In Silico Study Active Compounds of Jamu Against Pre-Eclampsia Through Anti-Vasoconstriction and Anti-Inflammation

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Preeclampsia; Jamu; In Silico; Inhibition.

ABSTRACT
Preeclampsia is one of serious pregnancy-related condition that marked by elevated blood pressure and proteinuria that typically emerges during the second trimester or above 20 week, this disease become the second common cause of maternal death globally per year. One factors that can initiate preeclampsia are immunologic factor. Preeclampsia is started with abnormal trophoblast development and poor or shallow placental blood vessel development. Several protein that are induce by pre eclampsia are ACE1 (as vasoconstrictor), p38α, and JNK (stress-related protein and induce inflammation). One of the natural medicine in Indonesia is a "Jamu" that refers to traditional herbal medicine derived from natural ingredients such as herbs, roots, and spices.. In this research we are trying to predict several compounds in early-month pregnant jamu to tackle activation of ACE1, JNK, and p38α. Firstly, all of jamu compound was screened using Lipinski and bioavaibility test. Then, all of the jamu compound that pass the test before will be docked with ACE1, JNK, and p38α using Vina wizard in PyRx. The highest affinity in docking result will be visualized using Biovia Discovery Studio 2019, and will advance to molecular dynamics simulation test to determine stability of the complex in cell environment. The result show that kaempferol can stabily bind to p38α protein, with only induce minimum fluctuation in all RMSD and RMSF result. Piperanine can stabily bind JNK protein with also minimum fluctuation in all RMSD and RMSF result. Both kaempferol and piperanine did't violate any Lipinski rule and Bioavaibility test.

1. Introduction

Preeclampsia is one of serious pregnancy-related condition that marked by elevated blood pressure (>140/90 mmHg systolic/diastolic blood pressure) and proteinuria (atleast 300 mg protein in 24-hours urine specimen) that typically emerges during the second trimester or above 20 weeks (Bisson et al., 2023a; Khan et al., 2022). Preeclampsia combined with other hipertensive disorder in pregnancy are the second common cause of maternal death globally per year (62,000-77,000 deaths per year). Preeclampsia are more common occur in developing countries than in developed countries. World Health Organization (WHO) estimate that preeclampsia are seven times higher in developing countries if compared to developed countries (Dimitriadis et al., 2023; Mou et al., 2021).

Generally, there are 2 types of preeclampsia, mild preeclampsia and severe preeclampsia. Mild preeclampsia is characterized by blood pressure (systole/diastole) above 140/90 mmHg, without thrombocytopenia, normal liver function, normal creatinine level, without headache, visual disturbance, upper abdominal pain, pulmonary edema, and convulsion. Severe type of preeclampsia characterized by blood pressure (systole/diastole) above 160/110 mmHg, thrombocytopenia, abormal liver function, abnormal creatinine level, proteinuria, new-onset headache, visual disturbance, upper abdominal pain, pulmonary edema, and convulsion (Chang et al., 2023; Fox et al., 2019). Preeclampsia also lead to several complications, like stroke, seizure, cerebral hemorrhagic, blindness, renal failure, cardiovascular disease, fetal growth restriction, fetal neural defect, and fetal distress.

Three factors can initiate preeclampsia. they are genetic factor, immunologic factor, and enviromental factor. Pathogenesis of preeclampsia is started with abnormal trophoblast development and poor or shallow placental blood vessel development that can lead to poor blood flow to the placenta and placental ischemia. Long-term placental hypoxic condition and reperfusion injury can induce inflammation and hypertension that lead to systemic dysfunction. Hypoxic placental condition can induce mother's body to activate protein that relate to hypoxia response such as HIF-1α, FLT-1, soluble endoglin, VEGF, PIGF and several pro-inflammatory

cytokines (Bisson et al., 2023b; Saleh et al., 2016). Preeclamptic condition also lead to ACE1 overexpression, that convert angiotensin I into active vasoconstriction factor angiotension II and favor hypertension condition (Sontag et al., 2022). Preeclampsia also induce expression of c-Jun N-terminal kinases (JNK) and p38α, that both are stress-related response proteins (Jung et al., 2020; Zhou et al., 2023). High level of JNK and p38α can exacerbate the inflammation because it can activate effector immune cell, activate pro-inflammatory cell, induce production of pro-inflmmatory cytokines, and lower regulatory immune cell. In addition, activation of p38α can also induce placental cell death with inhibit anti-apoptotic BCL-2 protein activity, increase pro-apoptotic BAX protein activity, ignite mitochondrial unstability, and lead to cytochrome-c release to the cytoplasm. Because of that, we need to discover another drug that act as anti-inflammatory to reduce systemic dysfunction that caused by preeclampsia (Canovas & Nebreda, 2021; Ehrig et al., 2015; Szabo et al., 2015).

Natural medicine is a traditional medicine that has been known since ancient times, especially in developing countries. Indonesia is one of the country that natural medicine became popular since past. One of the natural medicine is a “Jamu” that come from Indonesia. “Jamu" refers to traditional herbal medicine derived from natural ingredients such as herbs, roots, and spices. It is used for maintaining overall health, treating specific ailments, and enhancing both physical and mental well-being. Jamu can be consumed in various forms, including drinks, powders, or capsules, and plays a significant role in Indonesian cultural and health practices. The benefits of jamu are traditionally acknowledged, though empirical research on its efficacy and safety is still needed. The Indonesian government categorizes medicinal plants into three groups: jamu, standardized herbal medicines, and fitofarmaka (phytomedicines). Future research should address ethical concerns and explore the clinical potential of jamu (Woerdenbag & Kayser, 2014). Although most herbal medicines still lack scientific proof, but several studies of natural medicine are have potential against several disesase like cancer, bacterial infection, inflammation, and other disease (Woerdenbag & Kayser, 2014; Zuo et al., 2020).

Because of those reasons above, we conduct our research to predict the activity and effectiveness of one type of jamu that called “ Jamu Hamil muda” or early-month pregnant jamu based on in silico study. Hopefully, this research can be a first step to scientification of early-month pregnant jamu as an alternative drug against preeclampsia and enhace life expectation for pregnant mothers and their babies.

2. Material and Methods

Compound Characterization Using LC-MS

Four different of early-month pregnant jamu was obtained from local market . 40 grams from each jamu was dissolved in 800 ml methanol, then dissolved with 0.1% formic acid in water, and 0.1 % formic acid in acetonitrile. Each sample was inserted into “Hipersil GOLD aQ 50x 1 mm x 1.9 µm” LC-MS machine, with flow rate 40 µL per minute at 30℃ for 70 minutes. The machine automatically stopped at resolution of 70000. The result was analyzed in mzMine and compounds that excess mzCloud best match will be advanced to compound screening and bioavaibility test.

Data Mining

The compound IDs (CIDs), canonical SMILES, chemical formulas, and 3D structures of the Jamu compounds were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The 3D structures were saved in SDF format. The ACE1 (PDB ID: 1UZE), JNK (PDB ID: 4UX9), and p38α (PDB ID: 5LAR) protein structures were obtained from the RCSB-PDB database (https://www.rcsb.org/) and saved in PDB format.

Drug-likeness Test

The drug-likeness of all Jamu compounds was evaluated using the SwissADME web tool (http://www.swissadme.ch/). SwissADME is a bioinformatics tool that predicts various parameters such as pharmacokinetics, physicochemical properties, drug-likeness, lipophilicity, and solubility. Lipinski's Rule of Five was applied to assess the drug-likeness, which considers compounds with fewer than ten hydrogen bond acceptors, a molecular weight under 500, fewer than five hydrogen bond donors, and a calculated Log P (CLogP) below 5 (or, in the case of MLogP, under 4.15) (Lipinski et al., 1997).

Molecular Docking and Visualization

Ligands were prepared by minimizing their energy using OpenBabel within the PyRx software and saved as PDB files. Target proteins were prepared by removing water molecules and native ligands using Biovia

Discovery Studio Visualizer 2019. Molecular docking, performed with Vina Wizard in PyRx, predicted interactions between the target proteins and ligands (either native or test compounds). Specific docking grids were based on previous studies and the native ligand positions from RCSB-PDB (ACE1 PDB ID: 1UZE, JNK PDB ID: 4UX9, and p38α PDB ID: 5LAR). The binding affinities of the Jamu compounds were then compared with control compounds. The 3D docking results and 2D amino acid interactions were visualized using Biovia Discovery Studio 2019 (Meylani et al., 2023).

Table 1. RCSB-PDB ID and docking coordinate of each protein

No	Protein Name (RCSB-PDB ID)	Docking coordinate
1	ACE1 (1UZE)	Center X: 40.380 Y: 35.960 Z: 42.828 Dimension X: 22.020 Y: 18.152 Z: 23.369
2	JNK (4UX9)	Center X: 37.389 Y: 34.948 Z: 117.886 Dimension X: 20.498 Y: 26.220 Z: 21.197
3	p38α (5LAR)	Center X= 53.224 Y= 66.397 Z= 16.707 Dimension X= 22.104 Y= 23.889 Z= 24.603

Molecular Dynamics

Molecular dynamics simulations were conducted using the YASARA software with the AMBER14 force field. The simulation parameters included a temperature of 310K, pH of 7.4, 0.9% NaCl concentration, water density of 0.997 g/mL, pressure of 1 atm, and a duration of 20 ns. The Root-Mean-Square Fluctuation (RMSF) was used to indicate the per-residue fluctuations in Ångströms, while the Root-Mean-Square Deviation (RMSD) was employed to assess the stability of the ligand-protein complex and the structural integrity of the protein over time (Meylani et al., 2023; Widyananda et al., 2022).

3. Result and Discussion

LC-MS Result and Drug-likeness of Early-Month Pregnant

The LC-MS analysis identified 27 compounds and metabolites from four different Jamu formulations used during early pregnancy (see Table 2). According to the Lipinski test, all of these compounds met the necessary criteria (see Table 3). However, in the bioavailability assessment, five compounds failed to meet the required standards due to factors like low gastrointestinal (GI) absorption, high Topological Polar Surface Area (TPSA) exceeding 160 Å², or their potential to act as substrates for P-glycoprotein (P-gp), leading to cellular exclusion. The compounds excluded from the screening were choline, betaine, myricetin, DL-arginine, and adenosine (see Table 4). Compounds that have a TPSA (Topological Polar Surface Area) value of more than 140 Å² will have a low gastrointestinal absorption (GI absorption) value, while compounds that have a TPSA value below 140 Å² will have a high GI absorption value. Some compounds have the ability to penetrate the blood-brain barrier (BBB). The majority of compounds cannot be pumped out (efflux) by p-gp or pglycoprotein, compounds that are P-gp substrates will be easily pumped out by p-gp so that they are difficult to use as drug candidates because these compounds will be difficult to accumulate in cells so that they require high doses to be able to provide effects in cells (Juvale et al., 2022).

Table 2. Compounds from early-month pregnant jamu with its ID and SMILES from PubChem

No	Compound	Compound ID	Canonical SMILES
1	Choline	305	C[N+](C)(C)CCO
2	Betaine	247	C[N+](C)(C)CC(=O)[O-]
3	Zerumbone	5470187	CC1=CCC(C=CC(=O)C(=CCC1)C)(C)C
4	Myricetin	5281672	C1=C(C=C(C(=C1O)O)O)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O
5	Isoliquiritigenin	638278	C1=CC(=CC=C1C=CC(=O)C2=C(C=C(C=C2)O)O)O
6	DL-Arginine	232	C(CC(C(=O)O)N)CN=C(N)N
7	Isoleucine	6306	CCC(C)C(C(=O)O)N
8	Coumarin	323	C1=CC=C2C(=C1)C=CC(=O)O2
9	Ageratriol	181557	CC(=C)C1CC(C(=C)CCC(C(=C)C(C1)O)O)O
10	10-HAD	22501464	CC(CCCCCCCCO)C(=O)O
11	Trigonelline	5570	C[N+]1=CC=CC(=C1)C(=O)[O-]
12	Piperanine	5320618	C1CCN(CC1)C(=O)C=CCCC2=CC3=C(C=C2)OCO3
13	4-Methoxycinnamic acid	699414	COC1=CC=C(C=C1)C=CC(=O)O
14	L-Histidine	6274	C1=C(NC=N1)CC(C(=O)O)N
15	L-Phenylalanine	6140	C1=CC=C(C=C1)CC(C(=O)O)N
16	α-Eleostearic acid	5281115	CCCCC=CC=CC=CCCCCCCCC(=O)O
17	Leucylproline	80817	CC(C)CC(C(=O)N1CCCC1C(=O)O)N
18	Indole	798	C1=CC=C2C(=C1)C=CN2
19	α-Linolenic acid	5280934	CCC=CCC=CCC=CCCCCCCCC(=O)O

20	Adenosine	60961	C1=NC(=C2C(=N1)N(C=N2)C3C(C(C(O3)CO)O)O)N
21	trans-3-Indoleacrylic acid	5375048	C1=CC=C2C(=C1)C(=CN2)C=CC(=O)O
22	L-Norleucine	21236	CCCCC(C(=O)O)N
23	Glycyl-L-leucine	92843	CC(C)CC(C(=O)O)NC(=O)CN
24	9S,13R-12-Oxophytodienoic acid	14037063	CCC=CCC1C(C=CC1=O)CCCCCCCC(=O)O
25	Kaempferol	5280863	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
26	(-)-Caryophyllene oxide	1742210	CC1(CC2C1CCC3(C(O3)CCC2=C)C)C
27	Ferulic acid	445858	COC1=C(C=CC(=C1)C=CC(=O)O)O

Table 3. Lipinski result test of each early-month pregnant jamu

No	Compound	Molecular Weight (g/mol)	MLogP	N. ON	N. OHNH	Lipinski
		≤ 500 g/mol	≤ 4.15	≤ 10	≤ 5	
1	Choline	104,17	-3,46	1	1	Yes ; 0 violation
2	Betaine	117,15	-3,67	2	0	Yes ; 0 violation
3	Zerumbone	218,33	3,37	1	0	Yes ; 0 violation
4	Myricetin	318,24	-1,08	8	6	Yes ; 1 violation
5	Isoliquiritigenin	256,25	1,58	4	3	Yes ; 0 violation
6	DL-Arginine	174,2	-3,21	4	4	Yes ; 0 violation
7	Isoleucine	131,17	-1,82	3	2	Yes : 0 violation
8	Coumarin	146,14	1,65	2	0	Yes ; 0 violation
9	Ageratriol	252,35	1,66	3	3	Yes ; 0 violation
10	10-HAD	202,29	1,99	3	2	Yes ; 0 violation
11	Trigonelline	137,14	0,33	2	0	Yes ; 0 violation
12	Piperanine	287,35	2,47	3	0	Yes ; 0 violation
13	4-Methoxycinnamic acid	178,18	1,59	3	1	Yes ; 0 violation
14	L-Histidine	155,15	-3,74	4	3	yes ; 0 violation
15	L-Phenylalanine	165,19	-1,11	3	2	Yes ; 0 violation
16	α-Eleostearic acid	278,43	4,38	2	1	Yes ; 1 violation
17	Leucylproline	228,29	0,22	4	2	Yes ; 0 violation
18	Indole	117,15	1,57	0	1	Yes ; 0 violation
19	α-Linolenic acid	278,43	4,38	2	1	Yes ; 1 violation
20	Adenosine	267,24	-2,72	7	4	Yes ; 1 violation
21	trans-3-Indoleacrylic acid	187,19	1,32	2	2	Yes ; 0 violation
22	L-Norleucine	131,17-	1,82	3	2	Yes ; 0 violation
23	Glycyl-L-leucine	188,22	-0,3	4	3	Yes ; 0 violation
24	9S,13R-12-Oxophytodienoic acid	292,41	3,11	3	1	Yes ; 0 violation
25	Kaempferol	286,24	-0,03	6	4	Yes ; 0 violation
26	(-)-Caryophyllene oxide	220,35	3,67	1	0	Yes ; 0 violation
27	Ferulic acid	194,18	1	4	2	Yes ; 0 violation

Table 4. Drug-likeness test of each compounds from early-month pregnant jamu

No	Compound	Water Solubility (ESOL)			Pharmacokinetics			TPSA
		LogS	Solubility	Class	GI Absorption	P-gp	BBB	≤ 140 Å²
1	Choline	-0,1	8.24e+01 mg/ml; 7.91e-01 mol/l	very soluble	low	No	No	20,23
2	Betaine	-0,35	5.20e+01 mg/ml; 4.44e-01 mol/l	very soluble	low	yes	No	40,13
3	Zerumbone	-3,68	4.61e-02 mg/ml; 2.11e-04 mol/l	soluble	high	No	Yes	17,07
4	Myricetin	-3,01	3.14e-01 mg/ml; 9.88e-04 mol/l	soluble	low	No	no	151,59
5	Isoliquiritigenin	-3,7	5.09e-02 mg/ml; 1.99e-04 mol/l	soluble	high	no	Yes	77,76
6	DL-Arginine	2,05	1.95e+04 mg/ml; 1.12e+02 mol/l	highly soluble	low	No	no	127,72
7	Isoleucine	0,63	5.57e+02 mg/ml; 4.25e+00 mol/l	highly soluble	high	No	no	63,32
8	Coumarin	-2,29	7.42e-01 mg/ml; 5.08e-03 mol/l	soluble	high	No	Yes	30,21
9	Ageratriol	-2,12	1.92e+00 mg/ml; 7.59e-03 mol/l	soluble	high	no	no	60,69
10	10-HAD	-2,3	1.02e+00 mg/ml; 5.06e-03 mol/l	soluble	high	No	Yes	57,53
11	Trigonelline	-1,39	5.59e+00 mg/ml; 4.08e-02 mol/l	very soluble	high	No	no	44,01
12	Piperanine	-3,65	6.41e-02 mg/ml; 2.23e-04 mol/l	soluble	high	No	Yes	38,77

13	4-Methoxycinnamic acid	-2,78	2.98e-01 mg/ml; 1.67e-03 mol/l	soluble	high	no	Yes	46,53
14	L-Histidine	1,09	1.93e+03 mg/ml; 1.24e+01 mol/l	highly soluble	high	no	no	92
15	L-Phenylalanine	-0,08	1.38e+02 mg/ml; 8.35e-01 mol/l	very soluble	high	No	no	63,32
16	α-Eleostearic acid	-4,87	3.73e-03 mg/ml; 1.34e-05 mol/l	Moderately soluble	high	No	Yes	37,3
17	Leucylproline	0,18	3.48e+02 mg/ml; 1.53e+00 mol/l	highly soluble	high	No	No	83,63
18	Indole	-2,6	2.96e-01 mg/ml; 2.52e-03 mol/l	soluble	high	No	Yes	15,79
19	α-Linolenic acid	-4,78	4.64e-03 mg/ml; 1.67e-05 mol/l	Moderately soluble	high	No	Yes	37,4
20	Adenosine	-1,05	2.36e+01 mg/ml; 8.83e-02 mol/l	very soluble	low	No	No	139,54
21	trans-3-Indoleacrylic acid	-2,54	5.38e-01 mg/ml; 2.88e-03 mol/l	soluble	high	No	Yes	53,09
22	L-Norleucine	0,58	5.00e+02 mg/ml; 3.81e+00 mol/l	highly soluble	high	No	No	63,32
23	Glycyl-L-leucine	0,86	1.35e+03 mg/ml; 7.19e+00 mol/l	highly soluble	high	No	No	92,42
24	9S,13R-12-Oxophytodienoic acid	-3,89	3.78e-02 mg/ml; 1.29e-04 mol/l	soluble	high	No	Yes	54,37
25	Kaempferol	-3,31	1.40e-01 mg/ml; 4.90e-04 mol/l	soluble	high	no	no	111,13
26	(-)-Caryophyllene oxide	-3,45	7.84e-02 mg/ml; 3.56e-04 mol/l	soluble	high	No	Yes	12,53
27	Ferulic acid	-2,11	1.49e+00 mg/ml; 7.68e-03 mol/l	soluble	high	No	Yes	66,76

Docking Result of Early-Month Pregnant

Interaction between ACE1 and kaempferol has similarity binding with ACE1 and enalaprilat (EAL) in ALA354, HIS383, and VAL380 residues. Docking result of ACE1 with kaempferol has 1 hydrogen bond, 3 hydrophobic bond, and 10 Van der waals interaction.While docking result between ACE1 and EAL has 3 hydrogen bond, 5 hydrophobic bond, and 10 Van der waals. Interaction between JNK and piperanine has similarity binding with JNK and AMP-PNP (ANP) in LYS55, and MET111 residues. Docking result of JNK with piperanine has 2 hydrogen bond, 6 hydrophobic bond, and 7 Van der waals interaction.While docking result between JNK and ANP has 6 hydrogen bond, 3 hydrophobic bond, and 14 Van der waals. Interaction between p38α and kaempferol has similarity binding with p38α and 6SH in TYR35, LYS53, LEU75, ILE84, THR106 and ASP168 residues. Docking result of p38α with kaempferol has 1 hydrogen bond, 7 hydrophobic bond, and 9 Van der waals interaction.While docking result between p38α and 6SH has 5 hydrogen bond, 5 hydrophobic bond, and 18 Van der waals [Figure 1].

Hydrogen bonding occurs when hydrogen atoms from one molecule interact with another molecule, typically one with a higher electrostatic charge. These bonds play a key role in protein folding and ligand-protein binding, with an energy range of approximately 3 to 5 kcal/mol. Hydrophobic interactions, on the other hand, are driven by the presence of hydrocarbons or non-polar compounds that can aggregate in aqueous solutions. Van der Waals interactions arise when two atoms come close together, creating an attractive force without forming a bond. Although these interactions doesn't contribute significantly to binding affinity compared to other types of bonds, they can stabilize ligand poses and docking results (Poznański et al., 2014; Van der Lubbe & Fonseca Guerra, 2019).

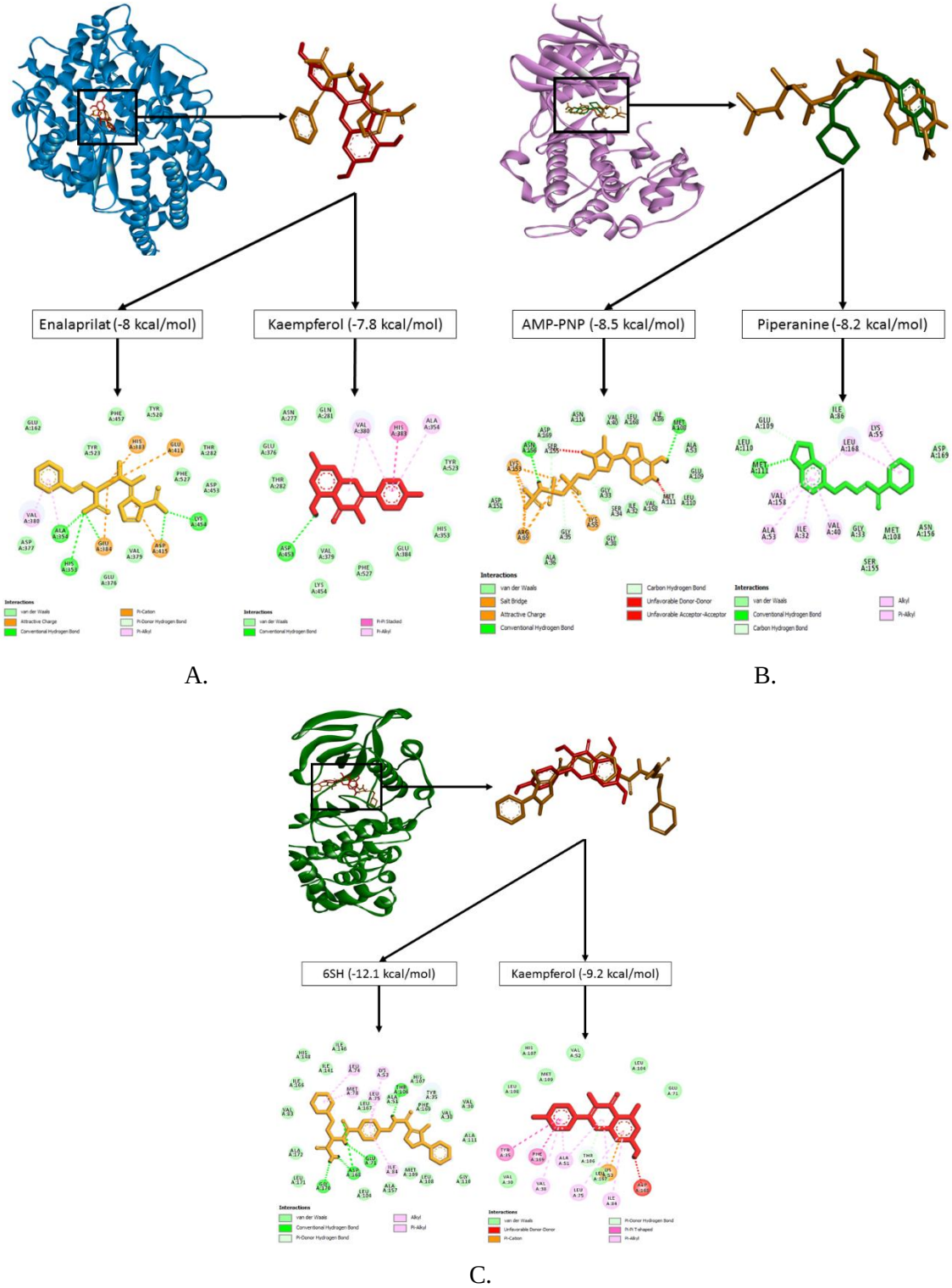
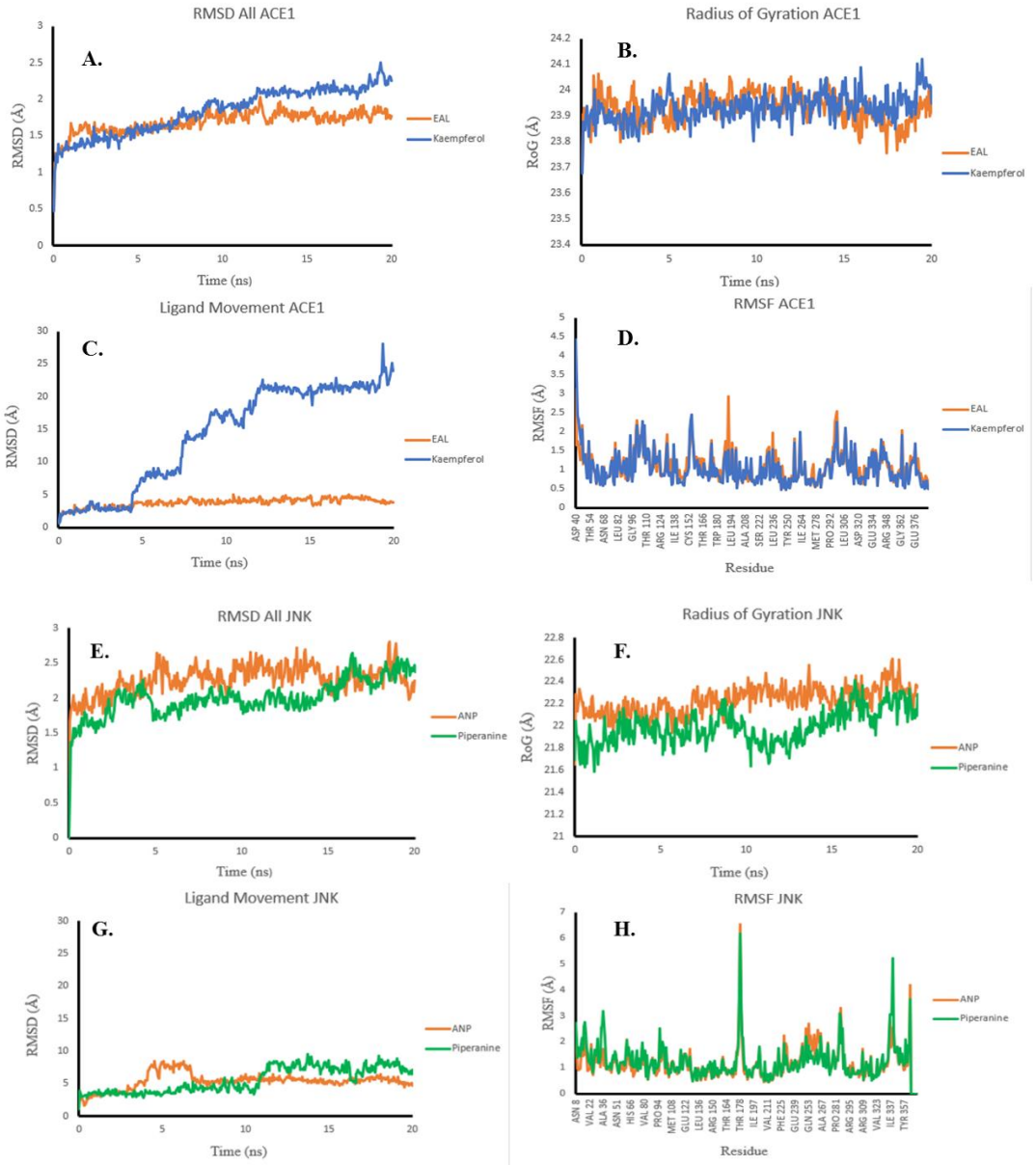


Figure 1. Binding affinity and binding position comparison of A. Enalaprilat (EAL) and Kaempferol in ACE1 protein. B. AMP-PNP (ANP) and Piperanine in JNK protein. C. 6SH with kaempferol in p38α protein.

Molecular Dynamics Result of Early-Month Pregnant

Based on RMSD result, we can conclude that in interaction ACE1 with kaempferol doesn't change significantly to the ACE1 protein structure compared to the EAL (control drug), which is indicated by RMSD value below 3Å, fluctuation in radius of gyration value below 1 Å, and RMSF value that similar to the control. In the ligand movement, there is a change of position after simulation in the kaempferol binding compared to the control. Indicated by ligand movement value above 5 Å and stable in 20 Å. In interaction between JNK with piperanine

doesn't change significantly to the JNK protein structure compared to the AMP-PNP (control drug), which is indicated by RMSD value below 3Å, fluctuation in radius of gyration value below 1 Å, and RMSF value that similar to the control. In the ligand movement, piperanine have only slightly movement compared to control. This is because the complex of JNK and piperanenin have stable value of RMSD in between 4 and 5 Å. In interaction between p38α with kaempferol also have same result with JNK and piperanine that indicating a more stable binding compared to ACE1 and kaempferol complex. RMSD value of p38α with kaempferol stable at 2 Å, that is same value with p38α with 6SH (control). Interaction of p38α both with kaempferol or 6SH also doesn't induce any significant fluctuation in radius of gyration, indicated with radius of gyration value below 1 Å, and RMSF value that similar to the control. In the ligand movement, piperanine have only slightly movement compared to control. This is because the complex of JNK and piperanenin have stable value of RMSD in between 4 and 5 Å.



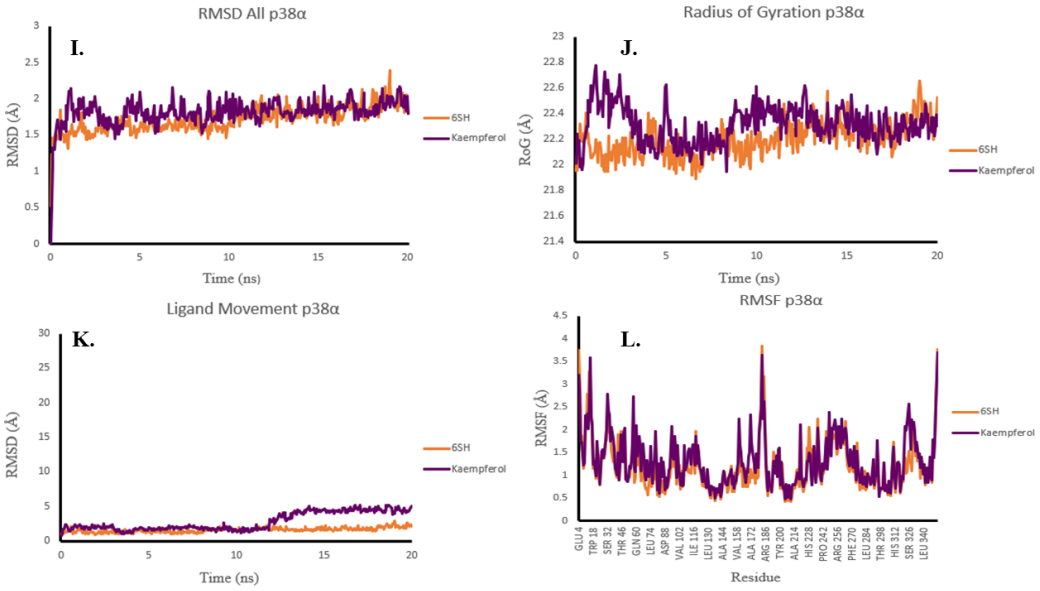


Figure 2. RMSD and RMSF comparison of each complex. A. RMSD all between Kaempferol and its native ligand Enalaprilat (EAL) in ACE1 protein. B. Radius of Gyration between Kaempferol and its native ligand Enalaprilat (EAL) in ACE1 protein. C. RMSD ligand movement between Kaempferol and its native ligand Enalaprilat (EAL) in ACE1 protein. D. RMSF value between Kaempferol and its native ligand Enalaprilat (EAL) in ACE1 protein. E. RMSD all between Piperanine and its native ligand AMP-PNP (ANP) in JNK protein. F. Radius of Gyration between Piperanine and its native ligand AMP-PNP (ANP) in JNK protein. G. RMSD ligand movement between Piperanine and its native ligand AMP-PNP (ANP) in JNK protein. H. RMSF value between Piperanine and its native ligand AMP-PNP (ANP) in JNK protein. I. RMSD all between Kaempferol and its native ligand 6SH in p38α protein. J. Radius of Gyration between Kaempferol and its native ligand 6SH in p38α protein. K. RMSD ligand movement between Kaempferol and its native ligand 6SH in p38α protein. L. RMSF value between Kaempferol and its native ligand 6SH in p38α protein.

Based on Figures 2, it could be shown all of complex have minor RMSD fluctuations. The structure could be stable if the RMSD and RMSF value is below 3Å. The compound with higher RMSD peak could indicate less binding stability because the compoud might have a weak binding affinity or could be released from the protein receptor. The compound with a higher RMSF peak could be indicate a high level of fluctuation and a significant conformational change. The RMSD Ligand movement shows the change in ligand position from before the simulation until the end of the simulation. The larger the value, the more changes occur in the position of the ligand bond (Meylani et al., 2023; Widyananda et al., 2022).

4. Conclusion

Based on the result, kaempferol and piperanine that derived from early-month pregnant jamu can be predicted have a potential effect as preventing pre-eclampsia by acting as anti-inflammatory. Kaempferol and piperanine don't violate any rule in Lipinski rules, and both (kaempferol and piperanine) have good bioavaibility. Docking and molecular dynamic result shows that kaempferol can stabily bind to p38α protein, with only induce minimum fluctuation in all RMSD and RMSF result. Piperanine can stabily bind JNK protein with also minimum fluctuation in all RMSD and RMSF result.

Conflict of Interest

The authors declare there's no conflict of interest.

Authors' Declaration

The authors declare that this article is original. The authors also give a special thank to Prof. Widodo, M.Si, Ph.D.Med.Sc. to lend us into a YASARA software to support our research.

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