International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 16, Issue 2, 2024

Original Article

MOLECULAR DOCKING OF THE KERUING's (DIPTEROCARPUS) GENUS, SECONDARY METABOLITES OF THE *DIPTEROCARPACEAE* FAMILY'S AS ANTI-INFLAMMATION AGAINST CYCLOOXYGENASE-2 (COX-2)

ADHE SEPTA RYANT AGUS[1*], SISWANDONO[2], MARIA ELVINA TRESIA BUTAR-BUTAR[3], MUH. TAUFIQURRAHMAN[4], ANDRIAN FERNANDES[5], RIZKI MAHARANI[6]

[1]Department of Pharmacology, Study Program of Pharmacy, Dirgahayu School of Health Sciences, Samarinda, Indonesia. [2]Department of Medicinal Chemistry, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia. [3,4]Department of Pharmaceutics and Pharmaceuticals Technology, Study Program of Pharmacy, Dirgahayu School of Health Sciences, Samarinda, Indonesia. [5,6]Research Center for Biomass and Bioproducts, National Research and Innovation Agency, Bogor, Indonesia

*Corresponding author: Adhe Septa Ryant Agus; *Email: adheseptara@gmail.com

Received: 10 Nov 2023, Revised and Accepted: 30 Dec 2023

ABSTRACT

Objective: Kalimantan, Indonesia, has a tropical forest abundant in forest products. One of these products is the Dipterocarp tree, which includes the Keruing genus (Dipterocarpus). Dipterocarpus contains secondary metabolites that may be potential sources for new drug compounds. One of these metabolites has the potential to act as an anti-inflammatory agent. Based on pharmacophore modelling and molecular docking, this study used molecular docking to investigate the inhibitory mechanism and affinity of Dipterocarpus secondary metabolites on the 3N8Y inflammatory receptor.

Methods: The study involved multiple stages, such as preparing and optimizing the structure of the test compounds, constructing a 3D receptor structure of 3N8Y, validating the methodology, and performing energy docking simulations to analyze the interactions. From the study that has been done, the results for the test compounds were evaluated for their MolDockScore, Pharmacokinetic parameters (ADME), and toxicity.

Results: The results revealed that the oligomer resveratrol compound exhibited the lowest MolDockScore value of-104.7400, comparable to natural ligands. In addition to that, this method produces reliable outcomes through pharmacokinetic predictions such as HIA (88.4794%), Caco2 (5.1917 nm/sec), and PPB (100%). Furthermore, the toxicity profile exhibited negative results for mutagenic, non-mutagenic, and carcinogenic tests, including genotoxic and nongenotoxic substances.

Conclusion: The oligomeric resveratrol (3',5',4-trihidroksi-trans-stilben) compounds have potential as anti-inflammatory agents by acting on the 3N8Y receptor, which further needs to be tested *in vivo*.

Keywords: Keruing, Dipterocarpus, Anti-inflammatory, COX-2, Pharmacophore modelling, Molecular docking

DOI: https://dx.doi.org/10.22159/ijap.2024v16i2.49836 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

The Keruing plant is a member of the *Dipterocarpaceae* genus and has a large family widely distributed in Asia, especially Melanesia, including Indonesia, as a pandemic plant in Kalimantan. The *Dipterocarpaceae* plant family consists of 16 genera, namely Anisoptera, Anisoptera, Balanocarpus, Neobalanocarpus, Cotylelobium, Dipterocarpus, Doona, Dryobalanops, Hopea, Isoptera, Parashorea, Shorea, Stemonoporus, Upuna, Vateria, Vatica dan Vateriopsis, and has 600 species. Indonesia is home to nine of the 16 genera in the world. These genera are Anisoptera, Cotylelobium, Dipterocarpus, Dryobalanops, Hopea, Parashorea, Shorea, Upuna, and Vatica. The *Dipterocarpaceae* family has three primary genera: Shorea, with 150 species; Hopea, with 100 species; and Dipterocarpus, with 75 species. In Indonesia, these three genera are known as Meranti (Shorea), Merawan or Tengkawang or Damar Mata Kucing (Hopea), and Keruing (Dipterocarpus), respectively [1, 2].

Keruing, also known as *Dipterocarpus* in botanical terms, is a significant genus of *Dipterocarpaceae*. It is a type of wood widely used in the wood processing industry [3]. The use of non-timber forest products (HHBK), specifically Keruing oil, has many benefits. *Dipterocarpus tuberculatus* Roxb. is one empirical example of a plant used as an anti-inflammatory for creating aromatic, waterproof coatings and lithographic ink. The ethanol extract of *Dipterocarpus alatus* contains vaticaffinol, a compound that helps prevent and treat gout.

Additionally, the seeds of *Dipterocarpus zeylanicus* contain oleanolic acid, which has anti-filarial properties and can help release free radicals from the body [4, 5]. The Dipterocarpus genus, which belongs to the *Dipterocarpaceae* family, is the most prominent. However, to determine their pharmacological effects, many studies still need to be conducted on its secondary metabolites, particularly the phenolic compounds class. Secondary metabolites possess various effects, including antibacterial, antifungal, antioxidant, anti-inflammatory, cytotoxic, and hepatoprotective properties. After conducting a phytochemical analysis, it has been discovered that the *Dipterocarpaceae* plant family contains a wide range of secondary metabolites. These include phenol groups such as oligostilbenoids, flavonoids, phenylpropanoids, phenolic acid derivatives, and non-phenolic groups like triterpenoids [3, 6].

It seems that Dipterocarpus contains compounds that can act as an anti-inflammatory by inhibiting the Cyclooxygenase (COX) enzyme. This enzyme converts arachidonic acid into prostaglandin pain mediators (PGs). There are two types of COX isoenzyme: COX-1 and COX-2. COX-1 helps maintain the body's normal state, while COX-2 triggers inflammation [7]. To accomplish a task and alleviate pain and inflammation, NSAIDs need to inhibit COX-2. NSAIDs reduce the production of pain mediators, such as prostaglandins, responsible for causing inflammatory reactions [8].

The immune system can be activated by specific compounds, leading to an inflammatory response that can cause tissue damage. This process can be intensified in a cyclic process, increasing angiogenesis and promoting tumour growth and metastasis. In the body, prolonged exposure of this inflammatory process to ROS can cause an accumulation of oxidative damage to tissues. The peroxisome proliferator-activated receptors (PPAR) regulate inflammation and angiogenesis. They control the expression of various genes, such as COX-2, nitric oxide synthase, and vascular endothelial growth factor (VEGF) [9].

Medicinal chemistry plays a crucial role in discovering new drug compounds. It can accelerate drug discovery by changing how new

drugs are designed and discovered. One effective method used in medicinal chemistry is molecular docking. The method used by computational studies includes employing computer-aided software to carry out the protein-ligand simulations of drug molecules to a given target, which means molecular docking is widely used in drug discovery and drug design. It can be used to suppose the predominant binding models of a ligand with a protein of known three-dimensional structure, perform virtual screening on large libraries of compounds, rank the results according to their binding affinities, and propose structural hypotheses of how the ligands inhibit the target [10].

This method involves docking drug molecules with the receptors responsible for their activity [11]. Matching molecules in 3D space to analyze the interactions between drugs and their receptors is known as docking. The active side of the receptor is observed during this process, as it influences the pharmacological effects. Researchers have extensively studied the docking system to design compounds that affect the drug receptor mechanism, particularly regarding enzyme activity or Inhibition [12].

The first step in drug development involves molecular docking and predicting new compounds: Absorption, distribution, metabolism, Extraction, and toxicity (ADMET). A drug's success largely depends on its ADMET profile, as a poor pharmacokinetic profile can lead to development failure during clinical trials [11].

In this study molecular docking was used to investigate the inhibitory mechanism and affinity of Dipterocarpus secondary metabolites on the 3N8Y inflammatory receptor.

MATERIALS AND METHODS

Materials

Chem Bio Draw Ultra v.12 (CambridgeSoft) program, Chem Bio 3D Ultra v.12 (Cambridge Soft) program, Molegro Virtual Docker 5.0 (Molegro ApS) program, PubChem (https://pubchem.ncbi.nlm.nih.gov), Lipinski's rule of five http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp, Pharmacokinetics prediction https://preadmet.webservice.bmdrc.org/, Protein Data Bank (https://www.rcsb.org/), 3D structure of Cyclooxygenase-2 (COX-2) receptor.

Tools

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

Method

The study used Molegro Virtual Docker 5.5 software to perform molecular docking of 21 secondary metabolites from *Dipterocarpus* to the Cylooxygenase-2 (COX-2) receptor.

Pharmacokinetic screening on chosen compounds

Twenty-one Dipterocarpus secondary metabolites were analyzed for the SMILES structure of the bioactive compounds taken from the PubChem database. Based on Lipinski's rule of five, the compounds were evaluated for their acceptability as oral drugs, which is essential for drug-like pharmacokinetic profile in rational drug design. ADMET analysis also predicts the druggability of ligand molecules, which computes a pharmaceutical compound's absorption, distribution, metabolism, excretion, and toxicity potential within an organism [13]. They filtered the results using the ADMET prediction application and Lipinski's rule of five. The ADMET prediction selection process was used to identify unlikely toxic compounds with favourable pharmacokinetic profiles. This prediction was based on factors such as high absorption in the gastrointestinal tract, non-carcinogenicity, non-mutagenicity, compatibility with colon adenocarcinoma (CaCo2), human intestinal absorption (HIA), and plasma protein binding (PPB).

Compound similarity evaluation prediction of physicochemical properties

Physicochemical properties predictions include Molecular weight (MW), Logarithmic partition coefficient of octanol-water (LogP), Hydrogen Bond Acceptors (HBA), Hydrogen Bond Donors (HBD), and molar refractivity (MR). The analysis of initial compounds before making predictions is based on Lipinski's rule of five. This evaluation is intended to determine the similarity of compounds to oral drugs that have biological activity in humans. The activity like absorption had several criteria must be met: (a) the molecule must have no more than five hydrogen bond donors, (b) no more than ten hydrogen bond acceptors, as a high number of these bonds can hinder diffusion permease passive into the lipid bilayer membrane from the water-soluble phase, (c) the molecular mass should be less than 500 Dalton, as high molecular mass may lead to reduced absorption due to lower concentration of compounds on the surface of the intestinal epithelium, (d) the octanol-water partition coefficient (LogP) should not exceed five, as a higher value may result in poor absorption [13, 14].

The structure of the cyclooxygenase-2 (COX-2) receptor analyzing

The 3D structure of the Cyclooxygenase-2 (COX-2) receptor, which is the prostaglandin-endoperoxide synthase 2 (PTGS-2) enzyme used in this study, was obtained from the protein data bank (PDB, https://www.rcsb.org/) in *format. pdb. This study focused on 9 specific receptors known as Cyclooxygenase-2 (COX-2), namely: 3LN0, 3MQE, 3NTI, 3NTB, 3NTG, 3N8Y, 3QH0, 3Q7D, 3RR3. The best ligand selection process involved validating dockings from these receptors. The goal was to find one receptor with the lowest root mean squared deviation (RMSD) that met the requirements<2,00Å [15].

Molecular docking

The molecules that needed to be docked were illustrated in 2D molecular structures using the Chem Bio Ultra v.12 program. The data was first stored and used to create 3D structures using the Chem Bio 3D Ultra v.12 program. These structures were then saved in the mol2 format. (*. mol2). The next step is the Molegro Virtual Docked (MVD) v.5.0 computer program used for the docking process of chosen enzymes. The outcome will be the Rerank Score (RS) value that measures the energy needed for the interaction between the ligand and receptor. This value will help to predict the best compound with anti-inflammatory properties through COX-2 enzyme inhibition. The MVD program is designed to predict how ligands and receptors (proteins) will interact with each other. Ligand molecules attach to the receptor, causing the ligand to perform a drug-like function or act as a competitor to the receptor. The MVD algorithm utilized cavity detection to identify protein binding sites that could serve as active sites for ligand binding (drugs). The stable ligand screening process will be merged with MM2 during the conformational search stage to generate a stable ligand pose within the active site of the Cyclooxygenase-2 (COX-2) receptor from the prepared designs.

The parameters utilized during the docking process are:

Score:	MolDock Score (GRID)
Grid resolution:	0.30 Å
Algorithm:	MolDock SE
Number of run algorithms:	10
Max iterations:	1500
Max population size:	50
Energy thresholds pose generation:	100

RESULTS AND DISCUSSION

This study analyzed the secondary metabolites of Dipterocarpus to aid in predictive analysis. The compounds identified are listed in table 1.

Pharmacokinetics and toxicity prediction

Based on table 1 need to identify potential anti-inflammatory compounds, select Cyclooxygenase-2 (COX-2) receptors, and dock the original ligands to determine the Root Mean Squared Deviation (RMSD) value. This value will validate the docking protocol. Nine COX-2 receptors are processed with the original ligand to locate the active side within the cavity crystal structure.

To dock with the receptor, MM2 was used to minimize energy. The yield parameters included MolDockScore, representing the energy used during the docking process, and RMSD, which indicates the

deviation between the ligand molecule and the reference ligand. The best ligand, 3N8Y (table 2), was obtained from these receptors and had a valid RMSD value, the smallest among the other receptors at 0.59. This value is considered valid because the RMSD from the docking process with the original ligand must be<2.00Å [16]. Additionally, the receptor was utilized for docking Dipterocarpus compounds.

Once the receptor was validated to determine the ideal ligand for the docking process, the next step involved screening based on Lipinski's Rule of Five predictions. This prediction resulted in eight compounds that met the criteria. Four compounds were suitable based on their ADME profile, and three met the toxicity profile requirements. Table 3 displays Lipinski's Rule of Five results and absorption profile, while table 4 shows the distribution, metabolism, excretion, and toxicity profiles.

Table 1: The effectiveness of keruing (Dipterocarpus) compounds

No	Compound	Code	Compound Formula
1	Oligomer resveratrol	U1	3',5',4-trihidroksi-trans-stilben
2	Oligomer resveratrol	U2	Trans-2,3-diaril-2,3-dihydrobenzofuran
3	Monomer resveratrol	U3	Resveratrol-12-C-β-glukopiranosida
4	Monomer resveratrol	U4	Resveratrol-10-C-β-glukopiranosida
5	Monomer resveratrol	U5	Resveratrol-13-C-β-glukopiranosida
6	Dimer Resveratrol	U6	(-)-ε-viniferin
7	Dimer Resveratrol	U7	Skopoletin
8	Dimer Resveratrol	U8	Bergenin
9	Dimer Resveratrol	U9	4-O-metilgalocatecin
10	Dimer Resveratrol	U10	5-hidroksi-2-metoksi benzoate acid
11	Dimer Resveratrol	U11	Sinamat acid
12	Dimer Resveratrol	U12	β-Sitosterol
13	Dimer Resveratrol	U13	Betulinat acid
14	Dimer Resveratrol	U14	Laevifonol
15	Dimer Resveratrol	U15	Malibatol A
16	Dimer Resveratrol	U16	Malibatol B
17	Dimer Resveratrol	U17	Shoreafenol
18	Trimer resveratrol	U18	Distikol
19	Trimer resveratrol	U19	Kanalikulatol
20	Trimer resveratrol	U20	Diptoindonesin E
21	Trimer resveratrol	U21	Beta-bisabolene

Table 2: Docking protocol validation on COX-2 receptor

PDB ID	Mol dock score	RMSD (Å)
3LN0	-103.921	0.78
3MQE	-99.994	1.60
3NTI	-104.990	0.85
3NTB	-102.233	1.04
3NTG	-101.628	0.98
3N8Y	-109.575	0.59
3QH0	-107.520	4.65
3Q7D	-105.008	1.59
3RR3	-105.097	1.98

Table 3: The results of screening for Lipinski's rule of five and absorption profile

Code	Parameters						
	Lipinski's rule of five					Absorption	
	MM (Da)	Log P	HBD	HBA	MR	HIA (%)	Caco2 (nm/sec)
U1	228	2.9737	3	3	66.8063	88.4794	5.1917
U2	454	4.2312	5	6	122.8179	90.6368	18.3887
U3	312	-0.0531	5	6	77.1457	93.9235	0.2775
U4	328	-1.0487	5	9	71.9754	25.8388	18.0220
U5	320	1.5547	5	7	79.1749	70.2582	5.5143
U6	168	0.6747	2	4	40.9981	85.3699	19.9369
U7	148	1.7866	1	2	41.5492	97.8452	21.0342
U8	414	8.0248	1	1	128.2167	100	23.4070
U9	456	7.0895	2	3	132.6115	95.8390	22.6284
U10	628	3.6918	7	12	155.2006	73.5559	9.7425
U11	380	6.0304	2	3	113.3035	95.1121	41.8797
U12	392	-1.4048	8	9	91.5453	19.8317	7.4073
U13	392	-1.9248	6	9	89.7807	19.8358	11.4522
U14	392	-0.4178	6	9	90.2762	34.5444	13.8249
U15	468	3.7244	6	7	123.4557	86.5158	16.0072
U16	484	48.2271	7	8	387.5202	79.9682	13.1015
U17	466	3.8968	5	7	121.5249	89.5007	15.9874
U18	696	5.2597	9	10	181.3573	0	0
U19	696	5.1008	9	10	180.6943	87.5093	19.5973
U20	204	5.0353	0	0	68.9029	0	0
U21	904	9.5329	9	12	250.8675	100	23.1934

Note: MM: Molecular mass; LogP: Octanol/water coefficient partition logarithm; HBD: Hydrogen Bond Donors; HBA: Hydrogen Bond Acceptors; MR: Molecular refractivity, HIA: Human Intestinal Absorption; Caco2: Colon adenocarcinoma.

During the screening process, the test compound is evaluated for its compatibility with the docking process using Lipinski's Rule of Five as a prerequisite. Based on the results, it was discovered that compounds U1-U7 and U17 were suitable for docking. Subsequently, these compounds underwent ADME profile testing, revealing that U1, U5, U7, and U17 had favourable profiles. After creating the compounds, toxicity tests were conducted to determine their mutagenic potential using the Ames test. The results showed that U1, U5, and U7 had no mutagenic potential, indicating they were safe for cells.

Table 4: The results of screening for distribution, metabolism, excretion and toxicity profiles

Code	Parameters						
	Distribution		Metabolism and excretion				Toxicity
	PPB (%)	BBB	CYP2-C19 inhibition	CYP2-C9 inhibition	CYP2-D6 inhibition	CYP-3A4 inhibition	Ames test
U1	100	1.7381	Inhibitor	Inhibitor	Non	Inhibitor	Negative
U2	100	4.0797	Inhibitor	Inhibitor	Non	Inhibitor	Negative
U3	29.4183	0.644	Inhibitor	Inhibitor	Non	Non	Positive
U4	35.4854	0.1206	Inhibitor	Inhibitor	Non	Inhibitor	Negative
U5	100	0.3353	Inhibitor	Inhibitor	Non	Inhibitor	Negative
U6	79.1163	0.6269	Inhibitor	Inhibitor	Non	Non	Negative
U7	60.8525	1.8648	Non	Inhibitor	Non	Non	Negative
U8	100	25.7962	Non	Inhibitor	Non	Inhibitor	Negative
U9	100	7.1823	Inhibitor	Inhibitor	Non	Inhibitor	Negative
U10	100	0.0816	Non	Inhibitor	Non	Inhibitor	Negative
U11	100	7.5432	Inhibitor	Inhibitor	Non	Inhibitor	Negative
U12	88.4329	0.0428	Inhibitor	Inhibitor	Non	Inhibitor	Negative
U13	85.1521	0.0465	Inhibitor	Inhibitor	Non	Inhibitor	Negative
U14	95.5581	0.0624	Inhibitor	Inhibitor	Non	Inhibitor	Negative
U15	100	1.1178	Inhibitor	Inhibitor	Non	Inhibitor	Positive
U16	100	0.5837	Inhibitor	Inhibitor	Non	Inhibitor	Positive
U17	100	1.1502	Inhibitor	Inhibitor	Non	Inhibitor	Positive
U18	0	0	0	0	0	0	-
U19	100	2.4071	Inhibitor	Inhibitor	Non	Inhibitor	Positive
U20	0	0	0	0	0	0	-
U21	100	10.359	Inhibitor	Inhibitor	Non	Non	Negative

Note: PPB: Plasma protein binding; BBB: Blood brain barrier; CYP: Cytochrome

The pharmacokinetic profile is significant in ensuring the interaction of compounds with receptors in the body. It is proven by predictions of pharmacokinetic parameters in the early stages of drug discovery. The process of discovering new drugs can pay attention to the prediction of ADME parameters, including absorption through passive diffusion gastrointestinal tract [17] and the value of bioavailability as a probability>10% in experiments, as well as Caco2 permeability for a compound [18]. The predicted value of the BBB indicates that a compound can penetrate the blood-brain barrier by predicting using preADMET, namely the value of BBB>2.0 (high absorption to CNS); BBB value 0.1-2.0 (middle absorption to CNS); BBB<0.1 (low absorption to CNS) [19].

The predicted value for the BBB of the 19 test compounds showed that compounds U2, U8-U9, and U19-U21 were able to penetrate the high absorption to the CNS; compounds U1, U3-U7, and U15-U17 were able to penetrate the intermediate blood-brain barrier (middle absorption to CNS); furthermore compounds U10, U12-U14 were able to penetrate the low barrier (low absorption to CNS).

The parameters for predicting the metabolism of compounds U1-U6, U9, U11-U17, U19, and U21 are CYP2C19 inhibitors. All compounds are inhibitors of CYP2C9 enzymes and non-inhibitors of CYP2D6. Compounds U1-U2, U4-U5, and U8-U19 are inhibitors of the CYP3A4 enzyme, while U3, U6-U7, and U21 are non-inhibitors of the CYP3A4 enzyme. Drugs that are CYP2C19 and CYP2C9 inhibitors can increase plasma protein concentration and can cause side effects [20, 21]. CYP2D6 is also responsible for drug metabolism, is present in several tissues, and is most abundant in the liver [22]. CYP3A4 is the main enzyme in the liver that metabolizes the oxidation pathway in xenobiotics molecules, including drugs and poisons [23]. The toxicity test uses the Ames test parameters to know the compound's mutagenic properties [24]. Based on the prediction that U3, U15-U19 give favourable mutagenic properties while the other compounds do not have non-mutagenic properties.

Refer to Lipinski's rule of five, which is the main requirement for a compound to be subjected to a docking test, some potential secondary metabolite compounds were tested, and a Rerank score, Moldock score, and Hydrogen interaction with amino acids from protein ligands were produced which can be seen in table 5.

Table 5, accumulation of the results, shows that the bond between the oligomer resveratrol (3',5',4-trihidroksi-trans-stilben) (U1) and the 3N8Y receptor as a target is the most stable, as indicated by the MolDock score of-104.7400 and the Rerank score of-84.7760. Although this value is higher than the natural ligand (Diclofenac Sodium), the oligomeric resveratrol (U1) compound has more hydrogen bonds in the amino acids Tyr355, Arg120, Ala527, Trp387, and the steric bond of Val349.

The results of the docking interaction can also be seen in fig. 1 and 2 below.

Table 5: Docking results of dipterocarpus potential compounds on 3N8Y receptor

Code	Molecules	Rerank score	Moldock score	Amino acids interaction (Hydrogen and steric bond)
1	Diclofenac Sodium (natural ligand)	-87.7657	-109.5750	Tyr385, Val349, Ser530
U1	Resveratrol (Oligomer)	-84.7760	-104.7400	Tyr 355, Arg120, Val349, Ala527, Trp387
U2	(-)-E-viniferin	246.5770	-83.0803	Tyr355, Val116, Ala527, Val349, Leu534, Leu531, Ser530, Ile523, Phe518, Leu 384, Met522, Tyr385
U3	Scopoletin	-88.2394	-99.5932	Tyr385, Thr206
U4	Bergenin	-38.8950	-76.2859	Tyr385, Ser530, Val349, Tyr355, Ile523, Phe518, Trp387, Gly526, Phe381, Tyr348

Code	Molecules	Rerank score	Moldock score	Amino acids interaction (Hydrogen and steric bond)
U5	4-O-metilgalocatecin	-57.2204	-111.3710	Tyr355, Ala527, Gly526, Trp387, Met522, Ser530, Val116, Arg120
U6	5-hidroksi-2-metoksi benzoate acid	-77.9424	-86.3431	Tyr385, Thr206, Ala202, Ala199
U7	Sinamic acid	-56.4152	-76.2539	Tyr385, Ser530
U11	Trans-2,3-diaril-2,3-dihidrobenzofuran	-57.7191	-127.5050	His90,Pro86,Leu93, Val116, Arg120
U12	Resveratrol-12-C-β-glucopyranoside	-46.2397	-70.5834	Tyr385, Phe518, Met522, Ile523, Leu531, Arg120, Tyr355, Ala527, Ser353, Val349, Ser530
U13	Resveratrol-10-C-β-glucopyranoside	-44.5909	-84.9482	Tyr385, Leu531, Val349, Leu384, Tyr355, Ile523, Met522, Leu384, Trp387, Ser530, Gly526, Ala527
U14	Resveratrol-13-C-β-glucopyranoside	-24.8240	958.3300	Tyr355, Arg120, Val116, Leu359, Leu531, Val349, Ser530, Gly526, Ala527
U15	Malibatol A	171.8270	-79.4923	Tyr385, Ser530, Val349, Leu531, Ile345, Met113, Ala527, Tyr355, Ile523, Trp387, Leu384
U16	Malibatol B	173.8780	-88.4844	Tyr385, Ser530, Val349, Met113, Ile345, Leu531, Ala527, Tyr355, Ile523, Leu384, Trp387, Met522
U17	Shoreaphenol	194.9500	-94.2240	Tyr355, Val349, Met113, Leu359, Leu531, Ser530, Ala527, Gly526, Leu384, Leu352, Phe518, Ile523, Ser353

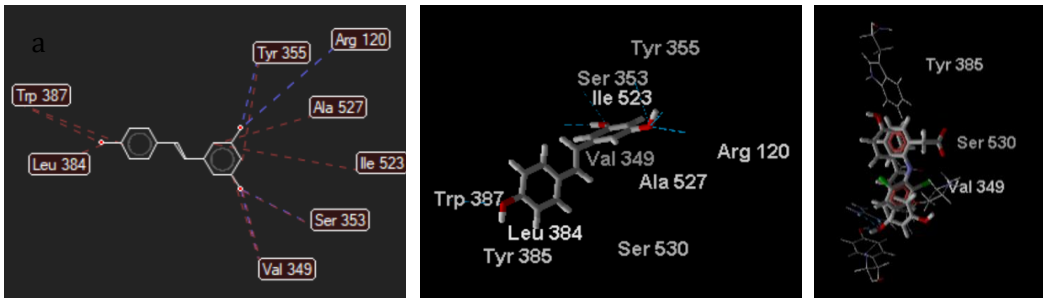

Fig. 1: 2D and 3D Interaction profile between resveratrol oligomer (U1) and natural ligand at 3N8Y receptor, (a) 2D interaction of resveratrol oligomer (U1), (b) 3D interaction of resveratrol oligomer (U1) and (c) interaction in the cavity the same between resveratrol oligomers (U1) and natural ligands

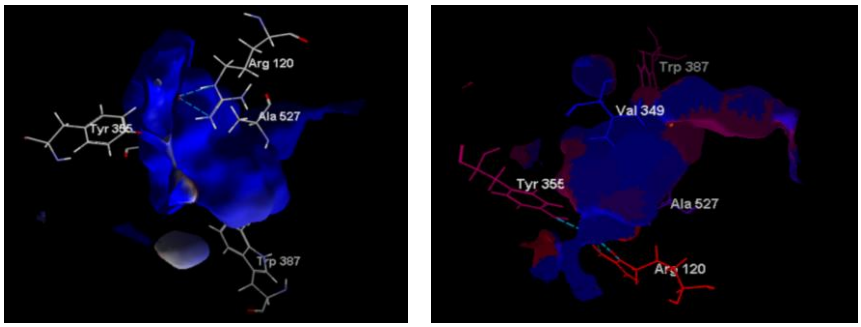

Fig. 2: Surfaces of residues with ligand based on the interactions of (a) the electricity bond and (b) the hydrophobicity bond of the resveratrol oligomer (U1) with the natural ligand on the 3N8Y receptor

In fig. 2(a), It can be explained that the electrostatic surface describes the relationship between the partial charge and the receptor bonds. Meanwhile, in fig. 2(b), it can be explained that the surface of the protein (residue) is hydrophobic, as shown on the blue surface of the residue. In contrast, the red surface indicates that the residue is hydrophilic.

DISCUSSION

Pharmacokinetics and toxicity prediction can be seen in table 1, which needs to identify potential anti-inflammatory compounds, select Cyclooxygenase-2 (COX-2) receptors, and dock the original ligands to determine the Root Mean Squared Deviation (RMSD) value. This value will validate the docking protocol. Nine COX-2 receptors are processed with the original ligand to locate the active side within the cavity crystal structure.

The best ligand, 3N8Y (table 2), was obtained from these receptors and had a valid RMSD value, the smallest among the other receptors at 0.59. This value is considered valid because the RMSD from the docking process with the original ligand must be<2.00Å [16]. Additionally, the receptor was utilized for docking Dipterocarpus compounds.

During the screening process, the test compound is evaluated for its compatibility with the docking process using Lipinski's Rule of Five as a prerequisite. Based on the results (table 3), it was discovered that compounds U1-U7 and U17 were suitable for docking. Subsequently, these compounds underwent ADME profile testing (table 4), revealing that U1, U5, U7, and U17 had favourable profiles. After creating the compounds, toxicity tests were conducted to determine their mutagenic potential using the Ames test. The results showed that U1, U5, and U7 had no mutagenic potential, indicating they were safe for cells.

The pharmacokinetic profile is significant in ensuring the interaction of compounds with receptors in the body. It is proven by predictions of pharmacokinetic parameters in the early stages of drug discovery. The process of discovering new drugs can pay attention to the prediction of ADME parameters, including absorption through

passive diffusion gastrointestinal tract [17] and the value of bioavailability as a probability>10% in experiments, as well as Caco2 permeability for a compound [18]. The predicted value of the BBB indicates that a compound can penetrate the blood-brain barrier by predicting using preADMET, namely the value of BBB>2.0 (high *absorption to CNS*); BBB value 0.1-2.0 (middle absorption to CNS); BBB<0.1 (low absorption to CNS) [19].

The predicted value for the BBB of the 19 test compounds showed that compounds U2, U8-U9, and U19-U21 were able to penetrate the high absorption to the CNS; compounds U1, U3-U7, and U15-U17 were able to penetrate the intermediate blood-brain barrier (middle absorption to CNS); furthermore compounds U10, U12-U14 were able to penetrate the low barrier (low absorption to CNS).

The parameters for predicting the metabolism of compounds U1-U6, U9, U11-U17, U19, and U21 are CYP2C19 inhibitors. All compounds are inhibitors of CYP2C9 enzymes and non-inhibitors of CYP2D6. Compounds U1-U2, U4-U5, and U8-U19 are inhibitors of the CYP3A4 enzyme, while U3, U6-U7, and U21 are non-inhibitors of the CYP3A4 enzyme. Drugs that are CYP2C19 and CYP2C9 inhibitors can increase plasma protein concentration and can cause side effects [20,21]. CYP2D6 is also responsible for drug metabolism, is present in several tissues, and is most abundant in the liver [22]. CYP3A4 is the main enzyme in the liver that metabolizes the oxidation pathway in xenobiotics molecules, including drugs and poisons [24]. The toxicity test uses the Ames test parameters to know the compound's mutagenic properties [25]. Based on the prediction that U3, U15-U19 give favourable mutagenic properties while the other compounds do not have non-mutagenic properties.

CONCLUSION

A secondary metabolite compound from Dipterocarpus that has anti-inflammatory potential through binding to the 3N8Y receptor is a resveratrol oligomeric compound because it has a good affinity close to that of natural ligands after a docking process as seen from the low MolDockScore value. The affinity can also be seen from the interaction of the hydrogen bonds between the amino acids Tyr 355, Arg120, Val349, Ala 527, Trp387, and the steric bond of Val349. In addition, based on the pharmacokinetic and toxicity predictions, it shows that resveratrol oligomers have good pharmacokinetics profiles, including HIA (88.4794%), Caco2 (5.1917 nm/sec), and PPB saw from the interaction of the hydrogen bonds between the amino acids Tyr 355, Arg120, Val349, Ala 527, Trp387, and the steric bond of Val349. In addition, based on the pharmacokinetic and toxicity predictions, It shows that resveratrol oligomers have good pharmacokinetics profiles, including HIA (88.4794%), Caco2 (5.1917 nm/sec), and PPB (100%). The toxicity profile, which shows negative results for non-mutagenic, also gives negative results in carcinogenic tests, which include genotoxic, nongenotoxic, and negative in mutagenic tests using the Ames test method. From these results, it can be concluded that some of the secondary metabolites of Dipterocarpus, particularly the oligomeric resveratrol (3',5',4-trihidroksi-trans-stilben) compounds, have the potential as anti-inflammatory agents by acting on the 3N8Y receptor, which further needs to be tested *in vivo*.

FUNDING

This research did not receive a specific grant from any funding agencies.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

REFERENCES

1. Talip N, Cutler DF, Ahmad Puad AS, Ismail BS, Ruzi AR, Ahmad Juhari AA. Diagnostic and systematic significance of petiole anatomy in the identification of Hopea species (Dipterocarpaceae). S Afr J Bot. 2017;111:111-25. doi: 10.1016/j.sajb.2017.03.008.
2. Muhtadi, Hakim EH, Juliawaty LD, Syah YM, Achmad SA, Latip J. Cytotoxic resveratrol oligomers from the tree bark of dipterocarpus hasseltii. Fitoterapia. 2006;77(7-8):550-5. doi: 10.1016/j.fitote.2006.07.004, PMID 17071016.
3. Muhtadi. Ilmu kimia tumbuhan keruing (Dipterocarpus) famili dipterocarpaceae. J Chem Inf Model. 2013;53(9):1689-99. PMID 25246403.
4. Saridan A. Keragaman jenis dipterokarpa dan potensi pohon penghasil minyak keruing di hutan dataran rendah kabupaten Berau, Kalimantan timur. Jur Pen Dip. 2012;6(2):75-84. doi: 10.20886/jped.2012.6.2.75-84.
5. Hesti LT, Merryana KA, Aswandi KCR, Muslimin I, Kurniawan A, Kusdi II. Bunga rampai pengembangan hasil hutan bukan kayu indonesia untuk mendukung sustainable development goals. IPB Press. 2019 Dec. p. 205-19.
6. De Oliveira MRD, Nabavi SF, Manayi A, Daglia M, Hajheydari Z, Nabavi SM. Resveratrol and the mitochondria: from triggering the intrinsic apoptotic pathway to inducing mitochondrial biogenesis, a mechanistic view. Biochim Biophys Acta. 2016 Apr;1860(4):727-45. doi: 10.1016/j.bbagen.2016.01.017, PMID 26802309.
7. Moussa N, Hassan A, Gharaghani S. Pharmacophore model, docking, QSAR, and molecular dynamics simulation studies of substituted cyclic imides and herbal medicines as COX-2 inhibitors. Heliyon. 2021;7(4):e06605. doi: 10.1016/j.heliyon.2021.e06605, PMID 33889764.
8. Walker C. Are all oral COX-2 selective inhibitors the same? A consideration of celecoxib, etoricoxib, and diclofenac. Int J Rheumatol. 2018;2018:1302835. doi: 10.1155/2018/1302835, PMID 30631366.
9. Castro AJGC, Castro L, Santos MSN, Faustino MGC, Pinheiro TS, Dore CMPG. Anti-inflammatory, anti-angiogenic and antioxidant activities of polysaccharide rich extract from fungi Caripia montagnei. Biomed Prev Nutr. 2013 Aug 9;4(2):121-9. doi: 10.1016/j.bionut.2013.08.004.
10. Mourad T, Alahmad S. A computational study of ciprofloxacin metabolites and some natural compounds against resistant methicillin staphylococcus aureus (MRSA). Int J Pharm Pharm Sci. 2022 Jun 16;14(8):22-8. doi: 10.22159/ijpps.2022v14i8.44560.
11. Lin ZM, Ma M, Li H, Qi Q, Liu YT, Yan YX. Topical administration of reversible SAHH inhibitor ameliorates imiquimod-induced psoriasis-like skin lesions in mice via suppression of TNF-α/IFN-γ-induced inflammatory response in keratinocytes and T cell-derived IL-17. Pharmacol Res. 2018;129:443-52. doi: 10.1016/j.phrs.2017.11.012, PMID 29155016.
12. Pratoko DK. Molecular docking senyawa fitokimia piper longum (L.) terhadap reseptor siklooksigenase-2 (COX-2) sebagai antiinflamasi. J Chem Program. 2019 Dec 13;5(1):31-6. doi: 10.35799/cp.5.1.2012.651.
13. Mathew C, Lal N, Lakhsmi S, Aswathy TR, Varkey J. Antioxidant, anticancer and molecular docking studies of novel 5-benzylidene substituted rhodanine derivatives. Int J Pharm Pharm Sci. 2023 May 17;15(7):7-19. doi: 10.22159/ijpps.2023v15i7.47421.
14. Lipinski CA. Lead- and drug-like compounds: the rule-of-five revolution. Drug Discov Today Technol. 2004 Dec;1(4):337-41. doi: 10.1016/j.ddtec.2004.11.007, PMID 24981612.
15. Liu YY, Feng XY, Jia WQ, Jing Z, Xu WR, Cheng XC. Identification of novel PI3Kδ inhibitors by docking, ADMET prediction and molecular dynamics simulations. Comput Biol Chem. 2019;78:190-204. doi: 10.1016/j.compbiolchem.2018.12.002, PMID 30557817.
16. Kroemer RT. Structure-based drug design: docking and scoring. Curr Protein Pept Sci. 2007;8(4):312-28. doi: 10.2174/138920307781369382, PMID 17696866.
17. Kimia Komputasi PH. Yogyakarta Pelajar P. editor. Vol. 1.; 2012.
18. Daina A, Michielin O, Zoete V. Swiss ADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017 Mar 3;7:42717. doi: 10.1038/srep42717, PMID 28256516.
19. Martin YC. A bioavailability score. J Med Chem. 2005 Apr 5;48(9):3164-70. doi: 10.1021/jm0492002, PMID 15857122.
20. Ma XL, Chen C, Yang J. Predictive model of blood-brain barrier penetration of organic compounds. Acta Pharmacol Sin. 2005;26(4):500-12. doi: 10.1111/j.1745-7254.2005.00068.x. PMID 15780201.

21. Van Booven D, Marsh S, McLeod H, Carrillo MW, Sangkuhl K, Klein TE. Cytochrome P450 2C9-CYP2C9. Pharmacogenet Genomics. 2010 Apr;20(4):277-81. doi: 10.1097/FPC.0b013e3283349e84, PMID 20150829.
22. Foti RS, Wahlstrom JL. CYP2C19 inhibition: the impact of substrate probe selection on *in vitro* inhibition profiles. Drug Metab Dispos. 2008;36(3):523-8. doi: 10.1124/dmd.107.019265, PMID 18048485.
23. Ali S, Mouton CD, Jabeen S, Zeng Q, Galloway G, Mendelson J. Suicide, Depression and CYP2D6: how are they linked? Curr Psychiatry. 2013 May;12(5):16-9.
24. Oyesakin YM, George DE, Fadare RY, Idris AY, Fadare OA. Molecular docking and *in silico* ADME prediction of substituted (E)-4-styryl-7,8-dihydroquinazolin-5(6H)-ones and 5-(E)-styryl pyrimidine[4,5-dypyrimidine-2,4(1H,3H)-diones as potential SERT inhibitors and antidepressants. Am J Pharmacol Sci. 2018;6(1):25-32. doi: 10.12691/ajps-6-1-5.
25. Prasetiawati R, Suherman M, Permana B, Rahmawati R. Molecular docking study of anthocyanidin compounds against epidermal growth factor receptor (EGFR) as anti-lung cancer. Indonesian J Pharm Sci Technol. 2021;8(1):8-20. doi: 10.24198/ijpst.v8i1.29872.