

COLON CANCER DRUG DEVELOPMENT STUDY OF ELLAGIC ACID DERIVATIVES

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ABSTRAK

Penelitian ini bertujuan untuk mengembangkan obat kanker kolon dengan bahan baku senyawa asam Elagat dan turunannya menggunakan metode Hubungan Kuantitatif Struktur-aktivasi (HKSA) dan penambatan molekular. Deskriptor yang dipakai HKSA meliputi deskriptor elektronik, sterik, dan hidrofobik. Karakter dari masing-masing deskriptor dikomputasikan menggunakan *software* NWchem dan MarvinSketch dengan teori HF (Hartree-Fock). Penambatan molekul dilakukan dengan menggunakan *software* Autodock Tools dan Biovia. Hasilnya menunjukkan bahwa model persamaan terbaik HKSA senyawa bahan obat dari asam elagat dan turunannya adalah $\text{Log P} = -7.103 + (-0.005 \cdot \text{PSA}) + (-0.729 \cdot \text{MR}) + (0.003 \cdot \text{Volume}) + (0.002 \cdot \text{SA}) + (-99.912 \cdot \text{Homo}) + (-38.893 \cdot \text{Lumo}) + (-0.072 \cdot \text{MD}) + (0.006 \cdot \text{Eh}) + (1.409 \cdot \text{P})$ yang diperoleh untuk senyawa 2,3,7-trichloro-8-methoxychromeno[5,4,3-cde]chromene-5,10-dione. Hasil penambatan molekular tersebut memiliki energi ikat sebesar -9.94 kkal/mol dan konstanta inhibisinya 51,54 nM.

Kata kunci: asam elagat, HKSA, kanker kolon, penambatan molekular

ABSTRACT

This study aimed to develop a colon cancer drug with a raw material of ellagic acid and its derivatives using the Quantitative Structure-Activity Relationship (QSAR) method and molecular docking. The descriptors used in QSAR were electronic, steric, and hydrophobic descriptors. The characters of each descriptor were computed using NWchem and MarvinSketch software with the HF (Hartree-Fock) theory. Molecular docking was performed using Autodock Tools and Biovia software. The results show that the best equation of QSAR model for medicinal compounds from ellagic acid and derivatives was $\text{Log P} = -7.103 + (-0.005 \cdot \text{PSA}) + (-0.729 \cdot \text{MR}) + (0.003 \cdot \text{Volume}) + (0.002 \cdot \text{SA}) + (-99.912 \cdot \text{Homo}) + (-38.893 \cdot \text{Lumo}) + (-0.072 \cdot \text{MD}) + (0.006 \cdot \text{Eh}) + (1.409 \cdot \text{P})$ obtained for 2,3,7-trichloro-8-methoxychromeno [5,4, 3-cde] chromene-5,10-dione compound. The result of molecular docking had a binding energy of -9.94 kcal/mol and an inhibition constant of 51.54 nM.

Keywords: colon cancer, ellagic acid, molecular docking, QSAR.

INTRODUCTION

Cancer of the colon or colorectal cancer (CRC) is a disease affecting the colon and rectum. Colon cancer ranks third in the world and the cause of death from cancer (Ceci *et al.*, 2018). At the beginning of 2020, approximately 147 950 people are diagnosed with colon cancer and 53 200 died of the disease, including 17 930 cases and 3,640

deaths in individuals aged under 50 years (Siegel *et al.*, 2020).

One of the causes of colon cancer is the uncontrolled growth of Leukotriene A4 hydrolase (LTA4H), an enzyme that acts as an epoxide hydrolase and an aminopeptidase (Noviardi and Fachrurrazie, 2015). LTA4H can cause carcinogenesis (Zhao *et al.*, 2019) and form leucotriene B4, which has a role in inflammation and cancer development (Vo, Jang and Jeong, 2018). LTA4H can be used as

an inflammatory marker in colorectal cancer. Therefore inhibition of LTA4H may decrease the development of colon cancer (Mira *et al.*, 2020). Colon cancer treatment by chemotherapy, surgery, and radiation has not been effective in healing cancer. Therefore, compounds obtained from plants have attracted attention lately as an alternative for cancer prevention and treatment. The compounds from plants have low toxicity, cost, and side effects.

Ellagic acid is a natural polyphenol compound that has anticancer and antioxidant properties (Ceci *et al.*, 2018). The anticancer activity present in the ellagic acid compounds can be used for various types of cancer (Wang *et al.*, 2019). Ellagic acid and some of its derivatives can inhibit the proliferation of cancer cells, induce cell cycle arrest, and modulate some of the important cellular processes associated with cancer. (Molina *et al.*, 2015). Ellagic acid can effectively inhibit the viability of colon cancer cells (HT29 and HCT 116) (Fang *et al.*, 2015). Ellagic acid also have potential as inhibitors for epoxide hydrolase with IC50 values of $15.4 \pm 1.3 \mu\text{M}$ (Luyen *et al.*, 2015).

Based on this research, it is necessary to conduct a new drug development study by analyzing the QSAR and molecular docking. QSAR equation model, to predict the activity of ellagic acid and its derivatives as colonic anticancer compounds, was performed by multiple linear regression analysis. QSAR model is used for prediction and interpretation,

so it can help to understand the mechanism of the molecule used as the target. Chemical descriptors in QSAR modeling are used to describe various levels of chemical, physical, and structural characteristics of a molecule or target (Cherkasov *et al.*, 2014)

Determination of molecular docking using the Discovery Studio Visualizer (DSV) program can provide visualization of ligand interactions with a target molecule, so that it appears that amino acids play a role in maintaining the stability of ellagic acid derivatives against colon cancer protein, leukotriene A4 hydrolase (LTA4H). Testing the activity of ellagic acid derivatives against colon cancer with LTA4H colon cancer protein was carried out in silico with the method of quantitative relationship to structure and activity as well as the binding of LTA4H colon cancer protein with the code PDB: 3U9W.

MATERIAL AND METHOD

Material

The compound used in this study is ellagic acid and its derivatives are shown in Table 1. Ellagic acid derivatives are the result of functional group substitution expected to reduce the reactivity of ellagic acid compounds as anti-colon cancer. Ellagic acid has an LD50 range between 500-5000 with a mild toxic classification (BPOM, 2014).

Table 1. Compounds of ellagic acid and their derivatives

No	Structure Name	LD50 (mg/Kg)
1.	Ellagic Acid	1712
2	3-chloro-2,7,8-trihydroxychromeno[5,4,3-cde]chromene-5,10-dione	931,6
3	2-chloro-3,7,8-trihydroxychromeno[5,4,3-cde]chromene-5,10-dione	849,3
4	2,7-dichloro-3,8-dihydroxychromeno[5,4,3-cde]chromene-5,10-dione	1158
5	2,8-dichloro-3,7-dihydroxychromeno[5,4,3-cde]chromene-5,10-dione	719,9
6	2,3,7-trichloro-8-hydroxychromeno[5,4,3-cde]chromene-5,10-dione	1030
7	2,3,8-trichloro-7-hydroxychromeno[5,4,3-cde]chromene-5,10-dione	1170
8	2,3,7,8-tetrachlorochromeno[5,4,3-cde]chromene-5,10-dione	2360
9	2,3,7-trihydroxy-8-methoxychromeno[5,4,3-cde]chromene-5,10-dione	2039
10	2,3,8-trihydroxy-7-methoxychromeno[5,4,3-cde]chromene-5,10-dione	2092
11	3,8-dihydroxy-2,7-dimethoxychromeno[5,4,3-cde]chromene-5,10-dione	2349
12	2,8-dihydroxy-3,7-dimethoxychromeno[5,4,3-cde]chromene-5,10-dione	2032
13	3-hydroxy-2,7,8-trimethoxychromeno[5,4,3-cde]chromene-5,10-dione	1599
14	2,7,8-trihydroxy-5,10-dioxo-5,10-dihydrochromeno[5,4,3-cde]chromene-3-carboxylic acid	1458

No	Structure Name	LD50 (mg/Kg)
15	8-chloro-2,7-dihydroxy-5,10-dioxo-5,10-dihydrochromeno[5,4,3-cde]chromene-3-carboxylic acid	1533
16	2-chloro-7,8-dihydroxy-3-methoxychromeno[5,4,3-cde]chromene-5,10-dione	1659
17	2,7-dichloro-3,8-dimethoxychromeno[5,4,3-cde]chromene-5,10-dione	1569
18	2,8-dichloro-3,7-dimethoxychromeno[5,4,3-cde]chromene-5,10-dione	1179
19	2,3,7-trichloro-8-methoxychromeno[5,4,3-cde]chromene-5,10-dione	861,2
20	2-chloro-3,7,8-trimethoxychromeno[5,4,3-cde]chromene-5,10-dione	1384

Methods

QSAR Method

The research used a theoretical experiment using the Quantitative Structure-Activity Relationship (QSAR). The chemical structure of ellagic acid and its derivatives was drawn using Avogadro 1.2.0. The calculation of electronic descriptors using NWChem with the HF (Hartree-Fock) theory based on 631G* and steric and hydrophobic descriptors using Marvin Sketch. Multiple linear regression analysis using the Backward method was performed using the statistical software program SPSS version 16.0. Statistical analysis was applied to determine QSAR the equation model of ellagic acid compounds and derivatives. Table 2 shows the parameters used in QSAR method.

Table 2. QSAR parameters

Parameter	Symbol	Description
Hydrophobic	Log P	Partition coefficient
Steric	SA	Surface Area
	MR	Molar Refractivity
	V	Volume
	PSA	Polar surface area
	P	Polarizability
Electronic	Lumo	Lumo energy
	Homo	Homo energy
	Δ	The difference between lumo and homo energy
	DM	Moment dipol
	H	Hydration energy

Molecular Docking

Optimization process in molecular docking studies used Autodock Tools 1.5.6 software. Optimization of the target structure for colon cancer with the code PDB: 3U9W included adding hydrogen atoms and kollman.

The optimization results were stored in .pdbqt format, then the optimization results of the ellagic acid ligand and their derivatives were stored in .pdbqt format with a grid box setting of 60x60x60 Å to determine the location of the target mooring with the ligand, then the lowest affinity value was calculated. Amino acid determination at the active site was used to analyze the docking evaluation results using the Biovia Discovery Studio 2019 software.

RESULTS AND DISCUSSION

Ellagic acid compounds can induce apoptosis in various colon cancer cell lines with different mechanisms (Montane *et al.*, 2020). This study using the QSAR method aimed to determine the correlation between biological activity and its properties. Physically, the parameters used were divided into three types including steric, hydrophobic and electronic. The biological properties of a molecule had many predetermined physicochemical parameters. The parameters described the biological activity used as the dependent variable and the physicochemical properties as the independent variable (Kapoor and Kumar, 2019).

Molecular descriptors were calculated using twenty compounds of ellagic acid and its derivatives which function as independent variables, while the observed inhibitory action (Log P) on cancer cells was the dependent variable with the QSAR model using multiple linear regression. Physicochemical properties are important properties of a molecule that affect the efficacy, safety, metabolism, and can predict using Lipinski's five rule, namely molecular mass <500, hydrogen bond donor <5, hydrogen bond acceptor <10, and LogP <5 (Lagorce *et al.*, 2017). Ellagic acid and its derivatives met Lipinski's rule. The molecular descriptor used to model the QSAR equation is shown in Table 3.

Table 3. Electronic, hydrophobic and steric descriptors

ID	Log P	PSA	MR	V	SA	Homo	Lumo	Δ Lumo- Homo	DM	H	P
1	1.16	133.52	70.61	219.86	319.91	-0.2004	-0.0301	0.1703	2.8153	29.87	26.99
2	1.31	113.29	73.43	256.57	369.63	-0.1991	-0.0337	0.1654	2.1839	27.09	28.29
3	1.96	113.29	73.43	258.34	372.63	-0.2049	-0.0291	0.1758	2.3317	24.34	28.56
4	2.76	93.06	76.26	260.91	372.97	-0.2113	-0.0293	0.1820	0.4431	20.47	29.84
5	2.11	93.06	76.26	262.70	377.06	-0.2050	-0.0339	0.1711	1.8496	39.34	29.86
6	2.92	72.83	79.08	261.71	370.83	-0.2109	-0.0346	0.1763	2.0417	16.79	31.44
7	2.27	72.83	79.08	263.51	375.03	-0.2047	-0.0380	0.1667	2.2654	36.34	31.18
8	3.07	52.60	81.90	264.30	372.49	-0.2104	-0.0387	0.1717	0.2293	29.50	32.76
9	0.54	122.52	75.09	271.48	356.75	-0.1982	-0.0286	0.1695	1.1093	28.09	28.88
10	1.19	122.52	75.09	273.26	356.86	-0.1992	-0.0287	0.1705	0.9530	25.32	29.14
11	1.22	111.52	79.57	290.76	393.77	-0.1997	-0.0289	0.1709	0.4041	22.53	31.30
12	0.57	111.52	79.57	290.09	393.89	-0.1987	-0.0286	0.1701	1.0804	24.39	31.04
13	0.6	100.52	84.05	308.27	430.70	-0.1992	-0.0288	0.1704	1.0892	21.43	33.20
14	0.96	150.59	75.88	275.22	345.85	-0.1987	-0.0559	0.1428	2.5584	30.78	28.96
15	1.11	130.36	78.71	277.81	350.54	-0.1985	-0.0570	0.1415	3.0007	43.84	30.26
16	1.34	102.29	77.91	272.70	361.73	-0.2041	-0.0288	0.1753	2.8987	23.41	30.45
17	1.53	71.06	85.52	294.14	403.58	-0.2083	-0.0289	0.1793	0.8162	31.94	33.90
18	1.53	71.06	85.22	294.14	403.38	-0.2048	-0.0339	0.1709	3.0767	34.45	33.92
19	2.3	61.83	83.56	279.22	371.41	-0.2094	-0.0342	0.1752	3.1339	34.91	33.33
20	0.76	80.29	86.88	309.06	435.72	-0.2038	-0.0289	0.1750	3.1903	19.37	34.50

The equation for the QSAR model used ten descriptors with the analysis method applied multiple linear regression. Multiple linear regression is a statistical technique used in developing models (Ibrahim *et al.*, 2018).

QSAR analysis of the Log P value with multiple linear regression carried out using the backward method. Statistical processing in this study resulted in 5 equation models.

Table 4. Statistical parameter data of equation models

Model	Variable	R	R ²	Adj R ²	SEE	Significance	F	F _{table}
1	P, DM, Eh, Homo, Lumo, SA, V, PSA, dan MR	0,996	0,991	0,984	0.10043	0	128,362	6,11
2	P, DM, Eh, Homo, Lumo, SA, PSA, dan MR	0,996	0,991	0,985	0,09767	0	152,628	5,86

Model	Variable	R	R ²	Adj R ²	SEE	Significance	F	F _{table}
3	P, DM, Eh, Homo, Lumo, SA, V, dan MR	0,995	0,990	0,985	0,09699	0	176,770	5,75
4	P, DM, Eh, Homo, Lumo, V, PSA, dan MR	0,994	0,989	0,984	0,10094	0	190,107	5,79
5	P, DM, Homo, Lumo, SA, V, PSA, dan MR	0,993	0,987	0,982	0,10584	0	207,033	5,99

In Table 4, the equation models 1-5 meet the requirements because F_{table} has a value > 1 with a 95% truth level and an r² value of more than 0.9. Equation model 1 is the best model with r² of 0.9911 with the nine descriptors required as follows:

$$\text{Log P} = -7.103 + (-0.005 \cdot \text{PSA}) + (-0.729 \cdot \text{MR}) + (0.003 \cdot \text{Volume}) + (0.002 \cdot \text{SA}) + (-99.912 \cdot \text{Homo}) + (-38.893 \cdot \text{Lumo}) + (-0.072 \cdot \text{MD}) + (0.006 \cdot \text{Eh}) + (1.409 \cdot \text{P}).$$

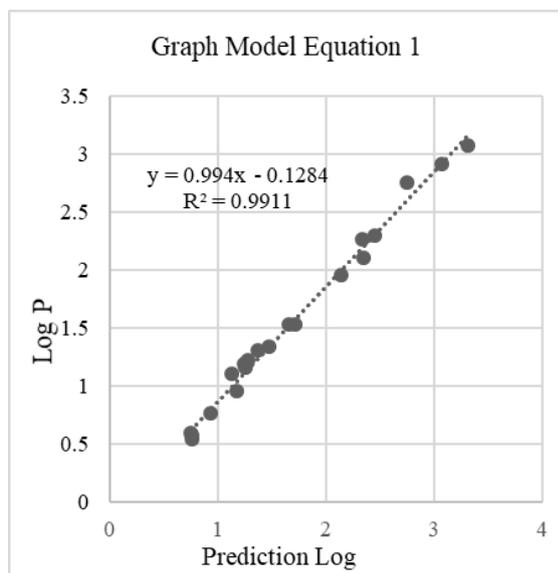


Figure 1. Graph Model Equation 1

Log P represents the hydrophobicity of a molecule. The more positive the log P value, the greater the lipophilicity. The greater

the P value, the more interactions the compound will have with the lipid phase (membrane)(Kapoor and Kumar, 2019). The compounds tend to be in a non-polar phase rather than a polar phase that causes compounds to penetrate easily the membrane and can bind to receptors. According to the log P parameter, ellagic acid is hydrophobic because log P is positive, so it has good bond selectivity to target proteins and is not toxic (Suciati, Lestari and Lukiaty, 2020) (Syahputra, Ambarsari and Sumaryada, 2014). Based on the correlation analysis, it can be seen that the dipole moment descriptors, E Homo, E Lumo, polarizability, hydration energy and Log P showed a very close correlation. This is indicated by the regression value of 0.9911. In addition, the low Delta Lumo-Homo value indicates the compound has high reactivity, Homo has electrons which tend to give electrons as electron donors, while Lumo contains free places to accept electrons (Kumer, Sarker and Paul, 2019).

Molecular docking provides information on the interactions between compounds such as drugs or called ligands and enzymes or receptors through the active position in the enzyme by calculating the binding energy. Molecular docking calculations to predict the strength of the interaction between ligands and receptors (Sethi, Joshi and Sasikala, 2020). The calculation of the interaction energy in the form of a score docking (Ibrahim *et al.*, 2018).

Molecular docking between Leukotriene A4 hydrolase and ellagic acid and its derivatives in Table 1. The following is the structure of the protein Leukotriene A4 hydrolase:

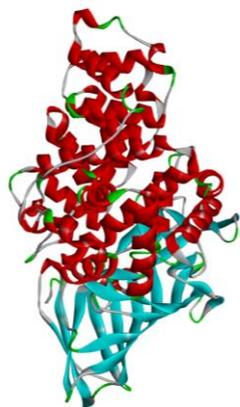


Figure 2. Protein structure of Leukotriene A4 Hydrolase

(Source: <https://www.rcsb.org/structure/3U9W>)

Tethering molecular compounds of ellagic acid was done to calculate the binding free energy (Gibbs energy, ΔG) of the ligand to the receptor protein and inhibition constant. Gibbs energy is an indicator to determine the stability of the interaction between ligands and receptors, so it can explain binding energies with different binding conformations. (IA, SO and OO, 2016). The inhibition constant was obtained from the binding energy (ΔG) using the formula $K_i = e^{\Delta G/RT}$, $R = 1.986$ kcal/mol K, $T = 298$ K (Cheshomi, Reza and Matin, 2020)(Rowaiye *et al.*, 2020). The lower the binding energy value, the smaller the inhibition constant value.

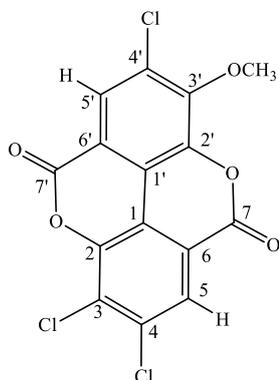
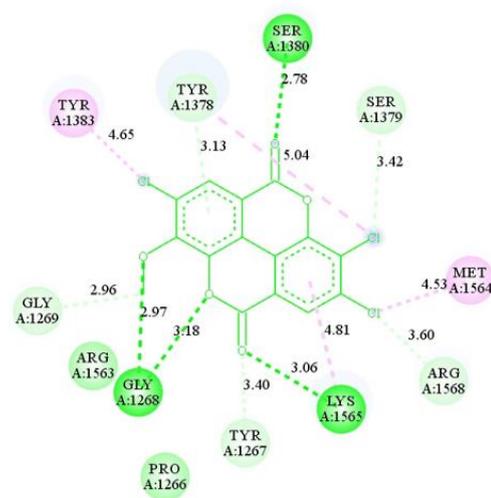


Figure 3. 2,3,7-trichloro-8-methoxychromeno[5,4,3-cde]chromene-5,10-dione Compound

Figure 3 shows the structure of the molecule if the OH group on the C atom numbers 3, 4, and 4' that had been replaced with Cl and the C atom number 3' with OCH3 which caused the binding energy and the inhibition constant to decrease. The lower the binding energy caused the compound to be stable and could become colonic anticancer compounds. The results obtained from molecular docking were the binding energy of -9.94 kcal/mol and the inhibition constant of 51.54 nM.



Interactions

- van der Waals
- Conventional Hydrogen Bond
- Carbon Hydrogen Bond
- Pi-Donor Hydrogen Bond
- Alkyl
- Pi-Alkyl

Figure 4. Visualization of Amino Acid Interaction between Ellagic Acid and Leukotriene A4 Hydrolase Protein by Biovia Discovery Studio 2019 Software

Ellagic acid compounds that interact via hydrogen bonds with the residue of Leukotriene A4 Hydrolase in colon cancer is the amino acid Gly1268 which bonded to the OCH3 group (2.97 Å), Gly1268 bonded to the ether group (3.18 Å), Lys 1565 bonded to the ketone group (3.06 Å) and Ser1380 bond to the ketone group (2.78 Å).

CONCLUSION

The QSAR equation model is shown with the results: $\text{Log P} = -7.103 + (-0.005 \cdot \text{PSA}) + (-0.729 \cdot \text{MR}) + (0.003 \cdot \text{Volume}) + (0.002 \cdot \text{SA}) + (-$

99.912*Homo) + (-38.893*Lumo)+ (-0.072*MD)+ (0.006*Eh) + (1.409*P). Molecular docking of ellagic acid and its derivatives obtained the lowest binding energy value of -9.94 kcal/mol and an inhibition constant of 51.54 nM in the 2,3,7-trichloro-8-methoxychromeno 5,4,3-cde] chromene-5 compound, 10-dione, so that it can inhibit the protein Leukotriene A4 Hydrolase in colon cancer.

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