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Research

Molecular Docking Investigation of *Muntingia calabura* L. Bioactive Compounds as Estrogen Receptor-α (ER-α) Inhibitors for Anticancer Therapy

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Abstract:
Introduction — Cancer is one of the leading causes of death in the world and its development is related to genetic changes and dysregulation of cellular signaling pathways. Kersen leaves (*Muntingia calabura* L.) are known to contain various bioactive compounds that have the potential to be natural anticancer agents. This study aims to evaluate the anticancer potential of kersen leaf bioactive compounds against Estrogen Receptor-α (ER-α) receptors through an in silico approach.
Methods — The study was conducted using PASS Online for prediction of biological activity, SwissADME for drug-likeness evaluation based on Lipinski's Rule of Five, molecular docking using PyRx AutoDock against ER-α receptors, and ADMET analysis using PreADMET and Toxtree.
Results — A total of 11 bioactive compounds were successfully identified from Kersen leaves. The results of PASS Online showed that all compounds had potential anticancer activity with a higher Pa value than Pi. Drug-likeness tests showed 8 of the 11 compounds met the Lipinski criteria. The results of molecular docking showed that 3'-Hydroxydaidzein (MC9) had the best binding affinity to ER-α receptors with a binding affinity value of −8.7 kcal/mol, lower than N-acetylcysteine (−6.6 kcal/mol). ADMET analysis showed that MC9 had high intestinal absorption (93.604%), good permeability, and was neither carcinogenic nor mutagenic in nature.
Conclusions — The compound 3'-Hydroxydaidzein (MC9) has the potential to be a candidate for natural anticancer agents through ER-α receptor inhibition because it exhibits a strong binding affinity, meets drug-likeness criteria, and has a good pharmacokinetic and safety profile.

Keywords: *Muntingia calabura* L., anticancer, molecular docking, Estrogen Receptor-α (ER-α).

1. Introduction

Cancer is a disease caused by abnormal cell growth in body tissues. Cancer cells develop very rapidly, uncontrollably, and continue to divide which will then enter the surrounding tissues and will continue to spread through blood tissues, binding, and attacking important organs in the body [1]. Cancer Ovaries are tumors that originate from malignant ovarian cells. Malignant tumors or

cancer are the abnormal growth of new cells that can invade parts of the body and spread to other organs. Malignant diseases are increasing every year, especially ovarian malignant diseases [2].

In Indonesia, out of 234,511 deaths caused by cancer in women, ovarian cancer ranks 7th with 4.1% of cases, after breast cancer, cervical cancer and colorectal cancer by Globocan 2021. In 2017 to 2019 it was 0.07%, 0.10%, and 0.14%, respectively. According to Kadir, based on data from the Global Burden of Cancer Study, as of June 2021, the prevalence of cancer patients in Indonesia reached 0.13% of the total Indonesian population. In 2022 in Indonesia, around 25-50% of deaths of women of childbearing age are caused by cysts of 2 Ovaries [3]. Besides, ovarian cancer is known as a silent killer, usually in the early stages there are no clinical symptoms. Although the exact cause of ovarian cancer is not yet known, previous studies have reported that several things can increase the likelihood of developing ovarian cancer, namely genetic mutations, older age, premature menarche, and women who have not yet given birth. One alternative so that cancer does not develop in the body is the administration of antioxidants [4].

Antioxidants play a role in capturing free radicals so that cancer cannot develop, both at the initiation, promotion and progression stages. Phytochemicals contain antioxidants that function as chemo preventive and curative which as anticancer, can help chemotherapy agents in forming pro-oxidant effects, so that cancer cell death is increasing and cancer cell proliferation can be inhibited [5]. One of the exogenous antioxidants that is recommended as a form of treatment, is N-acetylcysteine (NAC). NAC has been recognized to have a protective effect against oxidants, even if its bioavailability is not fully administered orally. High-dose oral NAC can be used in modulating inflammation, increasing glutathione levels, and lowering elastase activity [6].

A pharmacological approach in the prevention of genetic damage due to oxidative stress can be carried out through the administration of antimutagenic compounds, one of which is N-acetylcysteine (N-acetylcysteine, NAC). N-acetylcysteine acts as an antioxidant by increasing intracellular glutathione levels so that it is able to reduce cell damage due to free radicals. Although effective, the long-term use of synthetic drugs has the potential to cause certain side effects. Therefore, the search for natural antimutagenic sources is one of the alternatives that need to be developed. One of the plants that has the potential to be an antimutagenic agent is kersen or cherries or commonly called Jamaican cherry (*Muntingia calabura* L.) [7].

Cherries *(Muntingia calabura* L.) is a plant that has the potential as an antioxidant. Kersen leaf extract contains active components such as flavonoids, saponins, and tannins that have the highest content when extracted using methanol and ethanol solvents. Scientifically, it has been proven that kersen leaves have a wide range of pharmacological activities such as antioxidant, antiulcer, antipyretic, anti-inflammatory, antiproliferative, and antibacterial [8].

Based on previous research, it is explained that secondary metabolites such as flavonoids and phenols are antioxidants and have the ability to capture free radicals. The content of flavonoid and phenol compounds in kersen (*Muntingia calabura* L.) in addition to being efficacious as an antioxidant can also be used as sunscreen. One way to protect the skin from the sun's radiation is to use sunscreen [8]. Natural compounds contained in *Muntingia calabura* L. has the potential to be developed as an anticancer agent because it contains a variety of bioactive compounds, such as flavonoids and phenolic compounds, which are known to ward off free radicals and protect DNA from damage that can trigger mutations. Antimutagenic activity is important because genetic mutations are one of the factors that play a role in the development of various diseases, including cancer. Compared to synthetic compounds, compounds derived from natural materials generally have a better level of safety and a lower risk of side effects. Therefore, *Muntingia calabura* L. was

chosen as the object of the study to evaluate the potential of its bioactive compound as an antimutagenic agent through the molecular docking [1].

Molecular docking is a computational method used to predict the interaction between ligands and target proteins. This method is widely used in drug discovery because it is more efficient in terms of time and cost than experimental methods. Evaluation of docking results is based on the value affinity and similarity of amino acid residues interacting with the original ligand. The lower the value affinity, the stronger and more stable the interaction formed between the ligand and the receptor [9]. Based on this description, this study aims to evaluate the potential of bioactive compounds contained in *Muntingia calabura* L. as an anticancer agent through its interaction with the target protein Estrogen Receptor-α (ER-α) using the molecular docking. In addition, ADMET analysis was performed to predict the pharmacokinetic characteristics and safety profile of the compound being studied.

2. Method

2.1 Research location and time

This research will be conducted in May-July at the Biomedical Science Undergraduate Study Program, Faculty of Health Technology, Megarezky University, Makassar.

2.2 Tools and Materials

This research was carried out using a computer device in the form of a Lenovo IdeaPad Slim 3 running a 64-bit version of the Windows 10 operating system, supported by an Intel® Core™ i5-8265U processor, 8 GB of primary memory (RAM), and an AMD Radeon™ 530 Series graphics card. The process of data analysis and processing is carried out by utilizing several software and *Hosted by Snoop T*, i.e. ChemDraw Professional 17.1 for the creation of compound chemical structures, PyMOL 2.6 for protein preparation and visualization, PyRx for simulation *Molecular Docking*, and BIOVIA Discovery Studio 2021 for the analysis and visualization of ligand–receptor interactions. The research materials used include alpha-lasophoxyphene Estrogen Receptors as protein targets, as well as bioactive compounds derived from plants *Muntingia calabura* obtained through the KNApSAcK database. All data used in this study were obtained by *in silico* from online sources that have been validated and widely used in bioinformatics research and computational drug discovery.

2.3 Working Procedure

First of all, compound prediction was conducted. Bioactive compound data is collected from the KNApSAcK (https://www.knapsackfamily.com/knapsack_core/top.php) database, which contains information about secondary metabolite compounds from various biological sources. Furthermore, the prediction of biological activity of these compounds was carried out using the PASS Online (Prediction of Activity Spectra for Substances) web server which can be accessed through https://way2drug.com/PassOnline/predict.php. Prediction is made by evaluating the parameters Pa (Probability of Activity) and Pi (Probability of Inactivity), which are used to estimate the likelihood that a compound exhibits a particular biological activity.

Second phase is the ligand preparation stage is carried out by downloading the three-dimensional (3D) structure of the target compound from the PubChem database which can be accessed through the PubChem website. The ligand structure is downloaded in *Structure Data File* (SDF) format, which contains atomic coordinate information and molecular geometry. Next, the ligands undergo an optimization or energy minimization process to obtain a more thermodynamically stable conformation. After the minimization process is complete, the optimization result structure is stored in *.pdb* (Protein Data Bank) format so that it can be used in the next stage of analysis.

Third, a drug-likeness *analysis* was performed to predict the feasibility of compounds as oral drug

candidates based on their physicochemical properties. The initial stage of analysis was carried out by drawing the two-dimensional (2D) structure of each ligand using the ChemDraw Ultra 12.0 software. The structure that has been created is then analyzed using the SwissADME server available on SwissADME (http://www.swissadme.ch/index.php). The evaluation was carried out based on Lipinski's Rule of Five parameters, which included a molecular weight of ≤ 500 Da, a LogP value of ≤ 5, the number of hydrogen bond donors ≤ 5, and the number of hydrogen bond acceptors ≤ 10. Compounds that meet these criteria are predicted to have a better chance of demonstrating optimal oral bioavailability and absorption.

Fourth, receptor preparation was conducted. The structure of the target protein was obtained through a database available on the PubChem website (http://ncbi.nlm.nih.gov) and used as a receptor in in silico studies. The protein preparation stage is carried out to produce a receptor structure that is ready to be used in the molecular docking process. The three-dimensional (3D) structure of proteins is processed using PyMOL software by removing water molecules, solvents, and residues or other molecules that do not play a role in ligand binding interactions. This process of cleaning the structure aims to improve the accuracy of predicting the interaction between ligands and receptors. Once the preparation is complete, the purified protein structure is stored in the PDBQT (Protein Data Bank, Partial Charge, and Atom Type) format, which is the standard format used in docking software such as AutoDock to define the atomic type and partial charge of proteins.

Fifth, a molecular docking simulation was performed using PyRx AutoDock software to predict the affinity and interaction patterns between ligands and target receptors. Before docking the test, ligands and comparator ligands is carried out, redocking between the receptor and the native ligand (C3D) is carried out as a method validation stage. This validation aims to ensure that the docking parameters used are able to accurately reproduce the binding position of the native ligands at the active sites of the protein. Next, the entire ligand is docked on the target receptor using the same parameters. The docking results were evaluated based on the binding affinity value (kcal/mol), the type of interaction formed between ligands and receptors, and the identification of amino acid residues that play a role in the binding process.

Sixth stage is data analysis and validation of simulation results. The ligand-receptor complex obtained from the molecular docking results was visualized using the BIOVIA Discovery Studio Visualizer 2021 software. The analysis was carried out through 2D and 3D representations to evaluate the characteristics of the molecular interactions formed between ligands and target proteins. An ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction was performed to evaluate the pharmacokinetic characteristics and safety of test compounds in silico. The analysis was performed using the PreADMET web server and Toxtree software. The prepared compound file is uploaded into the *ADME Prediction* and Toxicity Prediction modules in PreADMET to obtain various prediction parameters. The parameters evaluated included the %HIA value as an indicator of the absorption ability of the human intestine, the permeability of Caco-2 to predict oral absorption, PPB to estimate the level of binding of compounds with plasma proteins, and BBB to assess the ability of compounds to penetrate the blood barrier of the brain.

3. Results

3.1 Prediction of Compound Potential

The initial screening step was performed to determine the predicted biological activity of the bioactive compounds identified from *Muntingia calabura* L. using PASS Online. The analysis focused on the Probability of Activity (Pa) and Probability of Inactivity (Pi) values for each compound. A higher Pa value relative to Pi indicates that the compound is more likely to exhibit the predicted biological activity and therefore provides a basis for selecting compounds for subsequent computational evaluation (see Table 1).

Table 1. Compound Pa and Pi Values *Mangifera indica* L.

Compound Name	Formula	Pa Value	Pi Value	SMILE
8,3'-Dihydroxy-7,4',5'-trimethoxyflavone (MC1)	C18H16O 7	0,940	0,001	COC1=C(C2=C(C=C1)C(=O)C=C(O2)C3=CC(=C(C(=C3)OC)OC)O)O
3'-Hydroxy-7,8,4',5'-tetramethoxyflavone (MC2)	C19H18O 7	0,940	0,001	COC1=C(C2=C(C=C1)C(=O)C=C(O2)C3=CC(=C(C(=C3)OC)OC)O)OC
7,8,3',4',5'-Pentamethoxyflavone (MC3)	C20H20O 7	0,892	0,002	COC1=C(C2=C(C=C1)C(=O)C=C(O2)C3=CC(=C(C(=C3)OC)OC)OC
Kaempferol 7-(6''-p-coumarylglucoside (MC4)	C30H26O 13	0,795	0,004	C1=CC(=CC=C1/C=C/C(=O)OCC2[C@H]([C@@H](C([C@@H](O2)OC3=CC(=C4C(=C3)OC(=C(C4=O)O)C5=CC=C(C=C5)O)O)O)O)O
Isoliquiritigenin (MC6)	C15H12O 4	0,759	0,005	C1=CC(=CC=C1/C=C/C(=O)C2=C(C=C(C=C2)O)O)O
Hiravanone (MC7)	C26H30O 6	0,457	0,018	CC(=CCC1=C(C(=C2C(=C1O)C(=O)CC(O2)C3=CC(=C(C=C3)O)OC)CC=C(C)C)O)C
5,7,3',4'-Tetrahydroxy-6,8-di-C-prenylflavanone (MC8)	C25H28O 6	0,463	0,017	CC(C)=CCc1c(O)c(CC=C(C)C)c2c(c1O)C(=O)CC(c1ccc(O)c(O)c1)O2
3'-Hydroxy Daidzein (MC9)	C15H10O 5	0,866	0,003	O=c1c(-c2ccc(O)c(O)c2)coc2cc(O)ccc12
(2R,3R)-3,5,8-Trihydroxy-7-methoxyflavanone (MC10)	C16H14O 6	0,870	0,003	COc1cc(O)c2c(c1O)O[C@H](c1ccccc1)[C@@H](O) C2=O
2,3-Dihydroxy3',4,4',5'-tetramethoxydi hydrochalcone (MC11)	C19H22O 7	0,561	0,012	Oc1ccc(CCC(=O)c2cc(OC)c(OC)c2)c(O)c1O
3',4',5',7,8-Pentamethoxyflavan(MC13)	C20H24O 6	0,608	0,010	COc1cc([C@@H]2CCc3ccc(OC)c(OC)c3O2)cc(OC)c 1OC

3.2 Druglikeness Test

Following the biological activity screening, the candidate compounds were evaluated for drug-likeness to assess whether their physicochemical characteristics were compatible with the general requirements for orally administered drug candidates. The assessment considered molecular mass, LogP, hydrogen-bond donors (HBD), hydrogen-bond acceptors (HBA), and molar refractivity (MR). The resulting parameters provide an early indication of the compounds' physicochemical suitability before molecular docking and pharmacokinetic analysis (see Table 2).

Table 2. Druglikeness test *Mutingia calabura* L.

Compound Name	Mass	Log P	HBD	HBA	MR
8,3'-Dihydroxy-7,4',5'-trimethoxyflavone (MC1)	344.32	1.59	2	7	91.44
3'-Hydroxy-7,8,4',5'-tetramethoxyflavone (MC2)	358.34	1.92	1	7	95.91
7,8,3',4',5'-Pentamethoxyflavone (MC3)	372.37	2.25	0	7	100.38
Kaempferol 7-(6''-p-coumarylglucoside (MC4)	594.52	1.89	7	13	149.51
Isoliquiritigenin (MC6)	256.25	3.18	3	4	72.76
Hiravanone (MC7)	438.51	6.21	3	6	125.50
5,7,3',4'-Tetrahydroxy-6,8-di-C-prenylflavanone (MC8)	424.49	5.89	4	6	121.03
3'-Hydroxy Daidzein (MC9)	270.24	1.33	3	5	73.99
(2R,3R)-3,5,8-Trihydroxy-7-methoxyflavanone (MC10)	302.28	2.16	3	6	77.20
2,3-Dihydroxy-3',4,4',5'-tetramethoxydihydrochalcone (MC11)	362.37	2.67	2	7	95.94
3',4',5',7,8-Pentamethoxyflavan(MC13)	360.40	3.67	0	6	97.54

3.3 Molecular Docking Table

Molecular docking was subsequently performed to characterize the potential binding of the selected bioactive compounds to the Estrogen Receptor-α (ER-α) target. The docking results were assessed using binding affinity and RMSD values, together with the amino acid residues and interaction types observed in the ligand–receptor complexes. The native C3D ligand was included as a reference for comparison, while N-acetylcysteine was used as the comparator compound. The complete docking results are summarized in Table 3.

Table 3. Results of complete molecular docking

No.	Compound Code	Binding Affinity	RSMD	Amino Acid Residues	Types of Bonds
1	C3D ligand	-6,5	0	ARG515, SER456	Conventional Hydrogen Bond
				LEU511, LEU500, ARG515	Pi-Alkyl
				LEU511, LEU500	Alkyl
2	2,3-Dihydroxy-3',4,4',5 Tetramethoxydihydroc	-6,5	0	ARG515, GLU385, SER456, ASN455	Conventional Hydrogen Bond
				TYR459, ASP480, THR483	Carbon Hydrogen Bond
				LEU508, ILE451	Alkyl
				LEU479, LEU511, HIS476	Pi-Alkyl
3	3- Hydroxy daidzein	-8,7	0	ARG394, GLU353	Conventional Hydrogen Bond
				ARG394	Unfavorable Donor
				MET421	Pi-Sulfur
				PHE404	Pi-Pi T-Shaped
				LEU525, ILE424, ALA350, LEU346, LEU391, LEU387, LEU349	Pi-Alkyl
4	3'-Hydroxy-7,8,4',5'-Tetramethoxyflavone	-6,7	0	ASN439	Conventional Hydrogen Bond

				ARG503	Unfavorable Donor
				ARG503	Pi-Cation
				GLU443, GLU44	Pi-Anion
				LEU495	Amide-Pi Staked
				ALA493, LEU495, LEU489	Pi-Alkyl
5	5, 7, 3', 4'-Tetrahydroxy-6,8-Di-C-Prenylflavanone	-8,0	0	ASP351, TYR526	Conventional Hydrogen Bond
				PRO535	Carbon Hydrogen Bond
				LYS529	Pi-Cation
				LEU536	Pi-Donor Hydrogen Bond
				VAL533, PRO535	Alkyl
				LEU525	Pi-Alkyl
6	7,8,4,5-Pentamethoxyflavone	-6,7	0	THR483, SER512, HIS476	Conventional Hydrogen Bond
				LEU509, LEU506, ILE542	Alkyl
				LEU508, ILE451, LEU479, LEU511	Pi-Alkyl
7	Hiravanone	-8,0	0	LEU536, LEU529	Conventional Hydrogen Bond
				LEU539	Pi-Sigma
				MET522, LEU536, LEU525, MET528, VAL534, VAL533	Alkyl
				LEU536, TRP383	Pi-Alkyl
8	Isoliquiritigenin	-6,3	O	GLU444, GLN441	Conventional Hydrogen Bond
				GLU444	Pi-Anion
				ALA493	Pi-Sigma
				LEU489	Amide-Pi-Stacked
				LYS	Pi-Alkyl
9	Kaempferol 7-(6''-P-Coumarylglucoside	-7,0	0	ASN455, ARG515, LEU479, THR483, TYR459	Conventional Hydrogen Bond
				LEU508,	Pi-Sigma
				LEU508, LEU479	Pi-Alkyl
10	3,4,5,7,8 Pentamotxy Flavan	-6,5	0	ARG503	Conventional Hydrogen Bond
				LEU495	Pi-Sigma
				LEU495, ALA493	Alkyl
				ALA493, LEU489	Pi-Alkyl
11	8,3'-Dihydroxy-7,4',5'-Trimethoxyflavone	-7,0	0	LEU525	Carbon Hydrogen Bond
				LYS529	Pi-Cation
				LEU536	Pi-Donor Hydrogen Bond
				LEU525	Pi-Sigma

				MET522	Pi-Sulfur
				TRP383	Pi-Pi Staked
				TRP526	Pi-Pi T-Shaped
				MET528, LEU525, PRO535, ALA350	Alkyl
				LEU525, TRP383	Pi-Alkyl
12	(2R,3R)-3,5,8-Trihydroxy-7-Methoxyflavanone	-7,0	0	LYS529, ASP534, VAL534	Conventional Hydrogen Bond
				TYR526	Carbon Hydrogen Bond
				ASP354	Bean-Anio
				LEU536	Alkyl
				LEU536, LEU525, ALA350	Pi-Alkyl
13	N-Acetylcysteine	-6,6	0	ASN455, SER456, GLU395, ARG515	Conventional Hydrogen Bond
				ARG515	Unfavorable Donor-Donor

In addition to the numerical docking scores, the interaction maps were examined to provide a structural interpretation of the predicted binding modes. These two-dimensional representations illustrate the specific contacts established between each ligand and the ER-α binding site, including hydrogen-bonding, hydrophobic, π-related, and other interactions. After docking analysis, the compounds were further evaluated using ADMET prediction to obtain an integrated view of their potential pharmacokinetic behavior and safety characteristics. The analysis considered intestinal permeability and absorption, plasma protein binding, blood–brain barrier penetration, P-glycoprotein inhibition, and toxicity-related indicators. These parameters complement the docking results by indicating whether compounds with favorable receptor interactions also exhibit physicochemical and safety profiles that support their consideration as prospective bioactive candidates (see Table 4).

Table 4. ADMET Mangiferonic Acid Analysis Results

Code Compounds	**Absorption**		**Distribution**			**Toxicity**	
	CaCOPH2	**Trials**	**PPB**	**BBB**	**Pgp Inhibition**	**Kroes TTC**	**Mutagen**
8,3'-Dihydroxy-7,4',5'-trimethoxyflavone (MC1)	0.327	91.247	94.3	0.80	Inhibitor	Safe	-
3'-Hydroxy-7,8,4',5'-Tetramethoxyflavone (MC2)	1.248	95.01	91.5	0.936	Inhibitor	Safe	-
7,8,3',4',5'-Pentamethoxyflavone (MC3)	1.316	97.931	91.0	1.007	Inhibitor	Safe	-
Kaempferol 7-(6''-p-coumarylglucoside (MC4)	0.082	54.817	91.0	1.752	Inhibitor	Safe	-
Isoliquiritigenin (MC6)	0.955	91.096	96.1	0.717	Phytochemical	Low Risk	Structures can interact with DNA
Hiravanone (MC7)	0.494	84.449	95.4	1.047	Inhibitor	Low Risk	Structures can

							interact with DNA
5,7,3',4'-Tetrahydroxy-6,8-di-C-prenylflavanone (MC8)	0.695	82.956	94.7	1.306	Inhibitor	Low Risk	Structures can Interact with DNA
3'-Hydroxy Daidzein (MC9)	0.938	93.604	86.6	1.023	Phytochemical	Safe	-
(2R,3R)-3,5,8-Trihydroxy-7-methoxyflavanone (MC10)	0.157	63.644	98.1	1.066	Phytochemical	Safe	-
2,3-Dihydroxy-3',4,4',5'-tetramethoxy-dihydrochalcone (MC11)	0.622	65.462	88.7	0.735	Inhibitor	Safe	-
3',4',5',7,8-Pentamethoxyflavan (MC13)	1.32	99.094	93.2	0.282	Inhibitor	Safe	-

4. Discussion

Kersen plant (*Muntingia Calabura* L.) It is a fast-growing plant, reaching 3-12 m in height with rowed leaves and dangling branches [10]. The results of phytochemical screening of crescents leaves contain flavonoids, alkaloids, saponins, tannins, and terpenoids. Kersen leaves are efficacious as antiseptic, anti-inflammatory, anti-tumor, and anti-gout [11]. Kersen (*Muntingia Calabura* L.) is a plant that is used as a natural source of antioxidants [12]. The data of chemical compounds contained in the *Muntingia calabura* L. was obtained from the Knapsack database, with a total of 11 compounds identified. Furthermore, biological activity predictions are carried out to evaluate the pharmacological potential of each compound. The assessment is based on the Potential Activity (Pa) and Potential Inactivity (Pi), which is used to estimate the likelihood that a compound exhibits certain biological activity [13]. Predictions are made using the web-based software Way2Drug PASS Online. The results of the analysis showed the potential antimutagenic activity of the compounds contained in the *Muntingia calabura* L., as shown in Table 1. Based on Table 1, it is known that 2 compounds that show potential activity, namely compounds 8,3'-Dihydroxy-7,4',5'-trimethoxyflavone and 3'-Hydroxy-7,8,4',5'-tetramethoxyflavone with a Pa value of 0.940. The PASS Online test is performed to display the bioactivity of each compound. A high Pa value, close to 1, indicates a high probability that the compound exhibits the mentioned activity, while a low Pi value indicates a low probability of inactivity, which confirms the reliability of the predicted effect [14].

The drug-likeness test is an important stage in the development of a computing-based drug that aims to identify the feasibility of a compound as a drug candidate. This evaluation was carried out with reference to Lipinski's Rule of Five, which is a set of criteria used to predict the oral bioavailability profile of a compound. The process is carried out through virtual screening by considering physicochemical parameters and similarity of molecular structures that play a role in determining pharmacokinetic potential [15]. The results of the drug-likeness test for 11 test compounds are presented in Table 2. The evaluation is carried out based on Lipinski's rule (Rule of Five) which includes five parameters, namely molecular mass <500 Da, the number of hydrogen bond donors (HBD) ≤5, the number of hydrogen bond acceptors (HBA) ≤10, the logP value ≤5, and molar refractivity in the range of 40 130 [16].

Based on Table 2, most of the compounds from *Mangifera indica* L. meets Lipinski's Rule of Five criteria, which include a molecular mass of <500 Da, a logP value of ≤5, HBD ≤5, HBA ≤10, and a molar refractivity (MR) in the range of 40–130. MC1, MC2, MC3, MC6, MC9, MC10, MC11, and MC13

compounds meet all these parameters, so they are estimated to have good oral bioavailability and membrane permeability [16]. In contrast, Kaempferol 7-(6''-p-coumarylglucoside) (MC4) showed several violations, namely a molecular mass of 594.52 Da, HBD 7, HBA 13, and MR 149.51. These values exceed the recommended limits, which can reduce the ability of the compound to be optimally absorbed through the biological membrane [17].

In addition, Hiravanone (MC7) and 5,7,3',4'-Tetrahydroxy-6,8-di-C-prenylflavanone (MC8) had logP values of 6.21 and 5.89 respectively that exceeded the Lipinski limit. High logP values indicate excessive lipophilic properties, which have the potential to decrease solubility in water and affect oral bioavailability [18]. Overall, the drug-likeness test results showed that 8 of the 11 compounds met all of the Lipinski parameters and had the potential to proceed to the next stage of research, such as molecular docking and ADMET prediction, while MC4, MC7, and MC8 compounds required further attention due to violations of one or more parameters that could affect their pharmacokinetic properties.

The next stage in this study is the implementation of molecular docking using PyRx software based on the AutoDock algorithm. The simulation was carried out by utilizing pre-prepared target proteins and ligands. Optimization of protein structure includes the removal of water molecules, native ligands bound to proteins, as well as residues or components that are not directly involved in the formation of protein-ligand complexes. The move aims to produce a more representative model of the receptor to be analyzed. Thus, the resulting molecular interaction prediction is expected to have a higher level of validity, while increasing the computational efficiency during the docking process [19]. In the protein preparation process, hydrogen atoms are added to perfect the structure of the receptors that will be used in the simulation. The presence of hydrogen atoms is very important because it contributes to the formation of hydrogen bonds that play a role in the stability and specificity of the interaction between ligands and target proteins. On the other hand, ligand preparation is carried out through geometry optimization with the energy minimization method to obtain the most stable molecular configuration. Conformation with the lowest energy level is considered to be more representative of the natural conditions of the compound in the biological system, so that it can improve the accuracy of predicting the interactions resulting from the molecular docking process [20].

The parameters evaluated in this study include the value of *Affinity*, *Root Mean Square Deviation* (RMSD), the type of interaction formed, and the amino acid residues involved. Based on the results presented in Table 3, the ligand 3- Hydroxy Daidzein Shows value *Affinity* lowest compared to other ligands. Increasingly negative bond energy values indicate an increasingly strong binding affinity to the target receptor. This condition suggests that the protein-ligand complex formed has higher stability, so the ligands have the potential to interact longer with the protein's active sites [21]. The RMSD value is used to assess the suitability of the docked ligand pose to its reference conformation. The lower the RMSD value obtained, the closer the position of the predicted ligand is to the ligand conformation on the crystal structure, so that the docking results are considered more accurate. In general, the docking method is declared to have good validity if it produces an RMSD value of ≤ 2 Å [22].

Based on the molecular docking data shown, C3D compounds form conventional hydrogen bonds (*Conventional Hydrogen Bond*) with amino acid residues ARG515 and SER456. Hydrogen bonds play an important role in maintaining the stability of the ligand-receptor complex because it helps direct the specific position of the ligand on the active side of the protein [23]. In addition, there is a Pi-Alkyl interaction with LEU511, LEU500, and ARG515 residues. Pi-Alkyl interaction is a hydrophobic interaction that occurs between the aromatic group of the ligand and the alkyl chain of amino acid residues, thus contributing to strengthening the affinity and stability of ligand binding at the receptor

[24]. C3D compounds also show Alkyl interactions with LEU511 and LEU500 residues. These interactions are hydrophobic and help maintain the ligand-receptor complex through intermolecular attraction in the nonpolar region of the protein [25].

In 3'-Hydroxy-7,8,4',5'-tetramethoxyflavone, only two amino acid residues involved in binding were found, namely MET655 forming four Conventional Hydrogen Bonds with residues ARG515, GLU385, SER456, and ASN455, which indicated a good binding orientation and a stable complex. In addition, the hydrophobic interaction of Alkyl with LEU508 and ILE451, as well as the interaction of Pi-Alkyl with LEU479, LEU511, and HIS476, also strengthened the ligand's binding affinity to receptors through the effect of hydrophobic and π interactions, thus supporting the stability of the ligand–receptor complex [23].

Results molecular docking show that the compound 3'-Hydroxy-7,8,4',5'-tetramethoxyflavone interacts with receptors via conventional hydrogen bond on ASN439 residues, which plays a role in improving the ligand binding stability [23]. Pi-Cation and Unfavorable Donor-Donor interactions with ARG503 residues indicate the presence of electrostatic interactions that may affect binding affinity [26]. In addition, the interaction of Pi-Anion with GLU443 and GLU444, as well as Amide-Pi Stacked with LEU495, contribute to the stability of the complex. The presence of hydrophobic interactions of Pi-Alkyl with residues of ALA493, LEU495, and LEU489 also helps to strengthen ligand binding to the active pockets of receptors [25].

The compound 5,7,3',4'-Tetrahydroxy-6,8-in-C-prenylflavanone interacts with the target protein via conventional hydrogen bond on the residues of ASP351 and TYR526, which plays a role in increasing the stability of the ligand-protein complex. In addition, the interaction of Pi-Cation with LYS529 and Pi-Donor Hydrogen Bond with LEU536 also support binding affinity. Hydrophobic interactions in the form of Alkyl and Pi-Alkyl in VAL533, PRO535, and LEU525 residues also contribute to strengthening the contact between ligands and the active side of proteins. The combination of these interactions showed that these compounds have good binding capabilities to the target protein [23].

The compounds 7,8,4',5'-pentamethoxyflavone interact with target proteins via conventional hydrogen bonds on THR483, SER512, and HIS476 residues. The hydrogen bond plays a role in maintaining the stability of the complex and helping the orientation of ligands on the active side of the protein [23]. In addition, hydrophobic interactions in the form of Alkyl with residues LEU509, LEU506, and ILE542, as well as Pi-Alkyl with residues LEU508, ILE451, LEU479, and LEU511, also strengthen binding affinity through increased hydrophobic contact between ligands and proteins. The combination of these interactions showed that this compound has a fairly good binding ability to the target protein [25].

The Hiravanone compound forms a conventional hydrogen bond interaction with LEU536 and LEU529 residues, which contributes to the stability of the ligand-protein complex. In addition, there is an interaction of Pi-Sigma with the LEU539 residue which also supports binding affinity. The hydrophobic interaction of Alkyl in the residues of MET522, LEU536, LEU525, MET528, VAL534, and VAL533, as well as Pi-Alkyl with residues of LEU536 and TRP383, plays a role in strengthening the contact between ligands and protein binding sacs. The existence of these interactions shows that Hiravanone has a good binding ability to target proteins [23].

Results molecular docking show that Isoliquiritigenin forms a Conventional Hydrogen Bond with residues of GLU444 and GLN441, which plays a role in improving the stability and specificity of ligand binding to receptors. In addition, there are interactions of Pi-Anion with GLU444, Pi-Sigma with ALA493, Amide-Pi-Stacked with LEU489, and Pi-Alkyl with LYS residues, which together contribute to the stability of the ligand-receptor complex [25].

The compound Kaempferol 7-(6''-p-coumarylglucoside) exhibits a strong interaction through the formation of Conventional Hydrogen Bond with residues ASN455, ARG515, LEU479, THR483, and TYR459. The large number of hydrogen bonds formed indicates a good binding affinity to the receptor [25]. In addition, the interaction of Pi-Sigma with LEU508 and Pi-Alkyl with LEU508 and LEU479 also strengthens the stability of the formed complex.

Results of docking showed that 3,4,5,7,8-Pentamethoxyflavan forms a Conventional Hydrogen Bond with ARG503 residues, which plays a role in maintaining the binding stability of the ligand. These compounds also form Pi-Sigma interactions with LEU495, Alkyl interactions with LEU495 and ALA493, and Pi-Alkyl interactions with ALA493 and LEU489, which contribute to the strengthening of ligand affinity through hydrophobic interactions [27]. The compound 8,3'-Dihydroxy-7,4',5'-trimethoxyflavone exhibits different types of interactions with receptors, including Carbon Hydrogen Bond with LEU525, Pi-Cation with LYS529, Pi-Donor Hydrogen Bond with LEU536, Pi-Sigma with LEU525, and Pi-Sulfur with MET522. In addition, there are aromatic interactions of Pi-Pi Stacked with TRP383 and Pi-Pi T-Shaped with TRP526, as well as hydrophobic interactions of Alkyl and Pi-Alkyl with some residues such as MET528, LEU525, PRO535, ALA350, and TRP383. The large number of types of interactions that are formed shows a fairly good binding ability and a relatively complex [28].

Comparative compounds N-acetylcysteine forms a Conventional Hydrogen Bond with residues of ASN455, SER456, GLU395, and ARG515, which play an important role in maintaining the stability of the ligand–receptor complex. However, an unfavorable donor-donor interaction with ARG515 was also found, which indicates an incompatibility of the orientation of the hydrogen donor so that it can slightly reduce the binding stability slightly. Nonetheless, the dominance of hydrogen bonds suggests that the comparator drug retains a good affinity for the target receptor [26].

ADMET analysis was performed to predict the pharmacokinetic properties and safety of compounds in silico. Absorption parameters include Caco-2 and Human Intestinal Absorption (HIA). The Caco-2 value is used to predict the permeability of compounds through the intestinal epithelium, whereas HIA indicates the rate of absorption of compounds in the human digestive tract. Distribution parameters include Plasma Protein Binding (PPB), Blood-Brain Barrier (BBB), and P-glycoprotein (P-gp) inhibition. PPB describes the degree of binding of a compound with plasma proteins, BBB indicates the ability of the compound to penetrate the blood barrier of the brain, while P-gp inhibition is related to the compound's ability to inhibit drug flux transporters. The toxicity parameters analyzed included Kroes TTC, carcinogenicity, and mutagenicity. Kroes TTC is used to estimate the safety level of exposure of compounds, while carcinogenicity and mutagenicity are used to predict the compound's potential to cause cancer and genetic mutations. Therefore, these parameters can be used to evaluate the potential of the compound as a safe and effective drug candidate [29].

Based on the results of ADMET prediction in Table 4, Compound 8,3'-Dihydroxy-7,4',5'-trimethoxyflavone (MC1) shows a good ADMET profile. A HIA value of 91.247% indicates high intestinal absorption, while a Caco-2 permeability of 0.327 indicates adequate membrane penetration ability. At distribution, the compound has high plasma protein bonds (PPB 94.3%) and is able to penetrate the blood barrier of the brain (BBB 0.80). The compound is also predicted to be a P-gp inhibitor. In terms of toxicity, MC1 is classified as safe based on the Kroes TTC and does not show carcinogenic or mutagenic properties. These results suggest that MC1 has the potential to be developed as a candidate for bioactive compounds with good pharmacokinetic and safety profiles [30].
The compound 3'-Hydroxy-7,8,4',5'-tetramethoxyflavone (MC2) exhibited a good ADMET profile with a Caco-2 value of 1.248 and a HIA of 95.01%, indicating high intestinal permeability and absorption. This compound has high plasma protein bonds (PPB 91.5%) and good ability to penetrate the blood

barrier of the brain (BBB 0.936). In addition, MC2 is predicted to be a P-gp inhibitor. These results suggest that MC2 has the potential to be a candidate for bioactive compounds with a good pharmacokinetic and safety profile [30].

The compound 7,8,3',4',5'-Pentamethoxyflavone (MC3) exhibits an excellent ADMET profile with a Caco-2 value of 1.316 and a HIA of 97.931%, indicating very high intestinal permeability as well as absorption. This compound has high plasma protein binding (PPB 91.0%) and the ability to penetrate the blood-brain barrier well (BBB 1.007). In addition, MC3 is predicted to be a P-gp inhibitor. Thus, MC3 has the potential to be a candidate for bioactive compounds with good pharmacokinetic and safety characteristics [31].

The compound Kaempferol 7-(6''-p-coumarylglucoside) (MC4) exhibits a fairly good ADMET profile. A Caco-2 value of 0.082 and a HIA of 54.817% indicated moderate intestinal permeability and absorption. This compound has high plasma protein binding (PPB 91.0%) and good ability to penetrate the blood barrier of the brain (BBB 1.752). In addition, MC4 is predicted to be a P-gp inhibitor. These results show that MC4 has a good safety profile even though its absorption capacity is lower than that of some other compounds [32].

The compound Isoliquiritigenin (MC6) showed a good ADMET profile with a Caco-2 value of 0.955 and a HIA of 91.096%, indicating high intestinal permeability and absorption. This compound has very high plasma protein bonds (PPB 96.1%) and good ability to penetrate the blood-brain barrier (BBB 0.717). Unlike other compounds, MC6 is not predicted to be a P-gp inhibitor. However, there are indications that its structure can interact with DNA, so further studies are needed to ensure its safety. Overall, MC6 has potential as a bioactive compound with a good pharmacokinetic profile [33].

The Hiravanone (MC7) compound showed a good ADMET profile with a Caco-2 value of 0.494 and a HIA of 84.449%, indicating high intestinal permeability and absorption. This compound has high plasma protein bonds (PPB 95.4%) as well as the ability to penetrate the blood barrier of the brain (BBB 1.047). Hiravanone is predicted to be a P-gp inhibitor, which has the potential to increase the retention of compounds within cells. Based on toxicity parameters, this compound is classified as low-risk and non-carcinogenic. However, there are indications that its structure may interact with DNA, so further research is needed to evaluate its safety aspects. Overall, Hiravanone has potential as a candidate for a bioactive compound with a supportive pharmacokinetic profile [33].

The compound 5,7,3',4'-Tetrahydroxy-6,8-di-C-prenylflavanone (MC8) exhibited a good ADMET profile with a Caco-2 value of 0.695 and a HIA of 82.956%, indicating high intestinal permeability as well as absorption. This compound has high plasma protein binding (PPB 94.7%) and good ability to penetrate the blood barrier of the brain (BBB 1.306). In addition, MC8 is predicted to be a P-gp inhibitor. Based on toxicity parameters, this compound is classified as low-risk and non-carcinogenic. However, there are indications that the structure may interact with DNA so further research is needed to ensure its safety. Overall, MC8 has the potential to be a candidate for bioactive compounds with a good pharmacokinetic profile [33].

The compound 3'-Hydroxydaidzein (MC9) showed a good ADMET profile with a Caco-2 value of 0.938 and a HIA of 93.604%, indicating high intestinal permeability and absorption. This compound has a fairly high plasma protein bond (PPB 86.6%) and a good ability to penetrate the blood barrier of the brain (BBB 1.023). Unlike some other compounds, MC9 is not predicted as a P-gp inhibitor. These results suggest that MC9 has a good pharmacokinetic and safety profile as a candidate for bioactive compounds [34].

The compound (2R,3R)-3,5,8-Trihydroxy-7-methoxyflavanone (MC10) showed a fairly good ADMET profile with a Caco-2 value of 0.157 and a HIA of 63.644%, indicating intestinal permeability and

absorption at moderate levels. This compound has very high plasma protein bonds (PPB 98.1%) as well as the ability to penetrate the blood barrier of the brain (BBB 1.066). MC10 is not predicted to be a P-gp inhibitor. Based on toxicity parameters, this compound is classified as safe and does not exhibit carcinogenic properties or potential interactions with DNA. Overall, MC10 has a good safety profile and has the potential to be a candidate for bioactive compounds, although its absorption capacity is relatively lower than that of some other compounds [32].

The compound 2,3-Dihydroxy-3',4,4',5'-tetramethoxydihydrochalcone (MC11) showed a fairly good ADMET profile with a Caco-2 value of 0.622 and a HIA of 65.462%, indicating moderate to high intestinal permeability and absorption. This compound has high plasma protein bonds (PPB 88.7%) and good ability to penetrate the blood barrier of the brain (BBB 0.735). In addition, MC11 is predicted to be a P-gp inhibitor. Based on toxicity parameters, this compound is classified as safe and does not show carcinogenic properties or potential interactions with DNA. These results suggest that MC11 has a pharmacokinetic and safety profile that supports further development as a candidate for bioactive compounds [30].

The compound 3',4',5',7,8-Pentamethoxyflavan (MC13) exhibited an excellent ADMET profile with a Caco-2 value of 1,320 and a HIA of 99,094%, indicating very high intestinal permeability as well as absorption. This compound has a high plasma protein binding (PPB 93.2%) and the ability to penetrate the blood barrier of the brain at a moderate level (BBB 0.282). In addition, MC13 is predicted to be a P-gp inhibitor. These results suggest that MC13 has a highly supportive pharmacokinetic and safety profile for further development as a candidate for bioactive compounds [31].

Conclusion

Based on the results of in silico analysis, bioactive compounds from kersen leaves (*Muntingia calabura* L.) showed potential as antimutagenic agents. Most compounds meet the drug-likeness criteria and have a good ADMET profile. The results of molecular docking showed that 3'-Hydroxydaidzein (MC9) had the best binding affinity to Estrogen Receptor-α receptors with a binding affinity value of −8.7 kcal/mol, better than the N-acetylcysteine comparison compound. In addition, this compound also exhibits a good pharmacokinetic and safety profile. Therefore, 3'-Hydroxydaidzein (MC9) has the potential to be further developed as a candidate for natural anticancer agents and needs to be confirmed through in vitro and in vivo studies.

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