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Evaluation of the interaction of diosgenin and its derivatives with cyclodextrin to form a water-soluble inclusion complex: A molecular docking study

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ABSTRACT

Diosgenin as an herbal compound has been shown to have activity as an atherosclerosis agent, but the low solubility of the compound may hinder the research process of diosgenin as a medicinal substance. This study aimed to examine the interaction and affinity of diosgenin compounds and their derivatives with the macromolecule cyclodextrin to increase solubility by inclusion complex formation. Alpha and beta cyclodextrins and all ligands were optimized using the density functional theory (DFT) method and the 6-31G base set with hybrid functional B3LYP. Next, molecular docking was carried out using AutoDock. Of the 12 compounds that were tethered to each macromolecule, the compound 2-chloro-3-(((4S,5'R,6aR,6bS,8aS,8bR,9S,10R,11aS,12aS,12bS)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)oxy)naphthalene-1,4-dione (**M18**) and the α-cyclodextrins were found to have the lowest binding free energy (ΔG) and inhibition constant (Ki) of -6.42 kcal/mol and 19.80 uM, respectively. The results of this study can be studied and continued as future research material to develop evidence of increasing solubility in compounds by forming inclusion complexes with macromolecules. In conclusion, diosgenin and cyclodextrin macromolecules interact to form a water-soluble inclusion complex.

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INTRODUCTION

Cardiovascular disease has been the leading cause of death in the world for the last three years (2020-2023), and atherosclerosis is one of the biggest contributors to these cases (World Health Organization, 2024). Atherosclerosis is a chronic disease of the blood vessels, where cholesterol and low-density lipoproteins accumulate on the inner walls of blood vessels forming plaques so that

the walls become thick and lose their elasticity. Some treatment methods for atherosclerosis include controlling blood pressure, dilating blood vessels, preventing platelet aggregation to prevent thrombotic complications, and others (C. Wang et al., 2018). Drugs used for the treatment of atherosclerosis such as the antiplatelet Aspirin, have adverse side effects such as gastrointestinal bleeding and increased drug resistance (Mora & Manson, 2016).

In recent years, herbal medicines have played an important role due to their potentially high therapeutic value. Some people use herbal medicines because they feel that existing allopathic medicines are not safe and adequate (Barkat et al., 2021; Philip F. Builders, 2019). Diosgenin is one of the herbal ingredients that have high therapeutic value, and can be used as anti-tumor, anti-diabetes (Gan et al., 2020), atherosclerosis therapy (Binesh et al., 2020), anti-inflammatory (H. Wang et al., 2020), and anti-cancer (Aumsuwan et al., 2016). The mechanism of action of diosgenin as an atherosclerosis therapy is by reducing the levels of COX-2, TNF-α, and NF-kB in the body (Binesh et al., 2018). Research into diosgenin and derivatives (Fig.3) as an atherosclerosis therapy is being widely developed as it has various advantages in the resulting mechanism of action (Rismawanti & Saidah, 2024). However, diosgenin has low bioavailability and water solubility (1 mg/L at 30°C) (Luo et al., 2018). One of the problems arising from the use of herbal extracts for medicinal purposes is poor solubility. The low solubility of a compound in water is a major obstacle to drug development because it can cause difficulty in reaching the target organ with a dose that is considered sufficient (Hotarat et al., 2019; Sogut et al., 2021).

Cyclodextrin is a compound used in various industrial fields such as the food industry and medicine. Cyclodextrins are naturally divided based on their glucose units, including having six units (α-cyclodextrin), seven units (β -cyclodextrin), and eight units (γ-cyclodextrin) (Cid-Samamed et al., 2022). Based on their low price, availability, and complex-forming capacity towards a wide variety of substances, α—cyclodextrin (ACD) and β-Cyclodextrin (BCD) are the most studied and most frequently used (Crini et al., 2018). Including the oligosaccharide group which is applied to increase the solubility of a compound in water (da Silva Júnior et al., 2017). Hydrophobic compounds will bind to cyclodextrin to form inclusion complexes that are easily soluble in water (Cid-Samamed et al., 2022). The most hydrophobic part of the host molecule will enter and bind to the CD cavity. The more hydrophobic molecules present in the host molecule, the more stable the inclusion complex formed (Crini, 2014).

RESEARCH METHOD

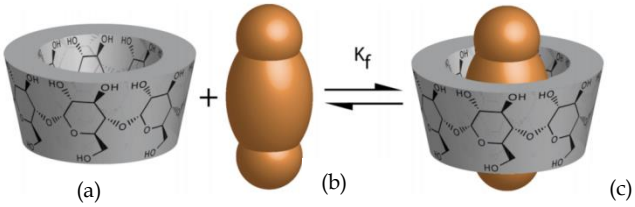


Figure 1. Cyclodextrin compound (a), Host Molecule (b), and Inclusion Complex of Cyclodextrin and Host Molecule (c) (Crini, 2014)(Crini, 2014).

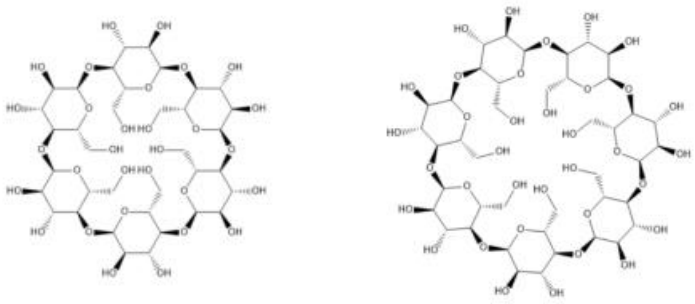
The use of cyclodextrins to increase solubility has been widely used by forming inclusion complexes (Fig. 1) including Cefixime compounds (Jadhav et al., 2013), Efavirenz (Braga et al., 2021), Naringenin (Papaioannou et al., 2020), and many more. Many studies related to the formation of inclusion complexes with compounds that are not easily soluble in water are carried out using computational methods better known as Computer-Aided Drug Design (CADD). CADD or designing using computers requires much less preparation time and lower costs compared to conducting studies or testing directly in the laboratory (Sliwoski et al., 2014).

This study aims to determine the interaction of complex formation between Diosgenin and its derivatives with Cyclodextrin using the molecular docking method on a computer. The interaction between Diosgenin compounds and their derivatives with cyclodextrin is expected to facilitate formulators in drug development using Diosgenin compounds as anti-atherosclerotic drugs. The molecular tethering on the computer of diosgenin and cyclodextrin compounds can also help formulators conduct research more effectively and efficiently.

Molecular docking studies were prepared and conducted using Gaussian09, AutoDock4, and AutoDockTools4 applications installed on a computer with Intel® Xeon® E5-2690 V3 2.60GHz processor with 32.0 GB RAM, Microsoft Windows 11 Pro 64 bit and Linux Ubuntu 22.04 as the operating system.

Macromolecule Preparation

The macromolecules (Fig. 2) used were retrieved from the website https://pubchem.ncbi.nlm.nih.gov/ using the keywords α- cyclodextrins and β-cyclodextrins.

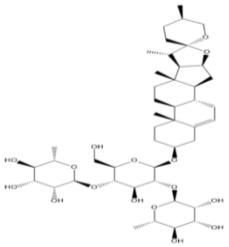


(a) (b)

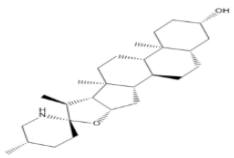
Figure 2. 2D chemical structure of α- cyclodextrins (ACD) (a) dan β-cyclodextrins (BCD) (b) (Crini, 2014).

Ligand Preparation

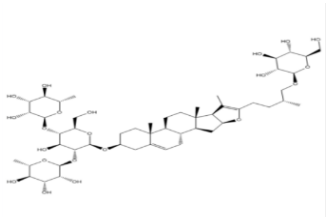
A total of twelve diosgenin ligands including their derivatives were used in this study. The diosgenin ligands including their derivatives were obtained from https://pubchem.ncbi.nlm.nih.gov/ and or independent modification of the main ligand.



M1: (2*S*,3*R*,4*R*,5*R*,6*S*)-2-[(2*R*,3*S*,4*S*,5*R*,6*R*)-4-hydroxy-2-(hydroxymethyl)-6-[(1*S*,2*S*,4*S*,5'*R*,6*R*,7*S*,8*R*,9*S*,12*S*,13*R*,16*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icos-18-ene-6,2'-oxane]-16-yl]oxy-5-[(2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxyoxan-3-yl]oxy-6-methyloxane-3,4,5-triol

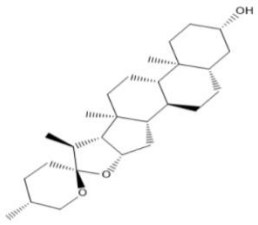


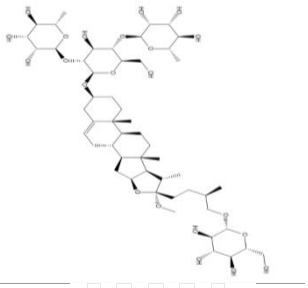
M2: (1*R*,2*S*,4*S*,5'*S*,6*S*,7*S*,8*R*,9*S*,12*S*,13*S*,16*S*,18*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane-6,2'-piperidine]-16-ol

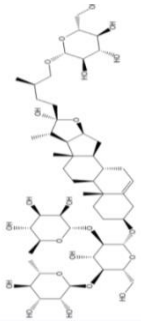


M3: (2*S*,3*R*,4*R*,5*R*,6*S*)-2-[(2*R*,3*S*,4*S*,5*R*,6*R*)-4-hydroxy-2-(hydroxymethyl)-5-[(2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxy-6-[[(1*S*,2*S*,4*S*,8*S*,9*S*,12*S*,13*R*)-7,9,13-trimethyl-6-[(3*R*)-3-methyl-4-[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxybutyl]-5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosa-6,18-dien-16-yl]oxy]oxan-3-yl]oxy-6-

methyloxane-3,4,5-triol



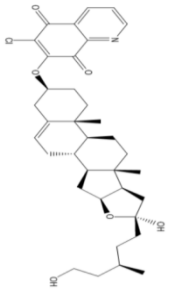


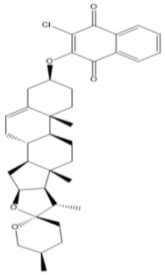


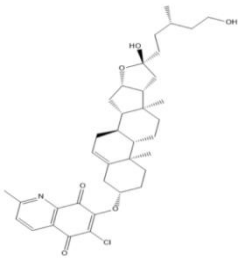
M4: (1*R*,2*S*,4*S*,5'*R*,6*R*,7*S*,8*R*,9*S*,12*S*,13*S*,16*S*,18*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane-6,2'-oxane]-16-ol

M5: (2*S*,3*R*,4*R*,5*R*,6*S*)-2-[(2*R*,3*S*,4*S*,5*R*,6*R*)-4-hydroxy-2-(hydroxymethyl)-6-[[(1*S*,2*S*,4*S*,6*R*,7*S*,8*R*,9*S*,12*S*,13*R*,16*S*)-6-methoxy-7,9,13-trimethyl-6-[(3*R*)-3-methyl-4-[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxybutyl]-5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icos-18-en-16-yl]oxy]-5-[(2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxyoxan-3-yl]oxy-6-methyloxane-3,4,5-triol

M6: (2*S*,3*R*,4*R*,5*R*,6*S*)-2-[(2*R*,3*S*,4*S*,5*R*,6*R*)-4-hydroxy-2-(hydroxymethyl)-6-[[(1*S*,2*S*,4*S*,6*R*,7*S*,8*R*,9*S*,12*S*,13*R*,16*S*)-6-hydroxy-7,9,13-trimethyl-6-[(3*R*)-3-methyl-4-[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxybutyl]-5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icos-18-en-16-yl]oxy]-5-[(2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxyoxan-3-yl]oxy-6-methyloxane-3,4,5-triol



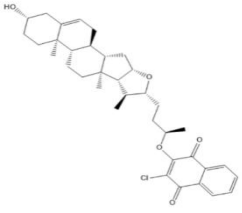


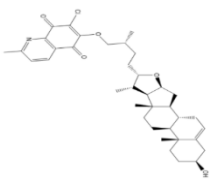


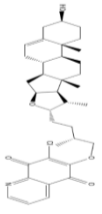
M7: 6-chloro-7-{[(1S,2S,4S,6R,8R,9S,12S,13R,16S)-6-hydroxy-6-(5-hydroxy-3-methylpentyl)-9,13-dimethyl-5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icos-18-en-16-yl]oxy}-5,8-dihydroquinoline-5,8-dione

M8: 2-chloro-3-(((4S,5'R,6aR,6bS,8aS,8bR,9S,10R,11aS,12aS,12bS)-5',6a,8a,9-tetramethyl-1,3,3',4,4',5,5',6,6a,6b,6',7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)oxy)naphthalene-1,4-dione

M9: 6-chloro-7-{[(1S,2S,4S,6R,8R,9S,12S,13R,16S)-6-hydroxy-6-(5-hydroxy-3-methylpentyl)-9,13-dimethyl-5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icos-18-en-16-yl]oxy}-2-methyl-5,8-dihydroquinoline-5,8-dione







M10: 2-chloro-3-(((R)-4-

M11: 7-chloro-6-((R)-4-

M12: 7-chloro-6-((R)-4-

((4S,6aR,6bS,8aS,8bR,9S,10R,11aS,12aS,12bS)-4-hydroxy-6a,8a,9-trimethyl-3,4,5,6,6a,6b,7,8,8a,8b,9,10,11a,12,12a,12b-hexadecahydro-1H-naphtho[2',1':4,5]indeno[2,1-b]furan-10-yl)butan-2-yl)oxy)naphthalene-1,4-dione	((4S,6aR,6bS,8aS,8bR,9S,10S,11aS,12aS,12bS)-4-hydroxy-6a,8a,9-trimethyl-3,4,5,6,6a,6b,7,8,8a,8b,9,10,11a,12,12a,12b-hexadecahydro-1H-naphtho[2',1':4,5]indeno[2,1-b]furan-10-yl)-2-methylbutoxy)-2-methylquinoline-5,8-dione	((4S,6aR,6bS,8aS,8bR,9S,10S,11aS,12aS,12bS)-4-hydroxy-6a,8a,9-trimethyl-3,4,5,6,6a,6b,7,8,8a,8b,9,10,11a,12,12a,12b-hexadecahydro-1H-naphtho[2',1':4,5]indeno[2,1-b]furan-10-yl)-2-methylbutoxy)quinoline-5,8-dione

Figure 3. Chemical structure of diosgenin derivatives

Geometry Optimization

Compounds that have been optimized using the Gaussian09 application were opened, and setup calculation was done with the optimization option on the job type, using the DFT method and the 6-31G basis set and hybrid functional B3LYP. The output of the optimization process obtained files in the form of *.chk and *.gjf.

Determination of Chemical Physical Properties Parameters

After obtaining the compound structure in 2D and 3D, all compounds were measured for physicochemical properties using the Gaussian09 application.

Molecular Docking Simulation

Ligand molecules and cyclodextrin macromolecules are docked using the Autodock application. Hydrogen atoms were added, and ligands were set to be in the inside and center of each macromolecule. Autogrid in the Autodock Tools 1.5.6 application is used for atom pre-calculation using a 40 x 40 x 90-point grid box with a distance of 0.375 A and focused on dimensions of 7.416 x -9.429 x -0.114 points. Lamarckian genetic algorithm (LGA) was used with 100 times docking used for each simulation, elitism 1, mutation rate 0.02, population size 100, crossover rate 0.08, and 2,500,000 energy evaluations.

Interpretation and visualization

All resulting interactions (hydrogen bonds, covalent bonds, hydrophobic bonds) were identified using the Discovery Studio Visualizer application.

RESULTS AND DISCUSSIONS

Geometry Optimization

Geometry optimization of each compound, both ligands, and macromolecules, is carried out to obtain structures with minimum energy or the lowest energy of each molecule where the structure that has the lowest energy is the structure that represents the most stable state (Leach et al., 2001). The geometry optimization method used in this research is the Density Functional Theory (DFT) method and 6-31G basis set with B3LYP hybrid functional. The DFT method has a high accuracy value so it is used in this geometry optimization process (Muttaqin et al., 2021).

Bonding Energy (HOMO-LUMO)

Calculation of geometry optimization results using the DFT method involves analysis of vibrational frequencies, electronic spectra, highest occupied molecular orbital energy (HOMO) - lowest unoccupied molecular orbital energy (LUMO), (Table.1) with various chemical reactivity parameters. The lower value of the HOMO and LUMO energy gap indicates that the studied molecule has high chemical reactivity, biological activity, and polarization (Mumit et al., 2020).

Table 1. Value of homo-lumo energy and energy gap of diosgenin derivatives, α- cyclodextrin, and β - cyclodextrin

No	Structure Code	HOMO	LUMO	Energy Gap
1	M1	-0.22825	0.02721	-0.25546
2	M2	-0.20674	0.06321	-0.26995
3	M3	-0.19732	0.02472	-0.22204

No	Structure Code	HOMO	LUMO	Energy Gap
4	M4	-0.23198	0.06346	-0.29544
5	M5	-0.21219	0.01978	-0.23197
6	M6	-0.22976	0.02573	-0.25549
7	M7	-0.11126	-0.10058	-0.01068
8	M8	-0.23477	-0.12758	-0.10719
9	M9	-0.10995	-0.9925	0.88255
10	M10	-0.22955	-0.12840	-0.10115
11	M11	-0.23096	-0.13107	-0.09989
12	M12	-0.23132	-0.13492	-0.0964
13	ACD	-0.21828	-0.01067	-0.20761
14	BCD	-0.22224	-0.00394	-0.2183

Binding mode

For all macromolecules and ligands that have been optimized, molecular docking is carried out using the AutodockTools application. Twelve ligands were docked to each macromolecule. Molecular docking is performed to predict the conformational state of the ligand flexibly, utilizing the map generated by AutoGrid to find the ligand-macromolecule interaction at each point in the docking simulation (Asnawi et al., 2023). Molecular docking simulation in this study uses a size 40 x 40 x 90-point grid box. This size has previously been adjusted to the size of the largest ligand of the 12 ligands used. This is done because the docking simulation must be done for each site predicted by the ligand (Valdés-Tresanco et al., 2020).

The parameters of this molecular docking are the value of the binding free energy (ΔG) and the inhibition constant (Ki). The binding free energy or delta G is a measure of the ligand's ability to bind to macromolecules. The smaller the value of bond-free energy or delta G, the higher the affinity of the macromolecule with the ligand and vice versa. One ligand was selected that had the lowest value of free energy of bonding (ΔG) and inhibition constant (Ki) with visualization results as shown in Figure 4. The lower the energy affinity value of a molecule, the stronger the bond that is formed (Asnawi et al., 2024).

(a) (b)

Figure 4 . Visualization of the results of docking of ligand molecules M8 (a) and M11 (b) with α- cyclodextrin as macromolecules. Conventional hydrogen bond, carbon hydrogen bond, hydrophobic colored in green, light green, and purple

Of all the compounds that have been docking to each macromolecule, one pair of compounds was found to have the lowest inhibition constant and bond energy. The compound with code M8 and macromolecule α-cyclodextrin (Fig.4a) is a compound pair that has the lowest 19.80 uM inhibition constant (Ki) value and -6.42 kcal/mol binding free energy (ΔG), code M11 with macromolecule α-cyclodextrin (Fig.4b) that has the lowest 61.67 uM inhibition constant (Ki) value and -5.74 kcal/mol binding free energy (ΔG) among all compounds that are carried out molecular docking. In addition, the inclusion complex of compound M8 and a-cyclodextrin has five conventional hydrogen bonds and one carbon-hydrogen bond. The presence of hydrogen

bonding and van der Walls interactions in the inclusion complex indicates the strength of the stability of the complex formed (Benaïssa et al., 2023). The second-best compound (Fig.4b) shows the resulting hydrophobic interaction, proving that the cyclodextrin compound cavity can encapsulate the lipophilic molecules of a drug (Kaur et al., 2019).

The study (Zhong et al., 2020) related to tea polyphenols inclusion complex formation experiments mentioned that when antioxidants enter the cyclodextrin cavity, phenolic hydroxyl groups form intramolecular hydrogen bonds while increasing the degree of hydroxylation. Hydrogen bonding in the inclusion complex of dexamethasone with β-cyclodextrin plays an important role in the stability of the inclusion complex formed (Belhocine et al., 2021). Another author in his study also mentioned that the complexation formed between β -CD and sesamol was confirmed through enhanced absorption and emission due to the non-covalent interaction of the hydrophobic cavity of β -CD (Han et al., 2021).

CONCLUSION

The results of the molecular docking simulation of 12 test compounds with 2 macromolecules resulted in a pair of test compounds with the best affinity (lowest ΔG and Ki values), namely compounds with structure code **M8** and macromolecule α-cyclodextrin. The results of this study can be studied and continued as future research material to develop evidence of increasing solubility in compounds by forming inclusion complexes with macromolecules.

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