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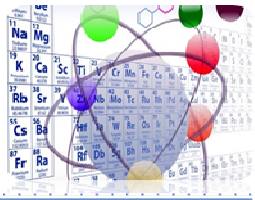

Identification of Lanosterol Protein As a Cataract Drug Candidate with Campheserol and Its Derivatives Using Docking and HKSA Computational Methods

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ABSTRACT

As time goes by, technological development is becoming increasingly rapid. Many researchers, especially chemists, take advantage of this situation to advance their research. Furthermore, to support their research, it generally requires a significant amount of funding, because identifying a single compound necessitates numerous tools to determine whether it contains other compounds or their derivatives that can be used as potential drug candidates. Cataract drugs are not widely available in the world, therefore this article discusses cataract drugs. Docking computational methods and HKSA were used to identify a compound and its derivatives as drug candidates. The identified compound is campesterol and its derivatives. In the lanosterol protein, there are campesterol compounds and their derivatives that can be used for toothache medication. The results obtained through the HKSA process indicate that campesterol and its derivatives can be used as cataract medication.

Keywords: Docking, HKSA, Lanosterol, Campesterol and its derivatives, Cataract Drug

1. INTRODUCTION

As time goes by, technological development is becoming increasingly rapid. Many researchers, especially chemists, take advantage of this situation to advance their research. In addition, to support their research, it generally requires a significant amount of funding, because identifying a single compound necessitates numerous tools to determine whether it contains other compounds or their derivatives that can be used as drug candidates. Therefore, many chemists use computers as tools for the computation of the compounds to be studied.

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In the world of computation, there are two methods used to identify a compound as a potential drug candidate, namely docking and QSAR. In molecular biology and bioinformatics, docking is one of the methods that can predict interactions between molecules, which can include proteins such as enzymes, DNA, carbohydrates, and fats with substrates, although it is more commonly explored with enzymes. Currently, docking is used in the design of drugs and antivirals, and it serves as an initial selection stage for many substrates, making laboratory experiments easier due to the reduced number of test samples, although discrepancies may occur between bioinformatics results and wet laboratory results. (false positive atau false negative). Meanwhile, HKSA (Quantitative Structure-Activity Relationship) is a regression model or classification model used in the fields of biology, chemistry, medicinal chemistry, and engineering. Like other regression models, the HKSA model is a regression model that relates a set of "predictor" variables (X) to the potential of the response variable (Y), while the HKSA classification is a model that relates predictor variables to categorical values of the response variable.

Cataracts are one of the main causes of blindness that occur due to opacification (clouding) of the eye lens, which disrupts the transmission of light to the retina[6]. The increase in the incidence of cataracts, especially among the elderly population, has become a global health issue[4]. Until now, the only widely recognized method for treating cataracts is through surgical procedures. However, the limited access to surgical facilities and the high cost of surgery make more affordable and non-invasive alternative methods highly necessary. Therefore, the development of drugs for the prevention and treatment of cataracts has become the focus of current research.

One of the latest and most interesting approaches in cataract treatment is the use of natural compounds that can modulate the protein aggregation process causing lens opacity. Previous research has shown that lanosterol, which is a sterol compound in the cholesterol biosynthesis pathway, has the potential to restore lens clarity by targeting and dissolving protein aggregates that cause cataracts[3]. In vivo and in vitro studies have demonstrated that the administration of lanosterol can improve lens clarity in test animals, thus opening up opportunities to develop lanosterol as a non-surgical cataract therapy[7].

Additionally, kaempferol, a flavonoid found in various plants, is known to possess antioxidant, anti-inflammatory, and protein-protective properties. These characteristics make kaempferol and its derivatives potential candidates for cataract therapy, either through protein protection mechanisms or by enhancing the action of lanosterol. The combination of kaempferol with lanosterol has the potential to increase the effectiveness of cataract treatment through synergistic mechanisms[1].

To explore the potential of this interaction more deeply, computational approaches such as molecular docking are used to predict the interaction between the target protein (lanosterol) and ligands such as kaempferol and its derivatives[2]. This method allows for an in-depth analysis of binding affinity and the stability of compound complexes, which can guide further drug development. Additionally, Hirshfeld Surface Analysis (HKSA) is used to examine the distribution of molecular interactions and binding patterns between lanosterol and ligands, providing a clearer picture of the effectiveness of these compound interactions in the context of cataract therapy[5].

Docking and HKSA computational methods were used to identify lanosterol protein in campesterol compounds and their derivatives as drug candidates. In campesterol and its derivatives, there is lanosterol protein that can be used for cataract medication. Generally, lanosterol is in the form of eye drops that are believed to be effective as a cataract treatment, especially for mild cataracts. This medication works by dissolving protein clumps in the eye lens. Research shows that lanosterol can be used as a cataract treatment

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and can improve the eye lens after 6 weeks of use. However, the effectiveness of lanosterol as a cataract treatment has not yet been clinically proven. The reason is that the drug has only been tested on animals, so its effectiveness in humans has not yet been confirmed. Therefore, this article will prove the effectiveness of lanosterol protein as a cataract medication.

2. EXPERIMENTAL

2.1. Chemicals, Equipment and Instrumentation

The hardware used is an HP 14 laptop, 8 GB RAM with Windows 10 Pro to download compounds from PubChem and access SwissADME, Mol Inspiration, and pkCSM to obtain the data needed in HKSA. The computer in the laboratory is used for docking and HKSA. The software used is Biovia to convert the sdf format to pdb and pdbqt. Then Avogadro is also used for HKSA, Autodock via, time viewer to transfer files from the computer to the laptop, SPSS to obtain the predicted log P results from the dependent and independent variables. Excel is used to facilitate data storage and to determine the value of y and the regression between log P and predicted log P.

2.2. Research Procedure

A. Preparation of Ligand Molecular Structure

Bioactive compounds of campesterol, namely ß-sitosterol, stigmasterol, ergosterol, and sitosteryl glucoside. The structures of these four active compounds were downloaded from the PubChem database (http://pubchem.ncbi.nlm.nih.gov), and prepared using the Biovia Discovery Studio 2019 and Autodock 1.5.7 software. After preparation, the ligand molecules are stored in one folder in pdb, nw, and pdbqt formats according to their respective names.

B. Preparation of Lanosterol Protein Structure

The structure of the Lanosterol protein was downloaded from the Protein Data Bank (PDB) (http://www.rcsb.org). The Lanosterol molecule was prepared using the Biovia Discovery Studio 2019 software. In this molecular preparation, the steps taken included the removal of H_2O groups (if present), the separation of the natural ligand (clokasilin) found in Lanosterol, and the addition of hydrogen atoms (usually, files in .pdb format are incomplete in terms of hydrogen atoms). After preparation, the Lanosterol molecule and the separated natural ligands (campesterol and its derivatives) were stored in a single folder in pdb, nw, and pdbqt formats.

C. Determination of the Active Site of Lanosterol

The active site of Lanosterol is the binding site for ligands of the campesterol compound group. In this study, the search for the active site where ligands bind to Lanosterol uses the Autodock Vina software, based on the same principle of searching for the lowest binding energy of H2O molecular bonds throughout the radius of the Lanosterol protein molecule.

D. Molecular Docking

In this study, molecular docking of four compounds of campesterol and its derivatives will be performed as ligands with proteins using the Autodock Vina version 1.1.2 software with the PyRx graphical user interface (GUI), which is an integrated program to predict the interaction (binding) between ligands and proteins. This software can handle all aspects of the docking process, from

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molecular preparation to determining the potential active binding sites of the target protein and predicting the binding model of the ligands. The ligand molecule binds to the receptor, inhibiting the receptor's function, thereby acting as a drug. The parameters used in the molecular docking process with Autodock Vina version 1.1.2 include an RMSD (Root Mean Square Deviation) < 2, with the smallest binding energy (kcal/mol) for the Lanosterol ligand protein.

E. Optimization of Compound Geometry and Descriptor Calculation

For each of the 5 compounds, geometry optimization was performed using the swisame, mol inspiration, and pkCSM software. Subsequently, for each optimized compound structure, descriptor values were calculated using Excel. The descriptors used in this study are the energy of HOMO/Highest Occupied Molecular Orbital (AM1_HOMO), energy of LUMO/Lowest Unoccupied Molecular Orbital (AM1_LUMO), hydration energy (kcal/mol), molar refractivity (Mr) (g/mol), surface area, TPSA, partition coefficient (Log P), and van der Waals volume. (Vol). The selection of these 10 descriptors was carried out by considering the electronic properties, hydrophobic properties, and steric properties of the compounds, all of which determine the pharmacokinetics and pharmacodynamics of the drugs.

F. Building the HKSA Model

The HKSA model was built using multiple linear regression analysis with the help of SPSS software version 19. The HKSA model connects descriptors as independent variables (X) and the Log P value of MEK inhibition activity as the dependent variable. The validity of the HKSA model is tested using statistical criteria, such as the coefficient of determination (R2) and the standard error of estimate (SEE).

3. RESULTS AND DISCUSSION

3.1. Docking

The docking study began by searching for the Lanosterol protein in RCSB in pdb format and the ligand compound campesterol and its derivatives in PubChem in sdf format. Then, the protein and compound were converted to the appropriate format using Biovia software.

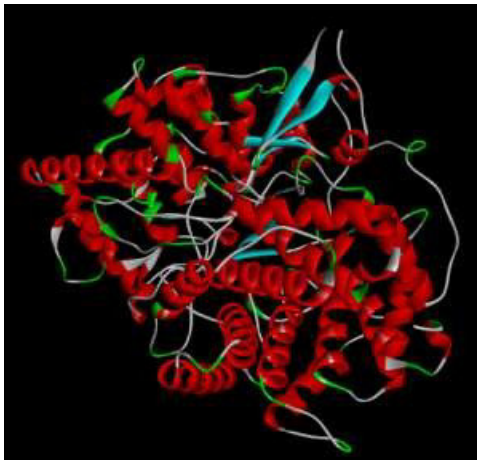

Figure 1. Protein Lanosterol

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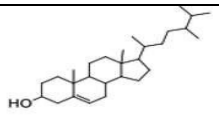
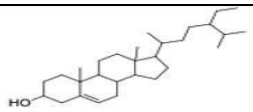
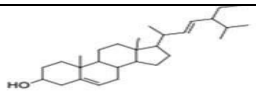
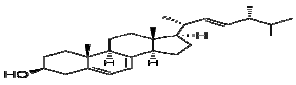
Table 1. Structure of Cholesterol Compounds and Their Derivatives

Nama senyawa	Struktur
Kampesterol	
ß-sitosterol,	
Stigmasterol	
Ergosterol	

Then, the protein and the campesterol compound and its derivatives were input into the autodock application with the output of Lamarckian GA(4.2) and the dpf and gpf formats. Five files were obtained, which are the campesterol compound and its derivatives, transferred to the computer, and docked using the terminal. The result was obtained in a file with the dlg format, opened with Notepad, and the result from the lowest was copied, then saved in pdb format. After that, it was docked using Biovia. The complex.pdb file was opened and the lowest.pdb was added, resulting in the output as shown in the image below.

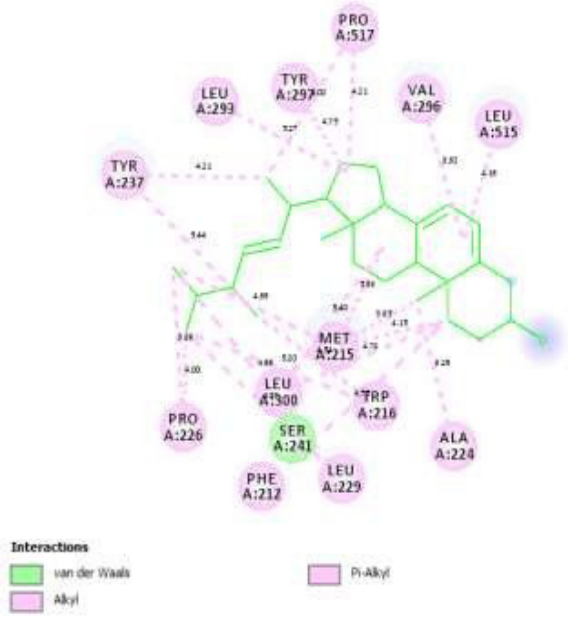


Figure 2. Docking the compound Stigmasterol.

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3.2. HKSA

The HKSA study begins with the optimization of the geometry of each compound in the data set, then the files are transferred to the computer using a time viewer. HKSA was performed on the computer to obtain the values of the Homo, Lumo, and Hydration Energy inhibitors. Continued with the search for other inhibitors such as Mr, surface area, TPSA, Volume, Log P, and ld50 on the web. For the dipole moment itself, it can be found using the Avogadro software.

Table 2. SPSS Regression Results

Model		Unstandardized Coefficients		Standardized Coefficients			95,0% Confidence Interval for B		Collinearity Statistics			
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound	Zero-order	Part	Tolerance	VIF
1	(Constant)	467.456	.000		.	.	467.456	467.456				
	E_hidrasi	-.001	.000	-.701	.	.	-.001	-.001	-.554	-.578	.680	1.470
	Survace_Area	.001	.000	2.503	.	.	.001	.001	-.172	.522	.043	23.014
	Volume	-.003	.000	-3.099	.	.	-.003	-.003	-.388	-.481	.024	41.484
	Lumominhomo	5.737E-6	.000	.232	.	.	.000	.000	-.694	.089	.145	6.875

The web used to search for inhibitors is swiisadme by entering the smile of the compound, then obtaining the values of Mr, TPSA, and Log P. After obtaining the inhibitor, it was also found that campesterol and its compounds can be used as cataract drug compounds. This can be seen in Lipinski, which is one of the parameters used for drugs. To determine whether the compound can be used as a drug, it must meet these parameters. Then the next website is Mol Inspiration, where you input the SMILES of the compound and obtain the inhibitor volume value. And the pkCSM web, by entering the compound's SMILES, yields the inhibitor surface area and LD50 values.

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After obtaining the values from each inhibitor, the data is entered into Excel to facilitate data entry. Then, in SPSS, the inhibitor data previously created in Excel is entered, and the analysis is conducted by finding the regression and entering the dependent variable as log P and the independent variables as homo, lumo, E.hydration, mr, surface area, TPSA, Volume, dipole moment, ▲lumo-homo, and ld50. (independent). The results obtained are as shown in Table 2. The results obtained are then input into the formula:

Log P prediction= B. Constant + (B. hidrasi x E.hidrasi) + (B. survace area x survace area) + (B. volume x volume) + (B. lumo-homo x lumo-homo)

The predicted Log P for compound 1 (campesterol) is 466.3094346, which is close to its Log P value of 4.79. Thus, it can be said that the dependent variable affects the descriptor, and it can also be said that the structure influences the activity of campesterol and its derivatives. Then, the inhibitor Log P values and the predicted Log P were graphed in Excel, resulting in the equation y = 127.17x and R^2 = 0.8128, which is close to one, as shown in Graph 1. Thus, it was found that the lanosterol protein from the compound campesterol and its derivatives is not too toxic and not passive. And the compound campesterol falls into category four, which means it is safe and non-toxic for treating cataract disease.

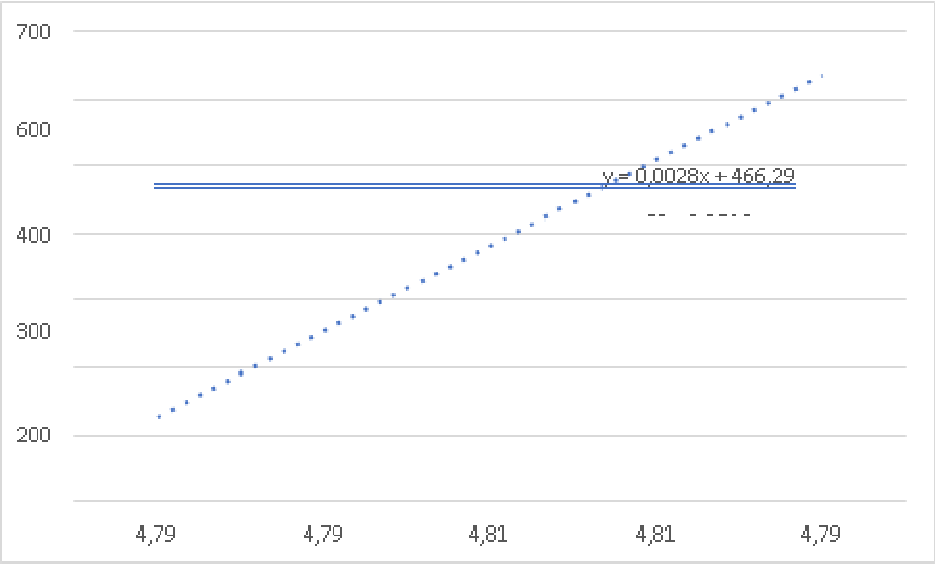

Figure 3. The relationship between predicted Log P and Log P

4. CONCLUSION

In this study, a valid docking and HKSA model has been developed that connects the chemical structure of campesterol derivatives with their inhibitory activity against Lanosterol. The design of new compounds using this docking model yielded one new compound with better predicted activity than the parent compound. Meanwhile, using the HKSA model, all compounds showed good predicted activity. Molecular docking studies show that the designed compound can interact with the allosteric site of the Lanosterol

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protein with crucial amino acid residues through hydrogen bonds and van der Waals interactions. This research indicates that the designed compound can be used as a drug for cataracts.

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