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ANTIHYPERTENSIVE ACTIVITY PROFILE OF BANGKIRAI LEAVES (*Shorea laevis* Ridl.) ETHANOL EXTRACT ON ANGIOTENSIN II (4ZUD) AND β-Adrenergic (6PS5) RECEPTORS

Profil Aktivitas Antihipertensi Ekstrak Etanol Daun Bangkirai (Shorea laevis Ridl.) Pada Reseptor Angiotensin II (4ZUD) dan β-Adrenergic (6PS5)

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ABSTRACT / ABSTRAK

Hipertensi merupakan gangguan sistem kardiovaskular yang ditandai dengan tekanan sistolik ≥ 140mmHg dan diastolik ≥ 90mmHg. Kenaikan tekanan darah tersebut dikarenakan adanya mekanisme dari reseptor angiotensin II dan β-adrenergik, sehingga dalam pengembangan obat untuk hipertensi diperlukan senyawa dalam penghambatan aktivasi angiotensin I menjadi angiotensin II, serta pada β-adrenergik. Kalimantan, Indonesia memiliki keanekaragaman hayati yang berpotensi sebagai obat seperti Bangkirai (Shorea laevis Ridl.). Berdasarkan penelitian sebelumnya mengenai metabolit sekunder telah teridentifikasi berbagai senyawa yang berpotensi sebagai calon obat baru, misalnya sebagai antihipertensi. Penelitian ini bertujuan untuk mengetahui profil farmakologi dan mekanisme inhibisi angiotensin I pada reseptor 4ZUD serta inhibisi β-adrenergik pada reseptor 6PS5, dari ekstrak etanol daun bangkirai dengan cara melakukan molecular docking yang diawali dengan beberapa tahapan antara lain preparasi dan optimasi struktur senyawa uji serta preparasi struktur 3D reseptor 4ZUD dan 6PS5. Untuk mengetahui kebenaran metode maka dilakukan validasi terhadap senyawa ligand olmesartan untuk 4ZUD dan ligand propranolol untuk 6PS5. Berdasarkan penelitian yang telah dilakukan pada kedua reseptor diperoleh hasil untuk senyawa uji berupa MolDockScore, profil farmakologi absorbsi, distribusi, metabolisme, ekskresi serta toksisitas. Hasil MolDockScore menunjukkan bahwa senyawa Colchicine,N-desacetyl-N-[4-hydroxy-3,5-dimethoxycinnamoyl] memiliki nilai paling rendah yakni -146.503 pada reseptor 4ZUD dan -129.718 pada reseptor 6PS5 yang mendekati nilai ligan alami dibandingkan senyawa metabolit lainnya. Selain itu juga memberikan hasil yang baik berdasarkan profil farmakologi pada reseptor 4ZUD & 6PS5 antara lain HIA (95,73%), Caco2 (35.14nm/detik) dan PPB (87.67%). Hasil uji negatif juga ditunjukkan pada profil toksisitas

mutagenik (Ames Test Method), non-mutagenik dan uji karsinogenik yang meliputi genotoksik dan nongenotoksik.

Hypertensive is a cardiovascular system disorder characterized by systolic pressure ≥ 140mmHg and diastolic ≥ 90mmHg. The increase in blod pressure is due to the mechanism of angiotensin II and β-adrenergic receptors, so in developing medicine for hypertension, compounds are needed to inhibit the activation of angiotensin II to angiotensin II, as well as β-adrenergic. Kalimantan, Indonesia has a biodiversity that has the potential as medicine such as Bangkirai (*Shorea laevis* Ridl.). Based on previous research on secondary metabolites, various compounds have been identified that have potential as new drug candidates, for example as antihypertensive. This study aims to determine the pharmacological profile and mechanism of angiotensin I inhibition at the 4ZUD and β-adrenergic receptors inhibition at the 6PS5 receptor, from ethanol extract of bangkirai leaves by carrying out molecular docking which begins with several stages including preparation and optimization of the structure of the test compound and structure preparation of 3D receptors 4ZUD and 6PS5. To find out the correctness of the method, validation was carried out on the Olmesartan ligand compound for 4ZUD and the propranolol ligand for 6PS5. Based on research carried out on both receptors, results were obtained for the test compounds in the form of MolDockScore, the pharmacological profile of absorption, distribution, metabolism, excretion, and toxicity. MolDockScore results show that the compound Colchicine, N-desacetyl-N-[4-hydroxy-3,5-dimethoxycinnamoyl] has the lowest values, namely -146.503 at the 4ZUD receptor dan -129.718 at the 6PS5 receptor, which is close to the natural ligand value compared to other metabolite compounds. Apart from that, it also provides good results based on the pharmacological profile of the 4ZUD and 6PS5 receptors including HIA (95.73%), Caco2 (35.14nm/second), and PPB (87.67%). Negative test results are also shown in the mutagenic toxicity profile (Ames Test Method), non-mutagenic, and carcinogenic tests which include genotoxic and nongenotoxic.

INTRODUCTION

Around eight million people die every year due to hypertension, 1.5 million of which occur in Southeast Asia, where 1/3 of the population has hypertension. Based on data from Riskesdas in 2018, it shows that 33,7% of hypertension occurs in rural communities and around 34.4% occurs in urban communities. Then, around 25% of the prevalence occurs in the farmer/fisherman group (Kemenkes R.I., 2019). Based on WHO data, Indonesia is included in the ten largest countries, namely 4th, with a prevalence of cases in women between 1990 and 2019 of 12% (WHO., 2021). If hypertension is not controlled or not controlled properly, complications can occur, especially in the internal organs. Damage and complications to these organs are influenced by previously undiagnosed and untreated blood pressure. Complications in this organ can occur in the brain, eyes, heart, kidneys, and peripheral blood vessels, resulting in manifestations of pathological conditions such as stroke, coronary heart disease, diabetes, kidney failure, and blindness. Referring to Indonesian sample registration system (SRS) data in 2014, around 5.3% of hypertension complications were the fifth cause of death at all ages. Meanwhile, in 2017, data from the International Health Metrics Monitoring and Evaluation (IHME) in Indonesia, the first cause of death was stroke, then ischemic heart disease and diabetes (Istiqomah and Azizah, 2022; Kemenkes R.I. 2019). Therefore, further studies are needed to identify the causes of risk, the therapies used, and the potential for new drug compounds as therapeutic options for hypertension.

Many Indonesian people use traditional medicine as an alternative to synthetic medicine, for example, for hypertension therapy. So, this becomes a challenge in the development and search for new medicinal compounds, especially

in plants that have compounds as potential antihypertensive bangkirai (Shorea laevis Ridl.) is an endemic plant to Kalimantan which has many benefits, in the form of wood or known as bangkirai wood which has good quality, especially as building wood. Bangkirai leaves have now become one of the non-timber forest products (NTFPs) as a diversification of herbal products from the dipterocarp forest ecosystem (Fernandes and Maharini, 2018). Based on research that has been conducted, bangkirai leaves have secondary metabolites such as alkaloids, triterpenoids, phenolic compounds, and flavonoids (Sudrajat and Kartika, 2016). Meanwhile, leaf distillation using water contains sesquiterpenes and has high antioxidant and antibacterial activity (Muhammad, et.al., 2011). Bangkirai leaves contain antioxidants such as alkaloids and terpenoids, which can inhibit free radicals. Besides that, they also have high potential as a functional food or snack. Empirically, bangkirai leaves have been used as boiled water to reduce high blood pressure, neck pain, and dizziness and make the body fresh again (Fernandes, et al., 2020).

To produce a pharmacological effect as an antihypertensive, the ethanol compound of Shorea laevis leaves must have the ability to inhibit the enzymes Angiotensin II (4ZUD) and β-Adrenergic (6PS5), which work to increase blood pressure. Angiotensin II (ATII) is the main vasoactive peptide in the RAAS and acts on two receptors, ATI and ATII. Activation of ATII receptors causes an increase in blood pressure due to the concentration of vascular smooth muscle, systemic vascular resistance, sympathetic activity, sodium (Na), and water retention due to increased sodium reabsorption in the proximal convoluted tubule. Furthermore, activation of ATII receptors causes renal sodium excretion. Agonism at the ATII receptor has anti-proliferative and cardiovascular protective effects (Cernes, et al., 2011). The ARB class of antihypertensive drugs include losartan, valsartan, irbesartan, candesartan, eprosartan, telmisartan and Olmesartan (Tjay and Rahardja, 2015). In this study, a comparison drug, namely Olmesartan, will be used. β-blockers are classified as non-selective and β-1 selective. There are also β-2 and β-3 selective drugs; however, they have no known clinical effects. Non-selective agents bind to both β-1 and β-2 receptors and induce antagonistic effects through both receptors. Examples of non-selective are labetolol, propranolol, sotalol, and carvedilol. Selective β-1 receptor inhibitors such as atenolol, bisoprolol, metoprolol, and esmolol bind only the one receptor, which is cardio selective (Farzam and Jan. 2023). As a comparison in this study, the β-blocker drug class is propranolol.

The basic principle of the in-silico method is to bind ligands or drug compounds in the form of macromolecules to obtain physical and chemical properties from the best to the worst (Wadood, et al., 2013). This is closely related to the ability to use various applications at once to reduce unsatisfactory results (Shityakov, et al., 2013). One effort can be made to correlate the structure of chemical compounds with Lipinski's Rule of Five, which needs to be developed further because of its potential as an active drug ingredient (Muchtaridi, et al.,2018). The in-silico method that is often used is molecular docking (Makatita, 2020). Docking between micro and macromolecules, such as docking proteins with ligands. Apart from that, docking is also used to predict the type of bond between two molecules, such as protein-protein docking (Prieto-Martínez, et al., 2018).

In modern drug design, molecular docking is used to understand drug-receptor interactions and is widely used to predict drug binding to target proteins. The interaction between the drug molecule and the target protein will provide the drug molecule's binding affinity value and activity. The binding energy resulting from molecular docking is a critical parameter determining the stability between ligands and proteins. The interaction between ligand and receptor is often at the lowest energy. When the energy produced is low, the molecules are stable. It can be concluded that the lower the binding energy, the better the receptor-ligand interaction (Arwansyah, 2014). The initial stage of drug development, which is carried out by molecular docking, can also be done by predicting the absorption, distribution, metabolism, excretion, and toxicity (ADMET) of new candidate compounds. A good ADMET profile determines the success of drug development because development failure seen in the pharmacokinetic profile often occurs in clinical trials (Agus, et al., 2024)).

METHOD

Materials.

Chem Bio Draw Ultra v.12 program (CambridgeSoft), Chem Bio 3D Ultra v.12 program (CambridgeSoft), Molegro Virtual Docker 5.0 program (Molegro ApS), PubChem (https://pubchem.ncbi.nlm.nih.gov), Lipinski's rule of five http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp, ADMET predictions https://preadmet.webservice.bmdrc.org/ Protein Data Bank (https://www.rcsb.org/), 3D structure

of Angiotensin II receptor (4ZUD) dan β-Adrenergic receptor (6PS5).

Tools.

Lenovo Computer, Windows 10 Pro 64-bit Operating System, Processor Intel® Core™ i5-2.7GHz, 20.480MB RAM.

Method.

In this study, ten *Shorea laevis* ethanol extract compounds were molecular docked based on GC-MS results on the Angiotensin II receptor (4ZUD) and β-adrenergic receptor (6PS5), which were first carried out compound screening requirements based on Lipinski rules of five, and then pharmacokinetic predictions were carried out on the preadmit application, based on the protein data bank for the fit receptor using Molegro Virtual Docker 5.5. software.

Compound selection based on ADMET predictions.

Ten compounds contained in Shorea laevis were analyzed for the SMILES structure of bioactive compounds taken from the PubChem data source, then selected using ADMET predictions and referring to Lipinski's rule of five parameters. ADMET selection is carried out to predict compounds that do not have potential toxicity and have an excellent pharmacokinetic profile based on parameters: high gastrointestinal tract absorption, non-carcinogenic, non-mutagenic, colon adenocarcinoma (CaCo2), Human intestinal absorption (HIA), Plasma protein binding (PPB).

Prediction of physicochemical properties and evaluation of compound similarity.

Prediction of physicochemical properties in the form of Molecular weight (MW), Logarithm of the octanol-water partition coefficient (LogP), Hydrogen Bond Acceptors (HBA), Hydrogen Bond Donors (HBD), and molar refractivity (MR). Apart from that, Lipinski's rule of five is the primary basis for initial compound analysis before making other predictions. This is intended to evaluate the similarity of compounds with the characteristics of oral drugs that have biological activity in humans. All of Lipinski's conditions must be met, including (a) no more than five hydrogen bond donors and (b) no more than ten hydrogen bond acceptors, because the high number of hydrogen bonds can reduce the partition of molecules from the water-soluble phase into the lipid membrane bilayer for passive diffusion permeation, (c) after all, high molecular mass can reduce the concentration of compounds on the surface of the intestinal epithelium which results in reduced absorption, the molecular mass must be less than 500 Daltons, (d) the octanol-water partition coefficient (Log P) is no more than of five, because if more can result in poor absorption (Lipinski, 2004; Liu, *et al.,*2019).

Receptor structure analysis:

Angiotensin II (4ZUD) and β-Adrenergic (6PS5) receptors

The 3D structures of the Angiotensin II receptor (4ZUD), which is an enzyme inhibiting the activation of Angiotensin I to II, and the β-adrenergic receptor (6PS5) as a selective inhibitor enzyme of the β-1 receptor were obtained from the protein data bank (PDB, https://www.rcsb.org/) in *.pdb format, which is used in this research. The two receptors underwent docking validation for the best ligand selection process until one receptor was obtained with the lowest root mean squared deviation (RMSD), which met the requirements <2,00Å (Kroemer, 2007).

Molecular Docking

The docking process begins with drawing the 2D structure of the compound using the Chem Bio ultra v.12 program, then continues with drawing the 3D structure using the Chem Bio 3D ultra v.12 program, then saved in mol2 (*.mol2). The next stage is to carry out a docking process for the selected enzymes using the Molegro Virtual Docker (MVD) v.5.0 program. MVD is a program to predict interactions between ligands and receptors (proteins). The result that will be obtained is the rerank score (RS), which is the energy value required in the ligand-receptor interaction process so that from this value, the best compound can be predicted which has antihypertensive activity based on the Inhibition of Angiotensin II and β-adrenergic receptors. The ligand molecule that binds to the receptor will inhibit or block the function of the receptor so that the ligand will act as a drug or competitor for the receptor.

Cavities in the MVD algorithm are used to detect protein binding sites that have the potential to be active sites for binding to ligands (drugs). Screening for the most stable ligands will be combined with MM2 in a conformational search to produce stable ligand poses with the active sites of the Angiotensin II (4ZUD) and β-adrenergic (6PS5) receptor proteins among the prepared designs.

RESULTS AND DISCUSSION

This test was carried out to determine the pharmacological profile regarding the antihypertensive activity of the ethanol extract of bangkirai leaves. The process is to analyze compounds that have been tested using GC-MS in previous research (Fernandes & Maharini,

2018).

The results of compound analysis using GC-MS can be seen in Table I.

Table I. GC-MS Results of Bangkirai Leaves (*Shorea laevis* Ridl.) Ethanol Extract (Fernandes & Maharini, 2018)

No	Compounds Code	Compounds Name	Structure
1	U1	Decane	C10H22
2	U2	Benzene, 1,2,4-trimethyl	C9H12
3	U3	Benzene, 1,3,4-trimethyl	C9H12
4	U4	Benzene, 1,2,3,4-tetramethyl	C10H14
5	U5	Benzene, 1,2,4,5-tetramethyl	C10H14
6	U6	1,3-Cyclopentadiene, 1,2,3,4-tetramethyl-5-methylene	C10H14
7	U7	Pentasiloxane,1,1,3,3,5,5,7,7,9,9-decamethyl	C10H32O4Si5
8	U8	Colchicine,N-desacetyl-N-[4-hydroxy-3,5-dimethoxycinnamoyl]	C31H33NO9
9	U9	Benzeneacetic acid, 3-methoxy-4-[(trimethylsilyl)oxy], ethyl ester	C18H34O5Si3
10	U10	4H-1-Benzopyran-4-one, 2-(3,4-dimethoxy phenyl)-3,7-dimethoxy	C19H18O6

Pharmacokinetics and Toxicity Prediction.

To determine the antihypertensive activity of bangkirai leaves (Shorea laevis Ridl.) ethanol extract, it is necessary first to determine the receptors in the protein data center, which will then bind to the ligand. A total of 10 compounds in Table I above, previously identified using GC-MS, will be analyzed for their potential as anti-hypertension. The search for potential antihypertensive activity was tested on two selected receptors with different mechanisms of action, namely the Angiotensin II receptor (4ZUD) and the β-Adrenergic receptor (6PS5).

Identification of compounds in Table I that have the potential to act as antihypertensives, then the next stage is to determine the selection of receptors for angiotensin II and β-Adrenergic to carry out a docking process on the original ligand to determine the Root Mean Squared Deviation (RMSD) value, which serves to see validation.

Docking protocols. At this stage, there are two receptors that will undergo a docking process with the original ligand after selection. This aims to see the location of the active side of the compound in its cavity. The validation process is carried out by minimizing energy with MM2, and the next step is the docking stage with the receptor. The results of the docking stage consist of the MolDockScore result parameter, which shows the energy used during the docking process, and RMSD, which determines the deviation between the test ligand molecule and the reference ligand. The receptors chosen are Angiotensin II (4ZUD) and β-Adrenergic (6PS5) receptors. The next stage is screening based on Lipinski's Rule of Five predictions to obtain compounds that meet the requirements, as seen in Table II.

Table II. Compound screening results for Lipinski's Rule of Five Profile

Compounds Code	Parameters				
	Lipinski's Rule of Five				
	MM (Da)	H Bond Donor	H Bond Acceptors	Log P	MR
U1	142	0	0	4.146999	48.283985
U2	120	0	0	2.61186	40.652996
U3	120	0	0	2.61186	40.652996
U4	134	0	0	2.92028	45.389996
U5	134	0	0	2.92028	45.389992
U6	134	0	0	2.04948	46.129993
U7	268	0	0	6.937402	89.486961
U8	591	2	10	4.4923	157.26767
U9	286	0	4	2.138	79.0959778
U10	342	0	6	3.128899	90.254478

In screening, it can be seen that the test compound is screened first based on Lipinski's Rule of Five, which requires that a test compound is suitable for the docking process to be carried out. In testing the ADME profile for the 4ZUD receptor and 6PS5 receptor, four compounds were produced that met the requirements, while for the toxicity profile, ten compounds were produced that met the requirements for the 4ZUD and 6PS5 receptors.

These compounds were then tested to obtain Absorption and Distribution profiles, which can be seen in Table III. The results for compounds U4, U5, U6, and U8 had good profiles for both receptors. These compounds were then subjected to toxicity tests to determine whether there was mutagenic potential for cells or not based on the Ames-test method, and it was found that these potential compounds did not show mutagenic activity, which can be seen in Table IV for the 6PS5 and 4ZUD receptors.

Table III. Compounds screening for the Absorption and Distribution profiles of 6PS5 and 4ZUD Receptors

Compounds Code	Parameters			
	Absorption of 6PS5 & 4ZUD Receptor		**Distribution of 6PS5 & 4ZUD Receptor**	
	HIA (%)	**Caco2 (nm/sec)**	**PPB (%)**	**BBB**
U1	100.00	22.19	100.00	13.91
U2	100.00	23.46	100.00	4.17
U3	100.00	23.46	100.00	4.17
U4	100.00	23.43	100.00	6.06
U5	100.00	23.46	100.00	6.06
U6	100.00	23.12	100.00	7.08
U7	98.73	54.97	88.68	1.07
U8	95.73	35.14	87.67	0.05
U9	97.59	41.94	100.00	1.02
U10	98.44	49.86	81.79	0.01

Description: HIA: Human Intestinal Absorption; Caco2: Colon adenocarcinoma; PPB: Plasma Protein Binding; BBB: Blood Brain Barrier

Table IV. Profile of compounds screening results for Metabolism, Excretion, and Toxicity in 6PS5 and 4ZUD Receptors

Compounds Code	**Parameters**				
	Metabolism and Excretion of 6PS5 dan 4ZUD Receptors				**Toxicity**
	CYP2-C19 Inhibition	**CYP2-C9 Inhibition**	**CYP2-D6 Inhibition**	**CYP- 3A4 Inhibition**	***Ames-test***
U1	Inhibitor	Inhibitor	Non	Inhibitor	Negative
U2	Inhibitor	Inhibitor	Non	Inhibitor	Negative
U3	Inhibitor	Inhibitor	Non	Inhibitor	-
U4	Non	Inhibitor	Non	Inhibitor	Negative
U5	Non	Inhibitor	Non	Inhibitor	Negative
U6	Non	Inhibitor	Non	Inhibitor	Negative
U7	Inhibitor	Inhibitor	Non	Inhibitor	Negative
U8	Non	Non	Non	Inhibitor	Negative
U9	Inhibitor	Inhibitor	Non	Inhibitor	Negative
U10	Inhibitor	Inhibitor	Non	Inhibitor	Negative

Description: CYP: Cytochrome

Pharmacokinetic profiles can describe interactions between receptors and compounds, where this data is needed in the early stages of drug discovery. Pharmacokinetic data in the gastrointestinal tract is the initial stage in the discovery of new drugs (Daina, *et al.,* 2017) by

passive diffusion; apart from that, for bioavailability in test animals, the probability value is >10%, and the Caco2 parameter is used to determine the permeability of the compound (Martin, 2005).

The distribution prediction value at the brain barrier (BBB) in Table III shows that a compound can penetrate the blood-brain barrier; it can be predicted using preADMET with a BBB value >2.0 (high absorption to CNS); BBB value 0.1-2.0 (middle absorption to CNS); BBB value <0.1 (low absorption to CNS) (Ma, *et al.,* 2005). The BBB prediction value of the 10 test compounds shows that compounds U8 & U10 can penetrate the high blood-brain barrier (high absorption to CNS; compounds U7 and U9 can penetrate the middle blood-brain barrier (middle absorption to CNS), while compounds U1-U6 can penetrate the blood-brain barrier low (low absorption to CNS).

At the metabolism stage, enzyme inhibition was evaluated. It can be seen in Table IV that the predictions for compounds U1-U3, U7, U9, and U10 are CYP2C19 inhibitors, and all compounds except U8 are CYP2C9 enzyme inhibitors. Drugs that are CYP2C19 and CYP2C9 inhibitors are capable of increasing plasma protein concentrations and can cause side effects (Van, *et al.,* 2010; Foti & Wahlstrom, 2008). All compounds are non-inhibitors for CYP2-D6, where the CYP2D6 enzyme is responsible for drug metabolism, found in several tissues and mainly in the liver (Ali, *et al.,* 2013). All compounds are non-inhibitors of the CYP3A4 enzyme, where CYP3A4 is the main enzyme in the liver, which metabolizes the oxidation pathway in xenobiotic molecules, including drugs and poisons (Oyesakin, *et al.,* 2018).

To determine the nature of toxicity, a prediction was carried out using the Ames test method, which aims to determine whether or not there are mutagenic properties of a compound (Prasetiawati, *et al.,* 2021), and from the test results, none of the compounds have mutagenic potential. Next, a docking test process is carried out, which refers to Lipinski's rule of five as the main requirement for compounds to be tested where the reference result is the Rerank score value. The results of the Moldock score and hydrogen interactions with amino acids of the ligand-protein in the 6PS5 receptor can be seen in Table V, and for the 4ZUD receptor, it can be seen in Table VI.

Table V. Potential compounds of *Shorea laevis* against the 6PS5 receptor Docking results.

Compounds Code	Compounds	Rerank score	Moldock Score	Amino acids interaction (Hydrogen & steric bonds)
1	**Propranolol (Natural Ligand)**	-94.8742	-110.256	**Asp-113, Asn-312**
U1	Decane	-60.3642	-74.7272	-
U2	Benzene, 1,2,4-trimethyl	-45.8729	-53.8796	-
U3	Benzene, 1,3,4-trimethyl	-46.3216	-52.9361	-
U4	Benzene, 1,2,3,4-tetramethyl	-47.9791	-53.6279	-
U5	Benzene, 1,2,4,5-tetramethyl	-46.5919	-55.1948	-
U6	1,3-Cyclopentadiene, 1,2,3,4-tetramethyl-5-methylene	-53.6719	-63.2641	Thr-195
U7	Pentasiloxane,1,1,3,3,5,5,7,7, 9, 9-decamethyl	-91.8285	-111.747	Phe-193
U8	Colchicine,N-desacetyl-N-[4-hydroxy-3,5-dimethoxycinnamoyl]	-34.9225	-129.718	Tyr-316, Phe-193, His-93, Asp-113, Asn-312, Tyr-308, Lys-305, Ile-309
U9	Benzeneacetic acid, 3-methoxy-4-[(trimethylsilyl)oxy], ethyl ester	-82.7972	-108.575	Tyr-308, Tyr-316
U10	4H-1-Benzopyran-4-one, 2-(3,4-dimethoxy phenyl)-3,7-dimethoxy	-94.3865	-121.536	-

Table VI. Potential compounds of ethanol extract Shorea laevis leaves against the 4ZUD receptor Docking results

Compounds Code	Compounds	Rerank score	Moldock Score	Amino acids interaction (Hydrogen & steric bonds)
1	**Olmesartan (Natural Ligand)**	-114.618	-151.815	Thr-88, Ser-109
U1	Decane	-65.4223	-84.1916	Ile-38
U2	Benzene, 1,2,4-trimethyl	-44.2632	-57.8851	Leu-13, Phe-182, Lys-1047
U3	Benzene, 1,3,4-trimethyl	-31.6454	-53.6722	Leu-81
U4	Benzene, 1,2,3,4-tetramethyl	-44.0782	-57.9374	Phe-182, Lys-1047
U5	Benzene, 1,2,4,5-tetramethyl	-0.1525	-53.2154	Tyr-35, Leu-81, Ile-288
U6	1,3-Cyclopentadiene, 1,2,3,4-tetramethyl-5-methylene	-49.0557	-59.5813	Phe-182
U7	Pentasiloxane,1,1,3,3,5,5,7 ,7,9, 9-decamethyl	-65.2525	-87.3742	Tyr-35, Leu-81, Tyr-92, Lys-199, Asn-200, Gln-257, Pro-285, Asp-281
U8	Colchicine,N-desacetyl-N-[4-hydroxy-3,5-dimethoxycinnamoyl]	-116.063	-146.503	Ala-21, Tyr-92, Asp-281
U9	Benzeneacetic acid, 3-methoxy-4-[(trimethylsilyl)oxy], ethyl ester	-65.5726	-83.6828	Val-108, Trp-84
U10	4H-1-Benzopyran-4-one, 2-(3,4-dimethoxy phenyl)-3,7-dimethoxy	-68.9835	-89.4614	-

Refer to Tables V and VI, the test compound which has the most stable binding to the 6PS5 and 4ZUD receptors with propranolol and olmesartan ligands is the compound Colchicine,N-desacetyl-N-[4-hydroxy-3,5-dimethoxycinnamoyl] as indicated by a MolDockScore of -129.718 and a Rerank score of -34.9225 on the 6PS5 and the 4ZUD receptors are the MolDockScore is -146.503 and the Rerank score is -116.063.

The compound Colchicine,N-desacetyl-N-[4-hydroxy-3,5-dimethoxycinnamoyl] with the 6PS5 receptor has steric interactions and hydrogen bonds at the amino acids Tyr-316, Phe-193, His-93, Asp-113, Asn- 312, Tyr-308, Lys-305, Ile-309. In contrast, the 4ZUD receptor has steric interactions and hydrogen bonds on the amino acids Ala-21, Tyr-92, Asp-281.

The results of the docking interaction on the 6PS5 receptor can be seen in Figure 1.

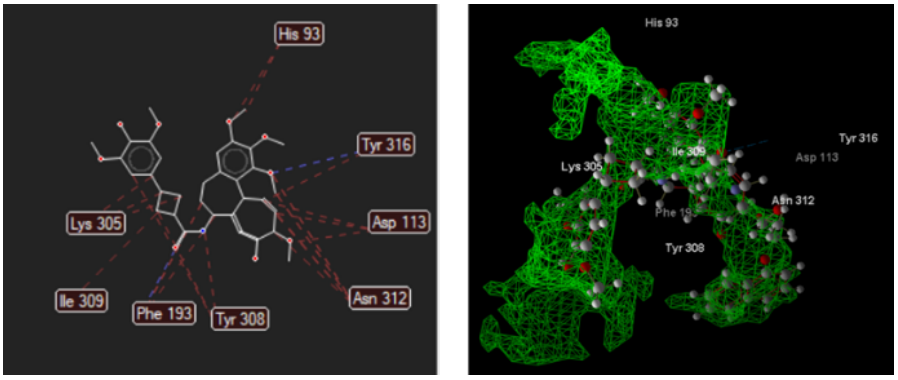

Figure 1. 2D & 3D interaction profile, between the compound Colchicine,N-desacetyl-N-[4-hydroxy-3,5-dimethoxycinnamoyl] (U8) with the natural ligand on the 6PS5 receptor, (a) 2D interaction of U8 compound, (b) 3D interaction, U8 compound in the same cavity as the natural ligand.

The results of the docking interaction on the 4ZUD receptor can be seen in Figure 2.

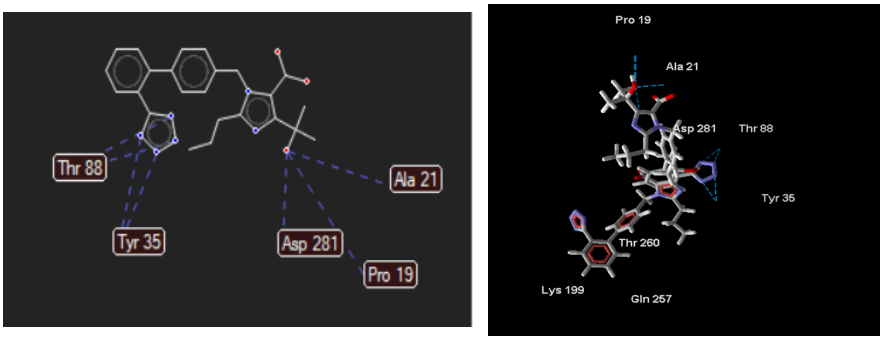

Figure 2. 2D & 3D interaction profile, between the compound Colchicine,N-desacetyl-N-[4-hydroxy-3,5-dimethoxycinnamoyl] (U8) with the natural ligand on the 6PS5 receptor, (a) 2D interaction of U8 compound, (b) 3D interaction, U8 compound in the same cavity as the natural ligand.

CONCLUSION

Based on the results of testing the antihypertensive activity profile of the bangkirai leaves (Shorea laevis Ridl.) ethanol extract in various interactions with the 6PS5 and 4ZUD receptors, it is known that the test compound-8 or Colchicine,N-desacetyl-N-[4-hydroxy-3,5-dimethoxycinnamoyl] has a good affinity close to the natural ligand, regarding the docking process it appears to have a low MolDockScore. It can also be seen that the hydrogen bond interactions of amino acids are Tyr, 316, Phe, 193 and steric bonds, namely Tyr-316, Phe-193, His-93, Asp-113, Asn-312, Tyr-308, Lys-305, Ile-309 for the 6PS5 receptor. Meanwhile, in the 4ZUD receptor, the amino acid hydrogen bond interactions are Tyr-35, Thr-88, Pro-19, Ala-21, Asp-281 and the steric bonds are Ala-21, Tyr-92, Asp-281. Apart from that, based on pharmacokinetic and toxicity predictions, it shows that the compound Colchicine,N-desacetyl-N-[4-hydroxy-3,5-dimethoxycinnamoyl], has a good pharmacokinetic profile, including HIA (95.73%), Caco2 (35.14 nm/sec) and PPB (87.67%). The toxicity profile shows negative results for non-mutagenic; it also gives negative results in the carcinogenic test, which includes genotoxic, nongenotoxic, and negative in the mutagenic test using the Ames test method. From the results of the tests that have been carried out, it can be concluded from several compounds in the ethanol extract of bangkirai leaves (Shorea laevis) that the compound Colchicine,N-desacetyl-N-[4-hydroxy-3,5-dimethoxycinnamoyl] has antihypertensive potential at the 6PS5 and 4ZUD receptors, which in turn can be tested in-vivo.

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