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To cite this article: Istiqomah Rahmawati *et al* 2020 *IOP Conf. Ser.: Mater. Sci. Eng.* **823** 012001

IOP Conf. Series: Materials Science and Engineering **823** (2020) 012001 doi:10.1088/1757-899X/823/1/012001

Molecular modelling of antioxidant agent by QSAR study of caffeic acid derivatives

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Abstract. Molecular modeling using Quantitative Structure and Activity Relationship (QSAR) has been performed on caffeic acid derivatives which is previously studied as an effective antioxidant agent. This research focuses on a set of experimentally IC_{50} value data of 4 caffeic acid derivatives. The mathematical method (i.e., multilinear regression calculation) was used to build the QSAR model. QSAR analysis was employed on fitting subset using log ($1/IC^{50}$) as a dependent variable and atomic net charges aromatic carbons, dipole moment and partition coefficient in n-octanol/water as independent variables. The PM3 method was used to calculate the quantum chemical descriptors, chosen to represent the electronic descriptors of molecular structures. The relationship between log ($1/IC_{50}$) and the descriptors was described by resulted in the QSAR model. The resulted QSAR model for caffeic acid derivatives as an antioxidant is presented below:

$$-7.858+1.149dipol+0.485logP-61.68C5$$
$$R=1;\ R^2=0.999;\ SE=0.008;\ F=342$$

QSAR model for caffeic acid derivatives showed the enhancement of antioxidant activity due to the decrease of electronic properties (derived from the dipole moment value and C5 atomic charge), Log P representing hydrophobicity did not show a significant effect on antioxidant activity while increasing the chain length of antioxidant molecules indicate an increase in steric hindrance causes a decrease in antioxidant activity. The calculated PRESS (Predicted Residual Error Sum of Square) value was 6.69E-05, which indicates the calculated log ($1/IC_{50}$) using QSAR Hansch Model of caffeic acid derivatives is similar with experimental data.

1. Introduction

Environmental pollution, unhealthy lifestyles, and current community habits can spur the growth of free radicals that can damage the body. Bad habits such as consuming fried foods, fatty foods, cholesterol foods, and low-fiber foods can cause deadly diseases such as cancer, heart disease, hypertension, and stroke. Various diseases are caused by free radicals [1].

The efforts to prevent or reduce the degenerative diseases caused by free radical activity are by consuming foods that contain antioxidants. Antioxidants are substances that can delay and prevent the occurrence of free radical reactions. Based on the source, antioxidants are divided into two groups, namely synthetic antioxidants and natural antioxidants. Synthetic antioxidants are such as butyl hydroxyanisole (BHA), butylhydroxytoluene (BHT) and propyl gallate (PG). Many foods can be a

source of natural antioxidants, such as spices, tea, chocolate, and vegetables. Most sources of natural antioxidants are plants and generally are phenolic compounds that are spread throughout all parts of plants both in wood, seeds, leaves, fruit, roots, flowers and pollen [2-6].

Phenolic compounds have been widely reported of their activity as natural antioxidants. Caffeic acid is one example of phenolic compounds that are mostly contained in coffee, apples, artichokes, and pears. Caffeic acid is working to press cancer and pro-inflammatory gene expression, as well as inhibiting enzymes inducing free radical and oxygen peroxidation. Caffeic acids and their derivatives have various mechanism which determines their bioactivity [7-11].

The new antiradical compounds can be found by molecular designs, by direct synthesis, or by a modeling approach using computational chemistry concepts. One application of computational chemistry that can be applied is the study of Quantitative Structure-Activity Relationship (QSAR) or quantitative relations of activity structure. QSAR studies quantitative correlations between molecular structure and the value of experimentally measured biological activities [12-13].

The research will analyze the relationship between the chemical structure and the bioactivity of 5 caffeic acid derivatives. In this study, QSAR analysis of caffeic acid derivative was carried out by using antiradical activity studies as a function of steric, hydrophobic, and electronic variables.

2. Methods

The material used in this study is antioxidant activity (expressed in IC_{50}) caffeic acid derivative compounds obtained from the literature. The compound antioxidant activity data are presented in Table 1. The structure of the caffeic acid derivative compound is shown in the following Figure 1.

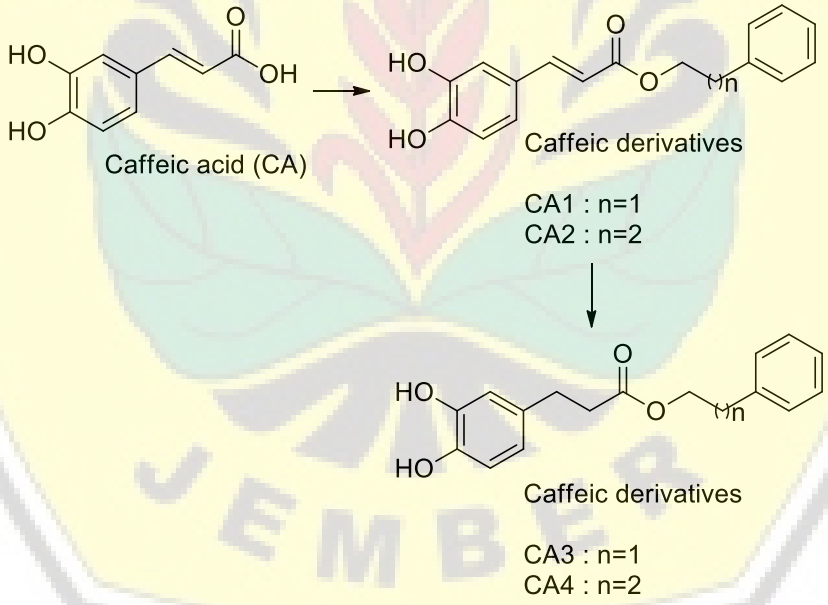

Figure 1. Caffeic acid derivatives [14].

Table 1. The experimental antioxidant activity of caffeic acid derivatives [14]

Compound	Antioxidant Activity	
	IC_{50}[x]	Log $(1/IC_{50})$[x]
CA	15.3	-1.18
CA1	16.5	-1.22
CA2	11.9	-1.08
CA3	24.6	-1.39
CA4	23,0	-1.36

[x]DPPH assay was used to assess the free radical scavenging activity

2.1. Equipment

This research used Intel (R) Celeron (C) processor with 204 MB RAM as computer hardware. Hyperchem 7.02 computational chemistry software for computational chemical calculations and SPSS 16.020 for statistical analysis, and Chemdraw Ultra 8.0 to create 2D molecular structures.

2.2. Research procedure

2.2.1. Collection of descriptors. Descriptor determination is important for determining the best QSAR equation. Descriptors used in this study are atomic charge, dipole moment (μ) and logarithm of partition coefficient (log P). The data can be seen in Table 2. For electronic descriptors, calculations are carried out covering the stages of computational chemistry modeling with the geometry optimization procedure of each compound structure. Each compound used in this study was made into a two-dimensional structure model using the Chemdraw Ultra 8.0 application. After that, the model is equipped with hydrogen atoms on each atom and is formed into a three-dimensional (3D) structure with the Build (Add H and Model Build) menu. The descriptors are atomic net charge, dipole, and log P (coefficient partition n-octanol/water). We analyze the atomic net charge of carbon numbers 11, 10, 9, and 5 for caffeic acid derivatives. The position of the carbon is shown in Figure 2. Atomic net charge is determined by comparing the number of proton (positive charge) and electron (negative charge) in an atom. If an atom gains electron then it has more electrons, which give it a negative charge, and vice versa. The atomic charge indicates the density of electron in atom. Dipole moment describes the polarity of molecules. Besides, log P represents hydrophobicity properties of a molecule.

Table 2. List of descriptors and how to optimize them

No	Symbol	Descriptor	Unit	Calculation Method
1	qC_5, qC_9, qC_{10}, qC_{11}	The atomic charge of C_5, C_9, C_{10}, and C_{11}	Coulomb	Semiempirical method of PM3, Hyperchem, compound optimization
2	μ	dipole moment	Debye	Semiempirical method of PM3, Hyperchem, compound optimization
3	Log P	Partition coefficient of n-octanol/water	-	QSAR Properties, Semiempirical method of PM3, Hyperchem, compound optimization

The next procedure is to perform structural geometry optimization by minimizing molecular energy in order to obtain the most stable molecular conformation. The calculation used the semiempirical method of PM3 with the convergence limit was 0.01 kcal / Å.mol for caffeic acid derivatives. The optimization method was based on the Polak-Ribiere algorithm.

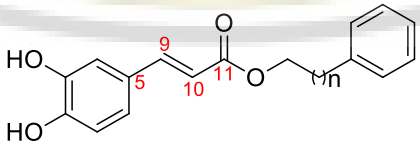

Figure 2. The label of selected carbon net charge

2.2.2. QSAR study. The best QSAR equation used to predict IC_{50} was determined by multilinear regression statistical analysis. The analysis was performed using SPSS application with the backward method. In this study, the original data using four compounds for caffeic acid derivatives were optimized by select the independent and dependent variables that influence the QSAR equation. Log

($1/IC_{50}$) data was set as the independent variable and combination value between dipole moment, atomic charge, and partition coefficient as independent variables. In general, the final relationship of the QSAR approach is expressed by the regression equation as follows

$$\text{Log } (1/IC^{50}) = \text{ k1log P + k2qC1 + k3qC2 + k4qC3 + k5qC4 + k6qC5 + k7qC12 + k8μ + k9}$$

Multilinear regression analysis is performed on the output data by statistical parameters as correlation coefficient R, R^2, standard deviation (SE) and significance value. The model is chosen based on the consideration of the statistical results obtained.

3. Results and Discussion

3.1. The result of descriptors calculation on caffeic acid derivatives

In this study, we investigate caffeic acid (CA) and four caffeic acid derivatives (CA_1, CA_2, CA_3, and CA_4) using QSAR method between dependent variable antioxidant activity (Table 2) and eight independent descriptors. In addition, four caffeic acid derivatives, synthesized by LeBlanc and co-workers (2012), are shown in Figure 2. CA_1 is synthesized by the incorporation of a phenyl ethyl ester to the carboxylic moiety on caffeic acid structure. Besides, incorporation phenyl propyl ester to the carboxylic moiety on caffeic acid structure generated CA_2. CA_2, a well-known compound, named CAPE (caffeic acid phenyl ethyl ester), is the most active compound in propolis [15]. Furthermore, CA_1 and CA_2 were converted to CA_3 and CA_4, respectively by hydrogenation reaction of caffeic acid. Table 2 listed the experimental result of antioxidant activity using DPPH assay. It is seen that CA, CA_1, and CA_2 have ethylene moiety which affords higher antioxidant activity (IC_{50}=12-15 μM) than their counterpart CA_3 and CA_4 (IC_{50}=23-25 μM).

Table 3 showed that modification of carboxylic moiety in caffeic acid structure generated higher log P in relative to those of CA_1-CA_4. Also, it is observed that the dipole of caffeic acid decreased, the CA_4 has the lowest dipole value. From CA to CA_4, the net charges of C_{11}, C_{10}, C_9 are decreased. Besides, the net charge in C_5 is only slightly decreased from CA-CA_4.

Table 3. Descriptor data as independent variables for caffeic acid derivatives

No	Compound	Atomic Net Charge (Coulomb)				Dipole (deybe)	Log P
		C_{11}	C_{10}	C_9	C_5		
1	CA	0.420043	-0.200263	0.012367	-0.083385	1.611	-0.66
2	CA_1	0.414012	-0.203953	0.006267	-0.079643	1.236	0.64
3	CA_2	0.412319	-0.201729	0.001791	-0.0786	1.246	1.03
4	CA_3	0.369905	-0.104317	-0.041991	-0.08621	0.759	0.56
5	CA_4	0.368428	-0.103922	-0.042344	-0.086329	0.622	0.95

The results of antioxidant activity are shown as IC_{50} (μmolar) of caffeic acid, and the derivatives are listed in Table 2. Generally, all compounds have good inhibitor activity (IC_{50} = 10-200 μmolar). CA_2 shows the highest activity compared to other CA derivatives. CA and CA_1 produce low cytotoxic activity. It could occur because the structures of CA and CA_1 produce electron deficiency conditions that interfere oxidation/reduction reactions of the catechol ring. The electron deficiency condition was caused by the high polarity of CA and CA_1 where it induced the electron density headed to the ester group. Meanwhile CA_3 and CA_4 produce low antioxidant activity. It could occur because steric hindrance conditions of the structure of CA_3 and CA_4 disrupt oxidation/reduction reactions of the catechol ring [16]. This condition caused low dipole value and high log P value on CA_3 and CA_4 does not affect antioxidant activity on CA_3 and CA_4.

3.2. Analysis of QSAR on caffeic acid derivatives

Table 4 denotes the best QSAR equation for caffeic acid derivatives. The descriptors such as dipole, logP, and atomic charge of C_5 have a strong correlation to the antioxidant activity. The results exhibit antioxidant activity influenced by a dipole, log P and atomic charge of C_5. Dipole values and the atomic charge of C_5 represent electronic variables, log P represents hydrophobicity, and chain length represents steric variables. The results showed the highest antioxidant activity value was obtained from the CA3 structure which showed the effect of low dipole values and atomic charge of C_5 as shown in table 3 and table 4. This shows an increase in antioxidant activity due to decreased electronic properties of antioxidants. The P log representing hydrophobicity did not show a significant effect on antioxidant activity. The steric effect shows a significant effect on antioxidant activity which can be seen from the decreased value of antioxidant activity with increasing chain length which indicates that steric barriers are getting higher.

Table 4. The result of the best correlation between descriptors and antioxidant activity for caffeic acid derivatives

Equation	-7.858+1.149dipol+0.485logP-61.68C_5
R	1
R^2	0.999
SE	0.008144
Sig	0.04
F	342

Table 5 showed the residual errors between the experimental log ($1/IC_{50}$) and the calculated Log ($1/IC_{50}$) is ignorable with the value of 6.69E-05. It indicates the calculation of the calculated log ($1/IC_{50}$) using QSAR Hansch Model for caffeic acid derivatives has excellent agreement with experimental data of Log ($1/IC_{50}$).

Table 5. Experimental log ($1/IC_{50}$), calculated log ($1/IC_{50}$), and PRESS value for caffeic acid derivatives

Compound	Experimental Log ($1/IC_{50}$)	Calculated Log ($1/IC_{50}$)	Residual error	[Residual error]^2
CA	-1.185	-1.183	-0.001	1.96E-06
CA1	-1.217	-1.214	-0.003	8.91E-06
CA2	-1.076	-1.078	0.003	7.03E-06
CA3	-1.391	-1.396	0.005	2.85E-05
CA4	-1.362	-1.357	-0.005	2.05E-05
		PRESS		6.69E-05

4. Conclusion

This research analyzed the relationship between the chemical structure and the bioactivity of 5 caffeic acid derivatives. In this study, the enhancement of antioxidant activity occurred due to decreased electronic properties (derived from the dipole moment value and C5 atomic charge), Log P representing hydrophobicity did not show a significant effect on antioxidant activity, while increasing the chain length of antioxidant molecules indicate an increase in Steric hindrance causes a decrease in antioxidant activity. The resulted QSAR model for caffeic acid derivatives as an antioxidant is presented below:

$$-7.858 + 1.149\ \text{dipole} + 0.485\ \log P - 61.68\ C5$$
$$R=1;\ R^2=0.999;\ SE=0.008;\ F=342$$

In the future study, this research suggests designing good partition coefficient of n-octanol/water and dipole moment caffeic acid derivatives giving excellent bio-activity.

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