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COMPUTATIONAL STUDY OF ANTIOXIDANT, TOXICITY, DRUG SCORING AND MOLECULAR DOCKING OF THE STRUCTURE OF CATECINS

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ABSTRACT

Chronic disorders such as cancer can be caused by an imbalance in free radical production with the body's antioxidant defenses. This research aims to obtain the best compounds as future drug candidates. The potential of catechin compounds and their derivatives as cancer drug candidates has been studied through antioxidant properties, toxicity, drug scores and molecular docking. In this research, antioxidant activity was studied using the DFT (Density Functional Theory)/B3LYP/3-31G method in the gas phase. Toxicity and drug scores were analyzed using OSIRIS Property Explorer software. Analysis of the interaction of catechin and modified catechin compounds with 5KYK cell protein using MOE (Molecular Operating Environment) software. The research results show that the antioxidant properties are well explained through the antioxidant reaction mechanism which occurs more easily in the Single Electron Transfer – Proton Transfer (SET – PT) mechanism. The total energy produced by IP (Ionization Potential) + PDE (Proton Dissociation Enthalphy) is smaller. From the pharmacophore study, it was found that the compound that had the best interaction with the 5KYK receptor was compound 1. Catechin compounds and their derivatives are not toxic (no risk) for gene mutations, tumors, irritation and reproduction. Catechin compounds and modified catechins (1-5) have a drug score value of (0.453-0.871). It is estimated that catechin compounds and their derivatives can be used as potential antioxidants and can be a drug candidate without side effects on biological systems.

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INTRODUCTION

A number of chronic disorders in humans such as cancer, diabetes, Alzheimer's, neurogenerative, cardiovascular, lung, liver, kidney and intestinal inflammation can be caused by oxidative stress induced by Reactive Oxygen Species (ROS) (Turkan 2018). The body has a normal defense mechanism provided by secondary metabolites called antioxidants so that it can neutralize these ROS. Antioxidant compounds can reduce the harmful effects caused by ROS and can prevent chronic diseases caused by oxidative stress. Antioxidants can be defined as substances that can delay or inhibit oxidative damage to a molecule (Ghitescu et al. 2018). Antioxidant activity is able to capture and neutralize free radical species, inhibit the production of reactive species, regulate antioxidant enzymes such as superoxide sismutase and glutathione peroxidase, counteract glutathione depletion, and prevent damage to lipids, proteins and nucleic acids (R. Xu et al. 2020).

The flavonoid extract content has very strong antioxidant activity (Lance, A. H 2024). (Phenolic compounds contain hydroxy groups so they are able to capture free radicals with a free radical capture mechanism via Hydrogen Atom Transfer (HAT) (Wang et al. 2018). Flavonoid compounds contain many hydroxy groups so they can transfer hydrogen atoms to bind more free radicals. False One flavonoid compound that contains high levels of antioxidants is catechin compounds and their derivatives (Ruengdech and Siripatrawan 2022). Apart from antioxidants, catechin compounds and their derivatives have antitumor bioactivity ((Katsoulieris and Rodriguez 2021), antibacterial (Ma et al. 2019), anti-infection (Steinmann et al. 2013), antifungal (Molina-Hernández et al. 2022), anticancer (Cheng et al. 2020) and cytotoxic (Y. Q. Xu, Gao, and Granato 2021).

In this study, an analysis of the antioxidant properties of catechin and modified catechin compounds was carried out theoretically using the DFT (Density Functional Thory) calculation method. Modification of catechin compounds aims to determine compounds that provide better antioxidant effects than theoretical catechins. The added substituents are electron withdrawing and electron pushing. Toxicity analysis and drug scores were also carried out on catechins and theoretically modified catechins using OSIRIS Property Explorer software to determine their potential as basic drug ingredients in the future. To determine the interaction, molecular docking analysis was also carried out using MOE (Molecular Operating Environment) software.

RESEARCH METHODS

Materials and tools

The materials used in this research are catechin molecules and their derivatives as well as 5KYK cell protein. The tools used are hardware in the form of a laptop with an Intel AtomTM CPU core i5-7200 U processor, 4.00 GB internal memory, 16 W Gaussian program software, OSIRIS Property Explorer and Molecular Operating Environment (MOE).

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Optimization of catechin molecules and derivatives

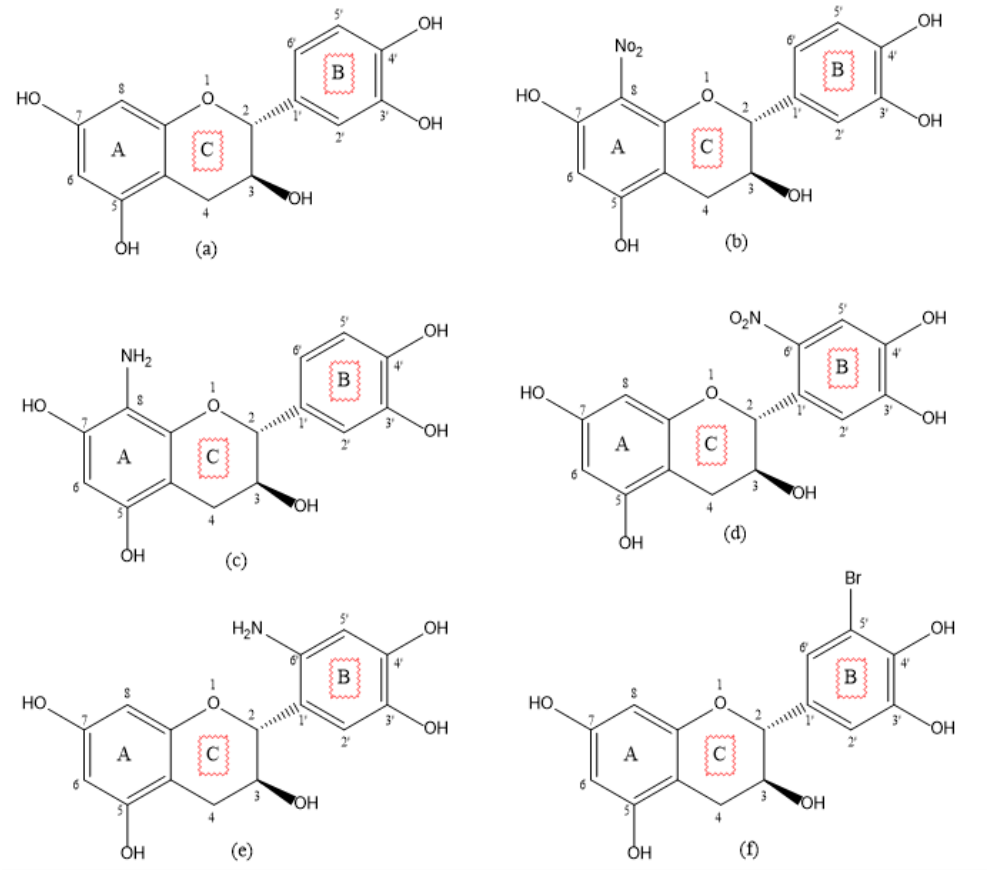

Figure 1. Structure of catechins (a), 3, 5, 7, 3', 4' pentahydroxy 8-nitro flavanol (b), 3, 5, 7, 3', 4' pentahydroxy 8-amino flavanol (c), 3 , 5, 7, 3', 4' pentahydroxy 6'-nitro flavanol (d), 3, 5, 7, 3', 4' pentahydroxy 6'-animo flavanol (e) and 5'-bromo-3,5, 7,3',4' pentahydroxy flavanol.

Catechin compounds contain a benzoyl ring and a cinnamoyl ring. The benzoyl ring is an aromatic ring arranged in a hexagonal shape with electron delocalization. This ring is usually known as the A ring. The A ring is often connected to the B ring via an oxygen bridge or directly by a carbon-carbon bond. The cinnamoyl ring is a more complex aromatic ring associated with a conjugated aliphatic chain. The cinnamoil ring is known as the B ring. The B ring is connected to the A ring via a three-carbon bridge on the C ring.

The three-dimensional (3D) structure model of the catechin compound and its derivatives was created using the Gaussian 16W program. Next, optimization of the molecular geometry was carried out on the structure of the catechin compound and its derivatives (Figure 1) by minimizing the molecular energy to obtain the most stable structural conformation. Calculations were carried out using the DFT method with a 6-31G basis.

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Antioxidant activity of catechins and their derivatives

The antioxidant properties of catechins and modified catechins were determined according to the procedure by Zheng., et all (2018) with the BDE, IP, PDE, PA and ETE methods. Radical chain cleavage can be inhibited through 3 main mechanisms, namely:

a. Hydrogen Atom Transfer (HAT)

$$ArOH \rightarrow ArO\bullet + H\bullet \quad (1)$$

The parameter influenced by this mechanism is the BDE (Bond Dissociation Energy) value, where the lower the BDE value, the easier it is to break the O-H bonds in phenolic compounds. The weak dissociation energy of the O-H bond will accelerate the reaction with free radicals (Equation 1).

b. *Single Electron Transfer followed by Proton Transfer* (SET-PT)

The first step is the formation of a radical cation, the second step is the deprotonation of ArOH+• followed by the protonation of ROO• (Equations 2, 3 and 4). The influencing parameters are potential ionisation (PI) and Proton Dissociation Enthalpy (PDE).

$$ArOH \rightarrow ArOH^{+\bullet} + e^- \quad (2)$$
$$ArOH+\bullet \rightarrow ArO\bullet + H^+ \quad (3)$$
$$ArOH \rightarrow ArO\bullet + e^- + H^+ \quad (4)$$

c. *Sequential Proton Loss Electron Transfer* (SPLET)

This mechanism occurs through 2 stages that occur sequentially, namely proton transfer and electron loss. The first corresponds to the proton affinity mechanism (Equation 5) of anionized phenoxide. In the second step, electron transfer occurs from the phenoxide anion to ROO• and a phenoxy radical is formed (Equation 6). Related parameters are proton affinity (PA) and electron transfer enthalphy (ETE).

$$ArOH \rightarrow ArO^- + H^+ \quad (5)$$
$$ArO^- \rightarrow ArO^\bullet + e^- \quad (6)$$

The total enthalpy of the variables X, H(X) at temperature T is usually estimated using the following equation (7):

$$H(X) = Eo + ZPE + \Delta Htrans + \Delta Hrot + \Delta Hvib + RT \quad (7)$$

From the total enthalpy calculation, the BDE, SET-PT, PA and ETE values can be calculated using equations (8, 9, 10 and 11) below:

$$BDE = \Delta H(ArO^\bullet) + \Delta H(H^\bullet) - \Delta H(ArOH) \quad (8)$$
$$SET\text{-}PT = \Delta H(ArO^\bullet) + \Delta H(e^-) + \Delta H(H^+) - \Delta H(ArOH) \quad (9)$$
$$PA = \Delta H(ArO^-) + \Delta H(H^+) - \Delta H(ArOH) \quad (10)$$
$$ETE = \Delta H(ArO^\bullet) + \Delta H(e^-) - \Delta H(ArO^-) \quad (11)$$

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Toxicity Properties and Drug Scores of Catechins and Derivatives

The toxicity of catechin and modified catechin compounds was determined based on working procedures according to Zheng, et all (2018). Toxicity risk (mutagenicity, tumorogenicity, irritation and reproducibility) and physico-chemical properties such as lopP, solubility (logS), molecular weight, drug-likeness and drug score are calculated via OSIRIS Property Explorer software: Drug score (DS) is a combination of properties physicochemical (LogP, logS, TPSA and molecular weight) and toxicity risk (mutagenic, tumorigenic, irritant and reproductive) are practical values that can be used to assess the potential of a compound to qualify as a drug (Escobedo-González et al. 2017). The drug score is calculated by summarizing the scores of each fragment in the molecule under investigation from a list of 5300 molecular fragments. The frequency of occurrence of each fragment was decided based on a collection of 3300 drugs and 15,000 commercially available chemicals that are not drugs (Hassan et al. 2015).

A positive drug score indicates that the molecule mostly has fragments similar to the drug used. Drug likeness, logP, logS, molecular weight and risk of toxicity combine into a global score, called drug score, for a potential new drug candidate. It can be calculated as:

$$DS = \pi \left(\frac{1}{2} + \frac{1}{2} Si\right) \pi ti \quad (12)$$

$$\text{Where is, } Si = (1 + Sap + b) - 1 \quad (13)$$

DS is the drug score and Si is the contribution of logP, logS, molecular weight and drug similarity (π) obtained from Equations (12) and (13), which are spline curves. „a‟ and „b‟ are parameters for logP, logS, molecular weight and drug similarity and have values (1, -5), (1, 5), (0.012, -6) and (1, 0) respectively. . 'Ti' is the contribution of the toxicity risk type and has a value of 1.0; 0.8 and 0.6 for no risk, medium risk and high risk respectively. A positive drug score indicates that the molecule predominantly has a pharmacological group and can be used as a potential drug (Rajan, Hasna, and Muraleedharan 2018).

Interaction of Catechin Compounds and Derivatives with 5KYK Cell Proteins

Molecular docking is a computational method used to analyze the interaction between the potential and active sites of protein ligands. It is the study of two or more molecular structures that fit together such as a drug and a protein or enzyme. This method can also be used to understand the biomolecular interactions of drugs for drug design and discovery by placing molecules (ligands) into the preferred binding sites of specific regions of DNA/protein targets (receptors in a non-lovalent manner to form stable complexes of potential efficacy and more specifications to support experimental results from a structural perspective (Rohs et al. 2005).

Virtual drug discovery approach screening can be carried out more specifically using molecular docking, predicting possible modes of interaction between the ligand and the therapeutic target so that it is an indication of the biological activity of the new molecule by only considering structural criteria (Houchi and Messasma 2022).

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RESULTS AND DISCUSSION

Structure Optimization Results

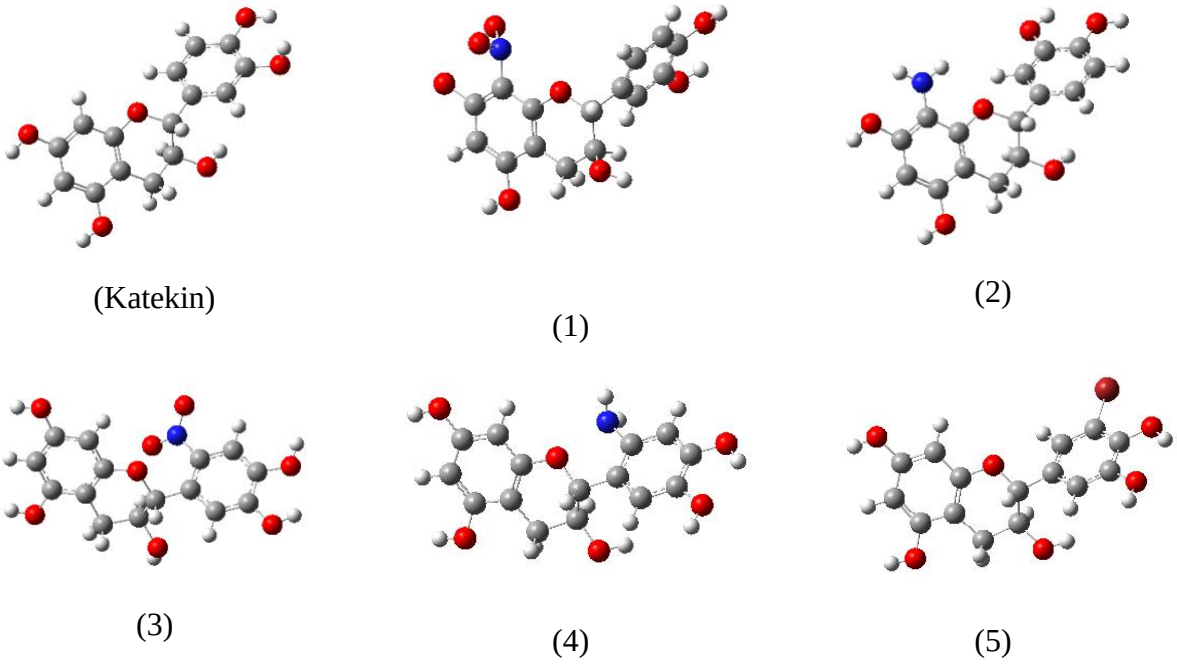
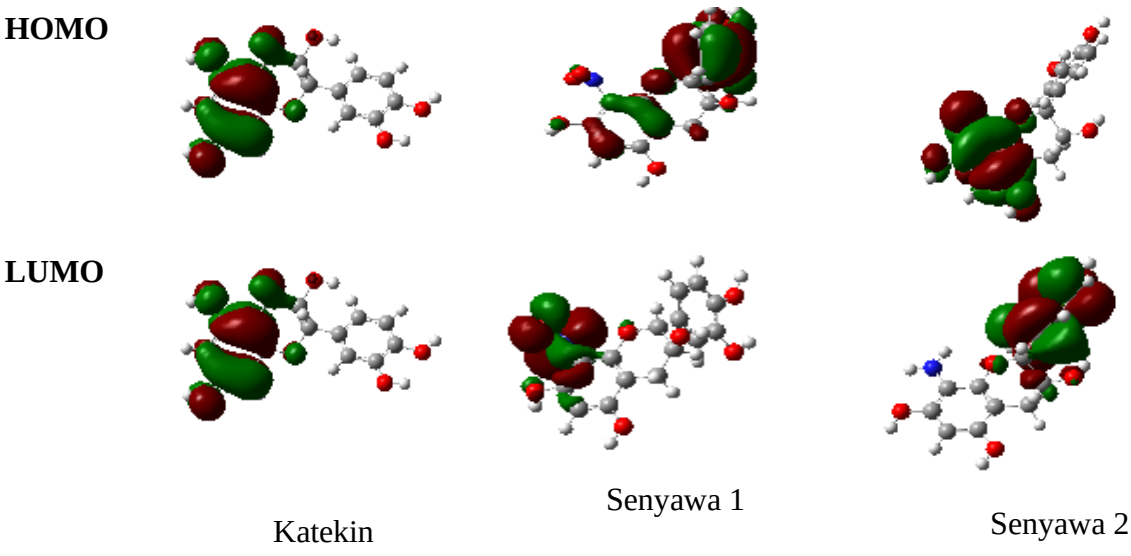


Figure 2. Structure of catechins and modified catechins as a result of optimization using the DFT method

Energy minimization is the process of finding the arrangement of atoms in space, where the forces between atoms are close to zero and the position on the potential energy surface is a stationary point. Bond lengths and angles reduce the forces between atoms so that the most stable structure is obtained (Rijal et al. 2022).

Countor HOMO-LUMO



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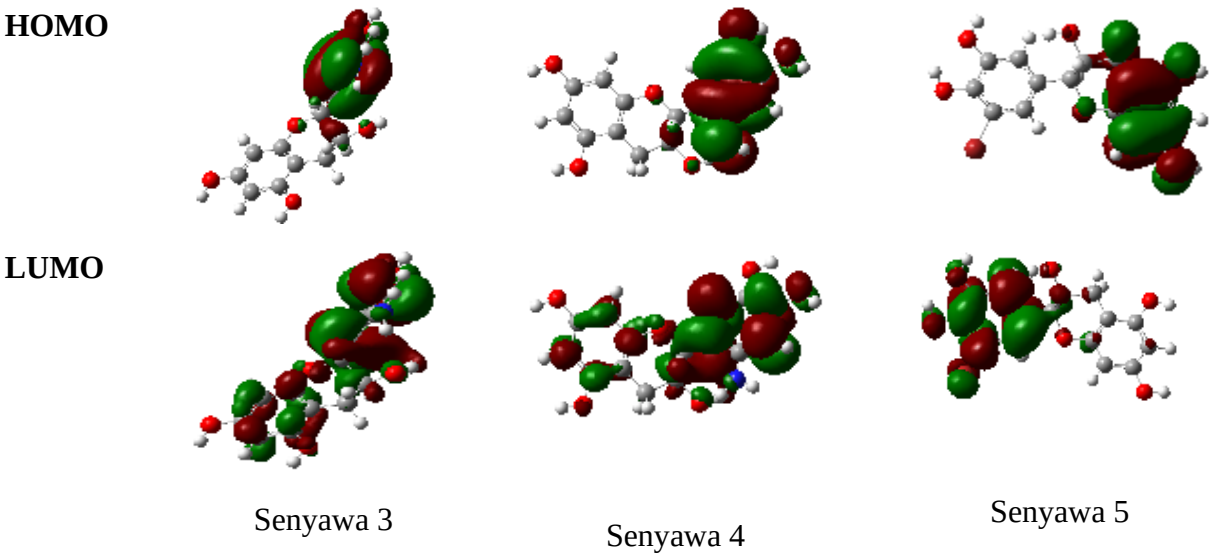

Figure 3. HOMO and LUMO contours of catechin compounds and derivatives

The most determining parameters in frontier molecular orbital analysis are HOMO and LUMO. The HOMO count shows the electron density in the HOMO band which acts as an electron donor. The LUMO factor determines the electron density in the LUMO band which acts as an electron acceptor. Longer conjugated л electrons can be characterized by smaller bandgaps.

Compounds 2 and 4 have the ability to donate electrons, because compounds 2 and 4 have electron-pushing substituents (-NH2) which can cause electrons to be pushed into the ring and the electron density in the ring increases so that the hydrogen in –OH in the ring is more easily broken off and attacked. by free radicals.

Table 1. EHOMO, ELUMO, gap energy, and dipole moment of catechin compounds and their derivatives

Senyawa	E_{HOMO} (eV)	E_{LUMO} (eV)	*Bandgap* (eV)	Momen dipol (Debye)
Katekin	-0,21290	-0,00497	0,20793	3,5078
Senyawa 1	-0,23005	-0,13078	**0,09927**	**5,8632**
Senyawa 2	-0,1646	-0,0058	0,1588	1,5656
Senyawa 3	-0,21357	-0,09559	0,11798	2,3036
Senyawa 4	-0,17974	0,00422	0,18396	3,7972
Senyawa 5	-0,2182	-0,01516	0,20304	5,3016

Compound 2 has a high HOMO energy value compared to catechin and other modified compounds, namely -0.16460 eV. The bandgap values and dipole moments of catechin and modified catechin compounds can be seen in Table 1. The reactivity of a molecule can be

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shown by the bandgap value (Alov, Tsakovska, and Pajeva 2015). The lower the bandgap value of a compound, the faster the electron transfer will occur from HOMO to LUMO and the more reactive the compound will be. From the data in table 1, it can be seen that compound 1 is the most reactive compound compared to other catechin and modified catechin compounds with a bandgap value of 0.09927 eV. The reactivity of this compound is influenced by the bound substituents. Compound 1 with an electron-withdrawing substiruent (-NO2) can reduce the gap energy. Meanwhile, compound 2 at the same carbon atom position (C-8) with an electron-withdrawing substituent (-NH2) has a bandgap value that is greater than compound 1, namely 0.1588 eV.

Antioxidant Mechanism

Analysis of antioxidant properties obtained from various plant sources or plants that have different activities. The antioxidant activity (AROH) of a compound can be observed from its ability to break O-H bonds in catechin and modified catechin compounds which produce H• and ArO•. H• can react with R• to produce RH molecules. The easier it is to form ARO• and RH, the better the antioxidant activity of these compounds will be (Richa et al. 2020). The smaller the energy required, the more unstable the O-H bonds in catechin and modified catechin compounds, so that it is easier to break the O-H bonds and the easier it is to inhibit radicals.

In catechin compounds, O-H cleavage tends to occur more easily at the C4'_OH position. This is because the resonance that occurs in ring B makes it easier for the H radical to be released at the C4''-OH position. In compound 1, the O-H cleavage tends to occur more easily at C7-OH. This is because the resonance occurs closer to the C7_OH atom. In compound 2, the O-H cleavage occurs more easily at the C7-OH position followed by C5-OH. This is due to the presence of an electron-pushing substituent which causes the electron density in the A and H radical rings to escape more easily. In compound 3, the O-H cleavage tends to occur more easily at the C4'-OH position. Compounds 4 and 5 break more easily in the C3'-OH position.

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Table 2. BDE, IP PDE, PA and ETE values (kJ/mol) of catechin compounds and derivatives

Senyawa	Posisi OH	BDE (kJ/mol)	IP (kJ/mol)	PDE (kJ/mol)	PA (kJ/mol)	ETE (kJ/mol)
Katekin	C3	1916,881166	703,206	995,705122	1524,2918	174,619379
	C5	1846,685798	703,206	925,509754	1439,5932	189,122641
	C7	1849,883657	702,206	928,707613	1453,6658	178,247821
	C3'	1868,396057	703,206	947,220013	1469,7208	180,705288
	C4'	1825,492762	703,206	904,316718	1394,7759	212,74689
Senyawa 1	C3	1677,054868	525,594	933,491274	15717818	-112,69696
	C5	1677,054868	525,594	933,491274	1391,9036	67,181294
	C7	1612,16301	525,594	868,599416	1402,1404	-7,9473885
	C3'	1728,498915	525,594	984,935321	1534,2162	-23,687261
	C4'	1704,86679	525,594	961,303195	1475,7804	11,116367
Senyawa 2	C3	1920,375706	595,487	1106,91868	1513,2962	189,109514
	C5	1803,241649	595,487	989,78462	1463,3776	121,894088
	C7	1800,655532	595,487	987,198502	1450,2186	132,466977
	C3'	1827,041807	595,487	1013,58478	1398,6406	210,431199
	C4'	1825,456005	595,487	1011,99897	1395,0778	212,408201
Senyawa 3	C3	1687,010764	709,074	759,966728	1588,8082	-119,76743
	C5	1620,863917	709,074	693,819881	1486,6762	-83,782331
	C7	1623,639071	709,074	696,595034	1502,4476	-96,778556
	C3'	1735,679658	709,074	808,635621	-518,1356	2035,84526
	C4'	1612,202393	709,074	685,158356	1487,1541	-92,921696
Senyawa 4	C3	1913,074191	609,843	1085,26093	1510,4843	184,619909
	C5	1841,676344	609,843	1013,86308	1421,0335	202,672847
	C7	1843,787246	609,843	1015,97398	1433,3366	192,480656
	C3'	1797,266011	609,843	969,452747	1418,5787	160,717357
	C4'	1862,299646	609,843	1034,48638	1464,2991	180,030535
Senyawa 5	C3	1919,367514	697,131	1004,26688	1488,6769	212,720635
	C5	1847,943412	697,131	932,842776	1426,4	203,573394
	C7	1851,521969	697,131	936,421332	1441,4468	192,105209
	C3'	1829,331243	697,131	914,230606	1368,9226	242,43867
	C4'	1861,887443	697,131	946,786806	1424,7066	219,210872

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Analysis of Pharmacokinetic Properties, Toxicity and Drug Score

The pharmacokinetic properties of catechins and their derivatives have been calculated using the online OSIRIS Property Explorer software and validated with Lipinski's rule 5 (RO5) (Veber et al. 2002), and (Wulandari et al. 2020). According to the rules, drug-like molecules that are received orally must have: hydrogen bond donor (HBD) < 5, hydrogen bond acceptor (HBA) < 10, molecular weight (BM) < 500 Daltons, LogP < 5, rotatable bond (ROTB) < 10.

Table 3. Pharmacokinetic properties of catechin and modified catechin compounds

Senyawa	Kelarutan Log S	TPSA	Log P	Rot B	HBA	HBD	Massa Molekul (g/mol)
Katekin	-1,763	110,3	1,508	5	6	5	290
1	-2,223	156,2	0,587	6	8	5	350
2	-1,839	136,4	0,381	6	7	6	305
3	-2,223	156,2	0,587	6	8	5	335
4	-1,839	136,4	0,381	6	7	6	305
5	-2,597	110,3	2,233	6	6	5	368

The solubility value (Log S) of catechin and its derivatives shows good solubility. The solubility values obtained indicate that catechin compounds and their derivatives have good solubility in blood. This solubility will determine the rate of absorption and distribution of the drug. Low solubility indicates little absorption in water. Catechin compounds and their derivatives have HBD > 5, HBA < 10, BM < 500, LogP < 5 and ROTB < 10. These values indicate that catechin compounds comply with Lipinski's rules except for the HBD value. In general, catechin compounds and their derivatives can be used as medicine.

Toxicity Risk and Drug Score

Table 4. Toxicity risk parameters and drug scores

Senyawa	Resiko Toksisitas[a]				
	Mutasi	Tumor	Iritasi	Reproduksi	Skor Obat[b]
Katekin	1,0	1,0	1,0	1,0	0,871
1	1,0	1,0	1,0	1,0	0,469
2	1,0	1,0	1,0	1,0	0,867
3	1,0	1,0	1,0	1,0	0,453
4	1,0	1,0	1,0	1,0	0.615
5	1,0	1,0	1,0	1,0	0,548

[a] 1,0: Tidak ada resiko(tidak toksik), 0,8: Resiko menengah, 0,6: resiko tinggi
[b] skor obat positif = berpotensi sebagai obat

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Table 4 data shows that catechin and modified catechin compounds can be used as drug candidates. The best compounds as drug candidates are catechin and compound 2 because they have a higher drug score than other compounds, namely 0.871 and 0.867. Table 4 shows that catechin and modified catechin compounds are not toxic because they have a value of 1.0 for mutation, tumor irritation and reproduction. A positive value indicates that the compound can act as a potential drug. This indicates that catechin and modified catechin compounds are not mutagenic, do not cause tumors, do not cause irritation and have no risk to the reproductive system.

Interaction of Catechin Compounds and Modified Catechins with Cell Protein 5KYK

The docking simulation process was carried out using the MOE 2022 application. The docking simulation results were obtained through experiments between antioxidant compounds and cancer cell proteins. Then, data was analyzed in the form of the number of interactions and docking energy values between catechins and modified catechins with cervical cancer cell proteins. The parameter used in molecular docking is RMSD (Root Mean Square Deviation) which shows the difference between the ligand coordinates and the conformation predicted by the docking program.

The visualization results of molecular docking show the interactions of amino acid residues with catechin compounds and the bond length of the interactions that occur. The negative sign indicates that the process is exothermic. The higher the docking energy, the stronger the interaction between catechin compounds and the protein amino acids 5KYK.pdb.

Table 5. Interaction of 5KYK receptor catechin compounds with several models

Ligan Uji	RMSD (Å)	Energi *docking* (Kj/mol)	Residu Asam Amino	Jarak Ikatan (Å)
Katekin	1,5598	-1,5	Asp 119	3,12
		-1,1	Lys 117	3,95
Senyawa 1	1,4963	-7,7	Asp 119	2,77
		-2,8	Ala 146	3,21
		-0,8	Lys 117	3,45
Senyawa 2	1,4411	-1,7	Asp 30	2,75
Senyawa 3	1,3482	-3	Gly 15	2,78
		-1,5	Lys 16	3,07
		-0,5	Gly 13	4,13
		-0,7	Thr 58	3,01

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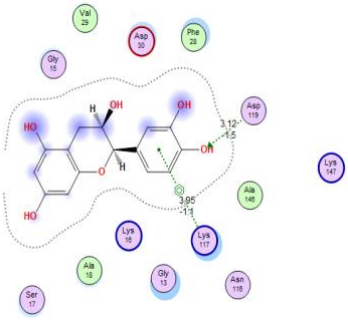
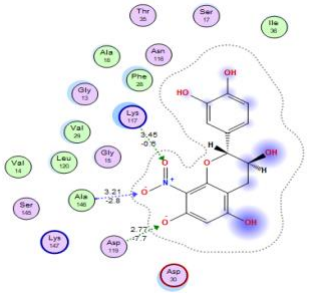
Senyawa 4	1,2041	-1,2	Ser 17	3,01
		-2,6	Val 29	2,84
Senyawa 5	1,1912	-10,1	Asp 119	2,85
		-0,6	Lys 117	4,36
		-0,5		4,52

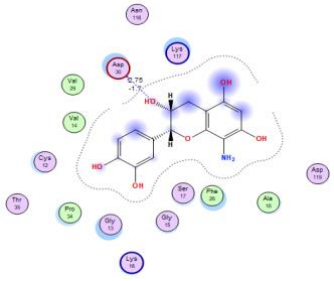
The docking results of catechin ligands and their derivatives with the 5KYK receptor have shown various interactions of amino acid residues. The more amino acid interactions that are bound, the ligand will have the best and most stable bond with the receptor used (Demir et al. 2018). Therefore, based on the results obtained, the compounds with the best sequence interactions with the 5KYK cell protein are compounds 1, 3, 5, catechin, 4 and 2. The amino acid residues that interact with the catechin compound and its derivatives are (Asp 119, Lys 117 , Ala, 146, Asp 30, Gly 15, lys 16, Gly 13, Thr 58, Ser 17and val 29). The interaction that often occurs is with the amino acid residue Aspartate (Asp 119).



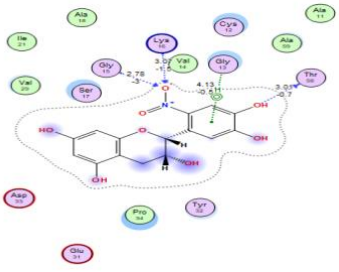
Katekin



Senyawa 1



Senyawa 2



Senyawa 3

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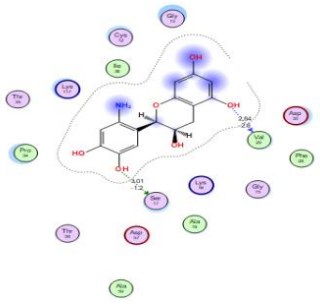
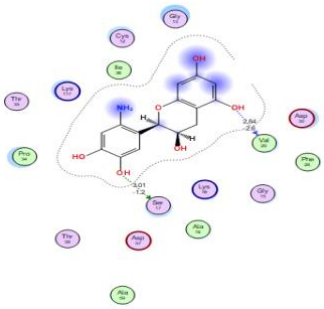


Senyawa 4



Senyawa 5

Figure 4. Visualization of the results of molecular docking of catechin models 1, 2, 3, 4 and 5 against the 5KYK receptor

CONCLUSION

Computational studies of catechin compounds and their derivatives show that, based on the antioxidant reaction mechanism, the breaking mechanism between O and H bonds that produces H• and ArO• is more compatible with the SET PT mechanism because it produces a smaller IP +PDE total energy. The compound that has the best antioxidant properties is compound 1. Analysis of toxicity properties and drug scores theoretically shows that catechin compounds and compounds 1, 2, 3, 4, and 5 are not toxic. Catechin compounds and modified catechins have positive drug score values (0.453 – 0.871). Catechins have a drug score of 0.871. The modified compound that has the highest drug score value is compound 2 with a drug score value of 0.867, close to the drug score value of catechin. Compounds 1, 2, 3, 4, and 5 are thought to be able to be used as potential antioxidants without side effects on biological systems. Of the catechin and modified catechin compounds, the compounds that have the best interaction with the cervical cancer receptor with the PDB code 5KYK are compounds 1, 1, 3, 5, catechin, 4 and 2.

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