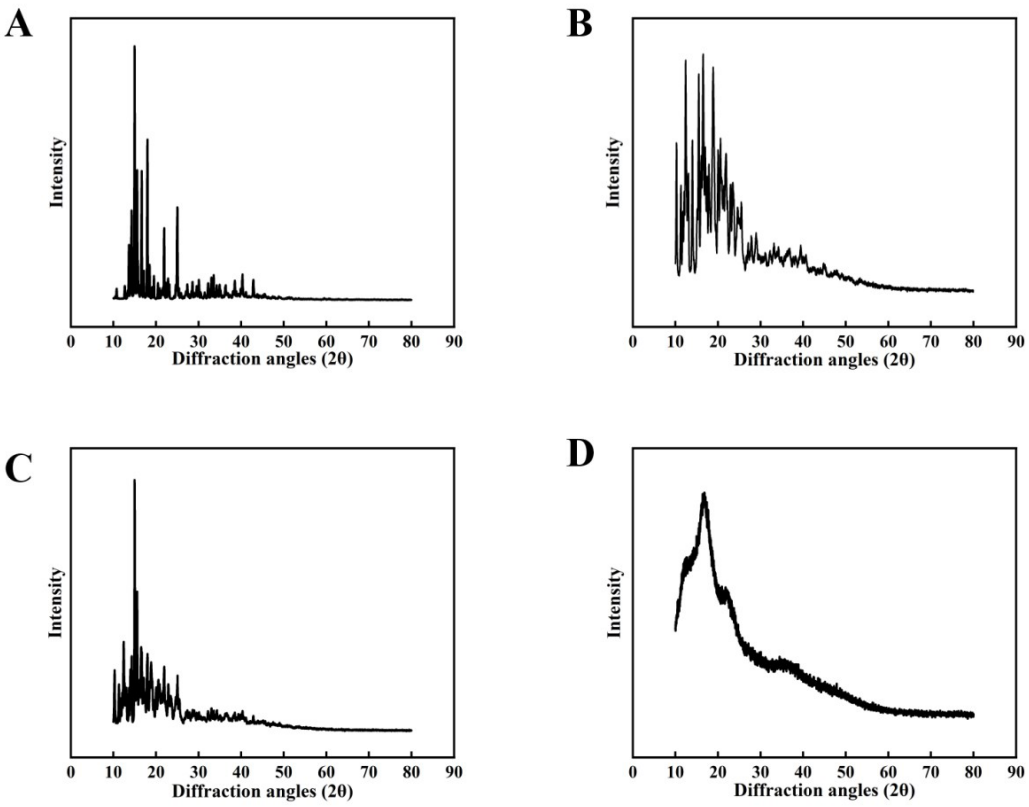


**Figure 6**. X-ray diffraction patterns of (A) oridonin, (B) γ-cyclodextrin, (C) the oridonin/γ-cyclodextrin physical mixture, and (D) the oridonin/γ-cyclodextrin complex.

in the physical mixture. However, the complex of oridonin and γ-cyclodextrin showed an amorphous bulk structure. Hence, the morphology of the complex was significantly different from that of oridonin and γ-cyclodextrin (Li et al., 2015; Srinivasan & Stalin, 2014).

Next, XRD analysis was used to analyze the spatial distribution of atoms in the crystals (Figure 6). Both oridonin and γ-cyclodextrin had multiple sharp crystal diffraction peaks, confirming their crystalline nature, coinciding with the SEM results. For the physical mixture, crystal diffraction peaks of γ-cyclodextrin and oridonin were observed. However, the crystal diffraction peaks of the complex showed a broad absorption peak, with the complete absence of the sharp diffraction peaks of oridonin and γ-cyclodextrin, indicating that oridonin and γ-cyclodextrin existed in an amorphous state after complexation and that oridonin was dispersed in γ-cyclodextrin (Srinivasan & Stalin, 2014).

### *3.4 Complexation improves the thermal stability of oridonin*

To evaluate how the complex behaves during heating, we performed TG/DSC measurements (Figure 7). The dehydration, melting process, and thermal stability of samples can be determined by the mutual verification of the thermogravimetric and differential thermal curves. The water loss of the physical mixture and the complex was obvious and occurred mainly between 60 and 150 °C, indicating that they contained bound

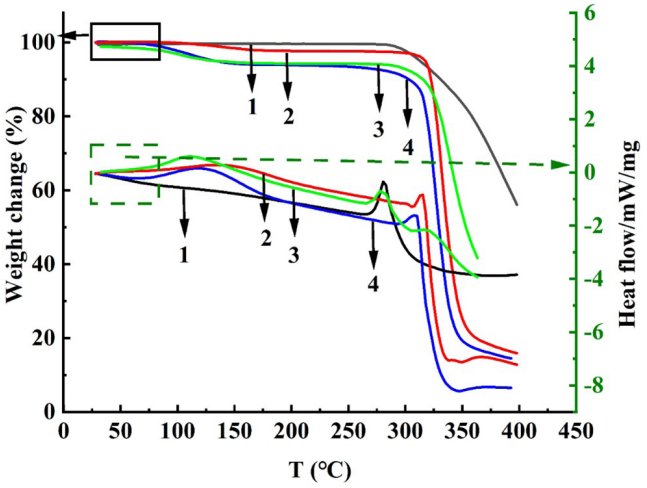


**Figure 7**. Thermogravimetry and differential scanning calorimetry curves of (1) oridonin, (2) γ-cyclodextrin, (3) the oridonin/γ-cyclodextrin physical mixture, and (4) the oridonin/γ-cyclodextrin complex.

and free water. γ-Cyclodextrin experienced less water loss, and the loss only occurred after 105 °C, indicating that more water was bound. The TG/DSC curve of oridonin began to endotherm at 260 °C and reached a maximum at approximately 280 °C, which represents the endothermic process of oridonin from solid-state to molten state. The mass of oridonin decreased

rapidly between 280 and 400 °C, accounting for approximately 43% of the total mass. During this time, oridonin underwent chemical reactions such as carbonization. The TG/DSC curve of γ-cyclodextrin showed an obvious endothermic process at 306 °C and reached a maximum at 315 °C, corresponding to its melting process. From 315 to 400 °C, γ-cyclodextrin rapidly lost mass, with the total loss ratio being approximately 81%, which is also attributed to carbonization and other reactions. The TG/DSC curve of the physical mixture exhibited two significant absorption peaks at 265 and 306 °C, indicating a simple superposition of the characteristic curves of oridonin and γ-cyclodextrin. For the complex, the endothermic peak started at 294 °C and reached its peak at 308 °C. Its mass loss occurred in the range of 308-400 °C, indicating that its thermal stability was superior to that of oridonin. It was thus speculated that oridonin enters the cavity of γ-cyclodextrin and is protected during heating, resulting in a significant improvement in thermal stability (Abarca et al., 2016).

## 4 Conclusion

Cyclodextrins have been used in food industry as a "carrier" to stabilized bioactive compounds for several years. However, this kind of classical role is giving way to novel applications. Cyclodextrins can be used i) as nutritional supplement in the form of prebiotic for weight and lipid control, ii) in active and smart food packaging, enabling the controlled release of antimicrobials, antioxidants, etc., iii) to form novel nanoparticles for functional food uses (Matencio et al., 2020).

Here, the capacities of α-, β-, and γ-cyclodextrin in improving the water solubility of oridonin were compared, and the performance of γ-cyclodextrin was found to be superior. According to the molecular docking results, the cavity size of the cyclodextrins determined their corresponding inclusion effect. The UV, IR, SEM, TG/DSC, and XRD analyses of the oridonin/γ-cyclodextrin complex suggested that no new covalent bonds formed during the inclusion process and that oridonin was completely distributed in γ-cyclodextrin, existing in an amorphous state. In addition, the thermal stability of oridonin improved after complexation. These results can prompt the application of oridonin and γ-cyclodextrin in foods and medicines.

## Acknowledgements

This work was sponsored by the Natural Science Foundation of Henan (No.202300410158) and the Training Plan of Young Key Teachers in Henan (No.2020GGJS167).

## References

Abarca, R. L., Rodriguez, F. J., Guarda, A., Galotto, M. J., & Bruna, J. E. (2016). Characterization of beta-cyclodextrin inclusion complexes containing an essential oil component. *Food Chemistry*, 196, 968-975. http://dx.doi.org/10.1016/j.foodchem.2015.10.023. PMid:26593579.

Abou-Okeil, A., Rehan, M., El-Sawy, S. M., El-bisi, M. K., Ahmed-Farid, O. A., & Abdel-Mohdy, F. A. (2018). Lidocaine/beta-cyclodextrin inclusion complex as drug delivery system. *European Polymer Journal*, 108, 304-310. http://dx.doi.org/10.1016/j.eurpolymj.2018.09.016.

Akman, P. K., Bozkurt, F., & Tornuk, F. (2022). Fabrication and characterization of curcumin loaded ovalbumin nanocarriers and bioactive properties. *Food Science and Technology*, 42, e38421. http://dx.doi.org/10.1590/fst.38421.

Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., Shindyalov, I. N., & Bourne, P. E. (2000). The Protein Data Bank. *Nucleic Acids Research*, 28(1), 235-242. https://doi.org/10.1093/nar/28.1.235.

Geng, S., Li, Y. B., Lv, J. L., Ma, H. J., Liang, G. Z., & Liu, B. G. (2022). Fabrication of food-grade Pickering high internal phase emulsions (HIPEs) stabilized by a dihydromyricetin and lysozyme mixture. *Food Chemistry*, 373(Pt B), 131576. http://dx.doi.org/10.1016/j.foodchem.2021.131576. PMid:34799133.

Hou, X., Du, J., Zhang, J., Du, L., Fang, H., & Li, M. (2013). How to improve docking accuracy of AutoDock4.2: a case study using different electrostatic potentials. *Journal of Chemical Information and Modeling*, 53(1), 188-200. http://dx.doi.org/10.1021/ci300417y. PMid:23244516.

Huang, W., Huang, M., Ouyang, H., Peng, J., & Liang, J. (2018). Oridonin inhibits vascular inflammation by blocking NF-kappa B and MAPK activation. *European Journal of Pharmacology*, 826, 133-139. http://dx.doi.org/10.1016/j.ejphar.2018.02.044. PMid:29518395.

Jambhekar, S. S., & Breen, P. (2016). Cyclodextrins in pharmaceutical formulations II: solubilization, binding constant, and complexation efficiency. *Drug Discovery Today*, 21(2), 363-368. http://dx.doi.org/10.1016/j.drudis.2015.11.016. PMid:26687191.

Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S., Li, Q., Shoemaker, B. A., Thiessen, P. A., Yu, B., Zaslavsky, L., Zhang, J., & Bolton, E. E. (2019). PubChem in 2021: new data content and improved web interfaces. *Nucleic Acids Research*, 49(D1), D1388–D1395. https://doi.org/10.1093/nar/gkaa971.

Li, J., Geng, S., Liu, B., Wang, H., & Liang, G. (2018). Self-assembled mechanism of hydrophobic amino acids and β-cyclodextrin based on experimental and computational methods. *Food Research International*, 112, 136-142. http://dx.doi.org/10.1016/j.foodres.2018.06.017. PMid:30131120.

Li, J., Geng, S., Wang, Y., Lv, Y., Wang, H., Liu, B., & Liang, G. (2019). The interaction mechanism of oligopeptides containing aromatic rings with beta-cyclodextrin and its derivatives. *Food Chemistry*, 286, 441-448. http://dx.doi.org/10.1016/j.foodchem.2019.02.021. PMid:30827631.

Li, S. J., Yue, J. Z., Zhou, W., & Li, L. (2015). An investigation into the preparation, characterization and antioxidant activity of puerarin/cyclodextrin inclusion complexes. *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, 82(3-4), 453-460. http://dx.doi.org/10.1007/s10847-015-0516-9.

Li, T., Wang, X., & Dong, K. (2022). Extraction and purification of oridonin from *Rabdosia rubescens* and its protective effect on intracerebral hemorrhage-induced brain injury in rats. *Food Science and Technology*, 42, e24921. http://dx.doi.org/10.1590/fst.24921.

Li, Y. B., Liu, B. G., Yu, M. M., & Geng, S. (2021). High-efficiency formation mechanism of mangiferin/gamma-cyclodextrin complex. *Food Science and Technology Research*, 27(5), 735-745. http://dx.doi.org/10.3136/fstr.27.735.

Liu, B., Li, W., Zhao, J., Liu, Y., Zhu, X., & Liang, G. (2013). Physicochemical characterisation of the supramolecular structure of luteolin/cyclodextrin inclusion complex. *Food Chemistry*, 141(2), 900-906. http://dx.doi.org/10.1016/j.foodchem.2013.03.097. PMid:23790865.

Liu, P., & Du, J. (2020). Oridonin is an antidepressant molecule working through the PPAR-gamma/AMPA receptor signaling pathway.

*Biochemical Pharmacology*, 180, 114136. http://dx.doi.org/10.1016/j.bcp.2020.114136. PMid:32628930.

Liu, X. L., Geng, S., He, C. Y., Sun, J. L., Ma, H. J., & Liu, B. G. (2022). Preparation and characterization of a dihydromyricetin-sugar beet pectin covalent polymer. *Food Chemistry*, 376, 131952. http://dx.doi.org/10.1016/j.foodchem.2021.131952. PMid:34973639.

Liu, X., Xu, J. M., Zhou, J., & Shen, Q. (2021). Oridonin and its derivatives for cancer treatment and overcoming therapeutic resistance. *Genes & Diseases*, 8(4), 448-462. http://dx.doi.org/10.1016/j.gendis.2020.06.010. PMid:34179309.

Matencio, A., Navarro-Orcajada, S., Garcia-Carmona, F., & Lopez-Nicolas, J. M. (2020). Applications of cyclodextrins in food science. A review. *Trends in Food Science & Technology*, 104, 132-143. http://dx.doi.org/10.1016/j.tifs.2020.08.009.

Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S., & Olson, A. J. (2009). AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility. *Journal of Computational Chemistry*, 30(16), 2785-2791. http://dx.doi.org/10.1002/jcc.21256. PMid:19399780.

Mura, P. (2015). Analytical techniques for characterization of cyclodextrin complexes in the solid state: a review. *Journal of Pharmaceutical and Biomedical Analysis*, 113, 226-238. http://dx.doi.org/10.1016/j.jpba.2015.01.058. PMid:25743620.

Song, L. X., Bai, L., Xu, X. M., He, J., & Pan, S. Z. (2009). Inclusion complexation, encapsulation interaction and inclusion number in cyclodextrin chemistry. *Coordination Chemistry Reviews*, 253(9-10), 1276-1284. http://dx.doi.org/10.1016/j.ccr.2008.08.011.

Srinivasan, K., & Stalin, T. (2014). Study of inclusion complex between 2,6-dinitrobenzoic acid and beta-cyclodextrin by H-1 NMR, 2D H-1 NMR (ROESY), FT-IR, XRD, SEM and photophysical methods. *Spectrochimica Acta. Part A: Molecular and Biomolecular Spectroscopy*, 130, 105-115. http://dx.doi.org/10.1016/j.saa.2014.03.106. PMid:24769381.

Su, L., Xiang, F., Qin, R., Fang, Z., Zeng, J., & Li, G. (2022). Study on mechanism of starch phase transtion in wheat with different moisture content. *Food Science and Technology*, 42, e106521. http://dx.doi.org/10.1590/fst.106521.

Tian, L., Xie, K. J., Sheng, D. L., Wan, X. Q., & Zhu, G. F. (2017). Antiangiogenic effects of oridonin. *BMC Complementary and Alternative Medicine*, 17(1), 192. http://dx.doi.org/10.1186/s12906-017-1706-3. PMid:28376864.

Uekaji, Y., & Terao, K. (2019). Bioavailability enhancement of hydrophobic nutraceuticals using gamma-cyclodextrin (2019). *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, 93(1-2), 3-15. http://dx.doi.org/10.1007/s10847-018-0856-3.

Wang, X., Han, L., Hu, X., Li, S., Ma, W., & Song, W. (2022). Photostability of the inclusion complex of isoamyl4-(Dimethylamino) benzoate with sulfobutylether-beta-cyclodextrin. *Journal of Photochemistry and Photobiology A: Chemistry*, 423, 113614. http://dx.doi.org/10.1016/j.jphotochem.2021.113614.