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MOLECULAR DOCKING ANALYSIS AND ADMET PREDICTION Of *Caesalpinia sappan* COMPOUNDS AS ANTIINFLAMMATORY THROUGH CYCLOOXYGENASE-2 INHIBITION

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ABSTRACT

Selective COX-2 inhibitors have been considered safer treatments than NSAIDs for inflammation from its side effect. Sappanwood was already known for its anti-inflammatory activity, but its selectivity towards COX-2 has not been tested. The purpose of this study was to determine the potential activity of compounds in Caesalpinia sappan as anti-inflammatory agents by inhibiting COX-2 and determine their ADMET's properties through in silico study. Qulified compound from Lipinski's rule of five evaluation would be continued to the molecular docking using Autodock Tools and ADMET prediction using SwissADME and ADMETLab. About 24 compounds out of 26 compounds passed Lipinski's rules evaluation. Three compounds known to have the best free bond energy (ΔG) values were Caesalpiniaphenol A, Sappankalkon, and Deoxysappanone B with ΔG values respectively (-9.36 ; -9.23 ; -9.02 kcal/mol) and their inhibition constant values of (124.44 ; 172.43 ; 244.75 nM) respectively. Amino acid residues that are known to involve to the formation of hydrogen bonds in ligands are GLN 192 and PHE518. Toxicity results showed that these three compounds were predicted to be neither hepatotoxic nor hERG inhibitors, but 3-deoxysappanone B and sappankalkon was predicted to cause AMES mutagenicity and skin sensitivity. It can be concluded that these third compound has the potential as an inhibitor of the COX-2 enzyme.

Keywords: *Anti-inflammatory, Caesalpinia sappan, 5KIR, In silico, ADMET*

INTRODUCTION

Inflammation is known as a biological response of the body which happens when the body senses some dangers either in the form of infection, trauma, ischemia, physical, chemical or otherwise. Therefore, inflammation is an important defense mechanism for the body. Inflammation is characterized by five classic symptoms, which are: pain (dolor), heat (calor), redness (rubor), swelling (tumor) and loss of function (function laesa)(1,2). NSAIDs (Non-steroidal anti-inflammatory drugs) are the most often prescribed to treat pain and

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inflammation. This class of drugs works by inhibiting the cyclooxygenase (COX) enzymes (3). Around 30% to 50% of patients who used NSAID were experiencing gastroduodenal-related injuries. The injuries that occurred were a combination of subepithelial bleeding, erosion, and ulceration, caused of COX-1 inhibition (3,4). Selective COX-2 inhibitors Coxibs, have been shown to a lower risk of symptomatic ulcers and serious complications in the upper GI tract than non-specific NSAIDs, used as an alternative treatment to traditional NSAIDs to prevent side effects on the gastrointestinal tract (4).

Secang or sappanwood (*Caesalpinia sappan*) is a medicinal plant that grows in Southeast Asia. In Indonesia, the secang wood often processed as a herbal drink to increase body immunity by the locals (5,6). Sappanwood has been discovered to have various biological activities such as antioxidant, antidiabetic, anticonvulsant, hepatoprotective, antibacterial, and anti-inflammatory (7–9). The ability of this biological activity is caused by the presence of secondary metabolites in sappanwood, such as, flavonoids, phenolics, alkaloids, triterpenoids, steroids, homoisoflavonoids, heterocyclic oxygen and tannins (9,10).

Research conducted by Nilash et al (11) showed that brazilin-rich sappanwood extract and crude ethanol extract from sappanwood might have anti-inflammatory abilities of approximately 50% inhibition, if used at low concentrations of 0.1 mg/mL. Meanwhile, Shengqian (12) concluded that 95% ethanol extract of sappanwood could effectively inhibit overexpression of inflammatory mediators induced by IL-1 at the transcriptional level in human chondrocytes and macrophages.

A method to assess the anti-inflammatory activity of secondary metabolites from a plant is through an in silico approach. Molecular docking is a part of in silico approach which aims to predict the affinity of a drug candidate (ligand) against the protein target and predict its most stable complex. The advantages of this method include its potential to decrease the expenses and time necessary for drug design. Some of the results from molecular docking simulations can simplify in vivo and in vitro research

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(13).

The objective of this study was to determine the ability of secondary metabolites of sappanwood as anti-inflammatory agents through inhibition of the COX-2 enzyme. It was done because even though several studies have been carried out regarding the anti-inflammatory ability of sappanwood extract, no research has been conducted on its selectivity in inhibiting COX-2 so that it can act as anti-inflammation.

METHOD

1. Equipment and Materials

This study was carried out in personal computer (PC) facilitated with 16.0 gigabyte RAM, dan SSD KINGSTON SA400S37/240G SATA Rev. 3.0 6Gb/s., ASUS Dual GeForce® GTX 1650 OC edition 4GB GDDR6, and Intel®Core(TM) i3-10105F Processor, which connected to the internet. The software used were Windows 10 pro 64-bit operating system, Autodock 4.2.6 for molecular docking, Avogadro® and Swiss PDB Viewer® for protein-ligand energy minimization, Discovery Studio Visualizer® and PyMOL® for visualization of protein's interactions. SwissADME and ADMETLab websites were used for ADMET screening.

2. Protein-Ligand Preparation

The cyclooxygenase-2 enzyme was taken from PDB (Protein Data Bank) with PDB ID: 5KIR. Receptor and native ligand were separated, then water and unnecessary chains were removed using BIOVIA Discovery Studio software. Each was added with hydrogen atom before saved in (.pdb) format (14,15). About 26 secondary metabolite compounds from sappanwood as test compounds and celecoxib as comparator compound were downloaded through the Pubchem. Those compounds were minimized using Avogadro with the MMFF94 force field parameter and tested with Lipinski's rule of five, then proceed to molecular docking. As for protein, minimization was carried out using Swiss PDB Viewer (16).

3. Protein-Ligand Docking

The validation was carried by redocking the native ligand (RCX601) to its active site using AutoDock Tools, which composed AutoGrid4 and AutoDock4 (17). Grid box dimension used was 40 x 40 x 40 with 0.375 Å for

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grid spacing. The procedure is said to be valid if the RMSD value obtained from the redocking results is < 2Å (18). Then, the test compounds and celecoxib were docked against the active side of the protein target about 100 runs. The results in the forms of energy binding value and inhibition constant value were acquired and then analyzed (15).

4. ADMET Prediction

This study used web servers to predict the ADMET properties of the native ligand, celecoxib and test compounds. using ADMETLabs and SwissADME (19).

RESULT AND DISCUSSION

In this study, the secondary metabolites of sappanwood were tested in silico, using a computational approach for modeling small molecules and macromolecules as well as for analyzing and predicting protein-protein interactions. The parameters that were analyzed and evaluated to determine the successful assessment of molecular docking results were the RMSD docking validation, the Gibbs Binding Energy (ΔG), and the Inhibition Constant (IC) (19).

The test compounds were prepared, then selected based on test results from Lipinski's rule of five Drug candidates that comply with Lipinski's rule tend to have lower drug attrition rates during clinical trials and therefore have a greater chance of reaching the market (20). About 2 compounds from 26 cmpounds didn't meet the criteria of Lipinkin's rule of five, namely Neosappanone A and Protosappanin E1, since both of them have H-donors greater than 5 and H-acceptors greater than 10. Therefore, it left only 24 compounds, along with native ligand and celecoxib, for molecular docking.

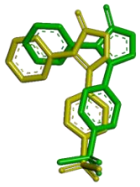

Figure 1. Visualization of native ligand RCX601 (green) overlapping with native ligand from redocking result (yellow)

The RMSD result from the redocking process for the validation was 1,262 Å (with coordinate : x = 23.346, y = 0.474, and z = 34.395). which comply the standard since it's under 2 Å. The closer the RMSD value to zero, the more similar the original

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native ligand's poses to the native ligand's poses from redocking result (21). The best docking result was determined by observing Gibbs Free Energy (ΔG) and Inhibition Constant (IC). ΔG reflects the strength of the bond between the protein and the ligand. The more negative the ΔG value, the stronger the affinity. Meanwhile, on the other hand, IC indicates the concentration of the ligand needed to inhibit the target protein (22). Based on observation of the molecular docking results against COX-2 (PDB ID: 5KIR) in the form of ΔG and KI values provided within Table 1, three test ligands from sappan wood secondary metabolites had the best ΔG values, namely Caesalpiniaphenol A, Sappankalkon, and 3-Deoxysappanone B, which yielded free bond energies of -9.36 kcal/mol, -9.23 kcal/mol, and -9.02 kcal/mol, respectively. The bond-free energy values of the three compounds are close to those of the native ligand (-10.63 kcal/mol) and celecoxib (-11.00 kcal/mol).

Gibbs free energy's results pointed out that Caesalpiniaphenol A is the most stable compound due it had

Table I. Docking result of protein-ligand with Autodock4

Compound		Gibbs free energy (ΔG) (kcal/mol)	Inhibition Constant (IC)
Native Ligand	RCX601	-10,63	16,21 Nanomolar
Comparator	Celecoxib	-11,00	8,62 Nanomolar
Test	Caesalpiniaphenol A	-9,36	124,44 Nanomolar
	Sappanchalcone	-9,23	172,43 Nanomolar
	3-Deoxysappanone B	-9,02	244,75 Nanomolar
	4-O-Methylsappanol	-8,97	266,48 Nanomolar
	Sappanone B	-8,91	294,05 Nanomolar
	3′-Deoxysappanone A	-8,89	305,39 Nanomolar
	Caesalpiniaphenol F	-8,86	318,48 Nanomolar
	Sappanol	-8,85	327,32 Nanomolar
	Isoliquiritigenin 2'-Methy Ether	-8,78	367,84 Nanomolar
	Ombuin	-8,75	387,48 Nanomolar
	Quercetin-3,7-Di-O- Methyl Ether	-8,50	587,57 Nanomolar
	4-O-Methyl Episappanol	-8,45	638,50 Nanomolar
	3′-Deoxy-4-OMethylepisappanol	-8,43	659,71 Nanomolar
	Episappanol	-8,41	440,79 Nanomolar
	Sappanone A	-8,14	1,08 Micromolar

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Caesalpin J	-7,71	2,22 Micromolar
8-Methoxybonducellin	-7,71	2,23 Micromolar
10,11-Dihydroxydracaenone C	-7,59	2,71 Micromolar
Protosappanin A	-7,29	4,51 Micromolar
Caesalpiniaphenol E	-6,97	7,81 Micromolar
Hematoksiklin	-6,75	11,37 Micromolar
3'-O-Methylbrazilin	-6,66	13,23 Micromolar
Brazilin	-6,58	15,02 Micromolar
Phanginin K	-6,57	15,34 Micromolar

the lowest value of ΔG compared to other test compounds then followed by Sappanchalcone and 3-Deoxysappanone B. The Inhibition Constant's results are correlates with the small value of the bond energy. The smaller ΔG value designates the lower the energy required by the ligand-protein complex to interact, which then indicates a strong interaction and the more stable the receptor ligand complex (23). Based on its docking score, some compounds has potential as an anti-inflammatory.

Sappanchalcone known had the ability to inhibit the production of NO and PGE2(24), and while 3-Deoxysappanone B was assumed to have anti-inflammatory activity because of its decent antioxidant activity with an IC50 value of 15,28 μM (25). These studies were correlated with our result, that those compounds approaching the ΔG value of native ligand and celecoxib which acts as an anti-inflammatory through COX-2 inhibition.

Observation on the interaction of Secang compounds with COX-2 aims to identify the amino acid residues involved that occured and expected to contribute in COX-2 inhibition, including such as hydrogen bonds, hydrophobic interactions, Van der Waals interactions, electrostatic interactions and halogens (15). Table II showed amino acid residue interactions to COX-2 (5KIR). GLN192 has 24 hydrogen bonds formed and PHE518 has 14 hydrogen bonds formed between compounds to 5KIR. Studies of Praceka et al (14) and Iswanti (26) also showed interactions between PHE518 and GLN19 to 5KIR. Visualization of amino acid residue interaction along with 3D visualization of Caesalpiniaphenol A were shown on Figure 2, including Van der Waals and

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hydrogen bonds as the most interaction.

Table II. Amino acid residue which interacted with ligands

Compound	Conventional Hydrogen Bond	Carbon Hydrogen Bond
Native ligand (RCX601)	ARG:513 (3,52 Å), PHE:518 (4,09 Å), ILE:517 (4,59 Å), SER:530 (4,06 Å)	ALA:527 (3,88 Å), HIS:90 (5,19 Å)
Celecoxib	SER:353 (4,38 Å), PHE:518 (3,17 Å), ILE:517 (4,18 Å), LEU:352 (5,59 Å)	SER:353 (3,83 Å), ALA:516 (3,70 Å), HIS:90 (6,33 Å)
Caesalpiniaphenol A	PHE:518 (3,97 Å), GLN:192 (4,80 Å)	TYR:385 (6,48 Å)
Sappanchalcone	MET:522 (3,59 Å), GLN:192 (5,00 Å;5,22 Å), PHE:518 (3,84 Å), SER:530 (4,48 Å)	TYR:385 (6,64 Å)
3-Deoxysappanone B	PHE:518 (3,65 Å), GLN:192 (5,16 Å)	VAL:523 (3,57 Å), ARG:513 (3,46 Å)

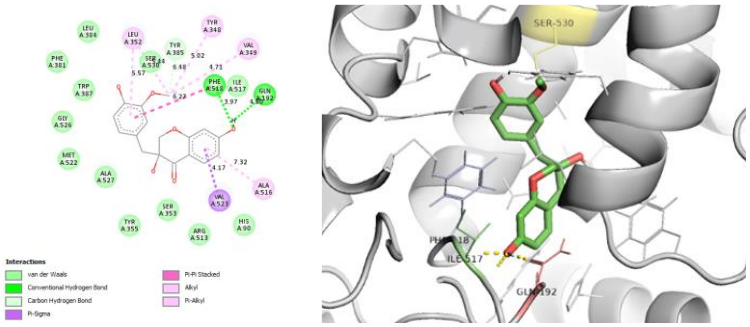

Figure 2. 2D and 3D Visualization of Caesalpiniaphenol A with A chain of protein 5KIR

Pharmacokinetic processes including Absorption, Distribution, Metabolism, and Excretion (ADME) (15). ADME and Toxicity in silico prediction methods have a significant impact to reduce the withdrawal of the drug from a certain stage of pre-clinical and clinical trials (27). In this study, ADMET properties were evaluated using SwissADME and ADMETLabs. The results of ADMET properties evaluation from Celecoxib and three compound with best docking score (Caesalpiniaphenol A, Sappankalkon, and 3-Deoxysappanone B) are shown in **Table 3.** The three compounds predicted to have high GI absorption, which means can be absorbed through human intestine. Caesalpiniaphenol A and 3-Deoxysappanone are predicted to be potential as Pgp substrates, to manipulate of P-glycoprotein-mediated transport, which may either be used for particular therapeutic benefits or lead to contraindications (28). Those 3 compounds have low skin permeabilities because their log Kp are more negative than -2.5 (19). Based on the BBB evaluations, those

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compound are known not to have the ability to penetrate the BBB and can't affect the central nervous system. The metabolic prediction show that Caesalpiniaphenol A has the potential to inhibit CYP3A4, while Sappanchalcone is predicted to have the potential to inhibit CYP1A2, CYP2C9 and CYP3A4. For 3-Deoxysappanone B, it does not have the potential to inhibit the metabolic process carried out by cytochrome P450. Caesalpiniaphenol A is included in the moderate category of clearance because its clearance value is between 5 and 15 ml/min/kg. As for the compounds sappankalcone and 3-deoxysappanone B, they are included in the high clearance category due to their clearance values of more than 15 ml/min/kg. These three compounds also are predicted to have short half-life.

Toxicity evaluation showed that, none of the three compounds are predicted to not work as hERG inhibitor and not potentially inducing any liver injury (HT-T), but both of Sappanchalcone and 3-Deoxysappanone are having high potential to cause AMES mutagenesis and skin sensitization.

Table 3. ADMET Prediction of Compounds with The Best Docking Score Using SwissADME and ADMETLab

ADMET	Parameter	Caesalpiniaphenol A	Sappan chalcone	3-Deoxysappanone B
Absorption	GI Absorption	High	High	High
	Pgp substrate	Yes	No	Yes
	log Kp (cm/s)	-6,91	-6,20	-6,91
Distribution	BBB permeability	No	No	No
Metabolism	CYP1A2 inhibitor	No	Yes	No
	CYP2C19 inhibitor	No	No	No
	CYP2C9 inhibitor	No	Yes	No
	CYP2D6 inhibitor	No	No	No

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ADMET		Caesalpiniaphenol A	Sappan chalcone	3-Deoxysappanone B	Parameter
	CYP3A4 inhibitor	Yes	Yes	No	
Excretion	CL	14,956	15,217	17,979	>15 ml/min/kg: high clearance; 5-15 ml/min/kg: moderate clearance; <5 ml/min/kg: low clearance (28).
	$T_{1/2}$	0,824	0,932	0,861	Molecules with $T_{1/2} \leq 3$ hours were classified as $T_{1/2}$+ (Category 1). The output value is the probability of being $T_{1/2}$ +, within the range of 0 to 1 (28).
Toxicity	hERG	0,038	0,045	0,04	Molecules with IC50 less than 10 µM or more than 50% inhibition at 10 µM were classified as hERG+ (Category 1). The output value is the probability of being hERG+, within the range of 0 to 1 (28).
	HT-T	0,116	0,143	0,172	The output value is the probability of being toxic, within the range of 0 to 1. Empirical decision: 0-0.3=excellent; 0.3-0.7=medium; 0.7-1.0: poor (red) (28).
	AMES	0,697	0,811	0,709	
	SkinSen	0,257	0,952	0,934	

CONCLUSIONS

Three compounds known to have the best free bond energy (ΔG) values were Caesalpiniaphenol A, Sappankalkon, and Deoxysappanone B with ΔG values respectively (-9.36 ; -9.23 ; -9.02 kcal/mol). Amino acid residues that are known to involve a lot to the formation of hydrogen bonds in ligands are GLN 192 and PHE 518. Toxicity results showed that these three compounds were predicted to be neither hepatotoxic nor hERG inhibitors, but deoxysappanone B was predicted to cause skin sensitization, while sappankalkon was predicted to cause AMES mutagenicity and skin.

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The results of this study can be used as information for future researchers to proceed to the advanced in silico test phase such as dynamic molecules. It is also recommended to conduct in vivo and in vitro studies considering the limited information regarding these three compounds both in terms of their anti-inflammatory activity through cox-2 inhibitors and their toxicity.

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