JFSP Vol.9, No.2, June 2023, Page: XXX-XXX, pISSN: 2549-9068, eISSN: 2579-4558
Jurnal Farmasi Sains dan Praktis
(JFSP)
http://journal.unimma.ac.id/index.php/pharmacy

MOLECULAR DOCKING OF SAPONINS AND FLAVONOIDS OF SOURSOP LEAVES (*Annona muricata* Linn.) AGAINST CYCLOOXYGENASE-2 (COX-2) AS ANTI-INFLAMMATORY

Annisa Ruhiyih Carmelita[1], **Rosario Trijuliamos Manalu**[1], **Nurul Akhatik**[1]

[1]Departement of Pharmacy, Faculty of Pharmacy, National Institute of Science and Technology, Jakarta, Indonesia

rio@istn.ac.id

https://doi.org/10.31603/pharmacy.v8i2.4668

Article info:
Submitted : D-3-2023
Revised : D-M-202X
Accepted : D-M-202X

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License

Publisher:
Universitas Muhammadiyah Magelang

ABSTRACT
There are many uses of natural products as anti-inflammatory, one of which is in soursop leaves (*Annona Muricata* L.). The place where inflammation takes place, is characterized by elevated levels of the cyclooxygenase-2 (COX-2) enzyme. Soursop leaves contain flavonoids and saponins which have molecular inhibitory activity as anti-inflammatory. This study aims to determine the molecular docking activity of saponins and flavonoids of soursop leaves (*Annona Muricata* L.) against cyclooxygenase (COX-2) receptors as anti-inflammatory. Prior to docking, prediction of physicochemical properties was carried out which refers to the parameters of Lipinski's Rule of Five. The protein model used is 4COX. Receptor and ligand preparation using the YASARA application. The 4COX receptor is declared valid because it has an RMSD value of <2Å. Docking is done using PLANTS, cmd, wingwm.dll, and notepad. The results showed that as many as 6 derivatives of saponins and 13 derivatives of flavonoids from soursop leaves (*Annona muricata* Linn.) have druglike properties because they comply with Lipinski's Rule of Five, compound 2,3-epoxydasqualene has a score the best docking for protein (PDB ID: 4COX) compared to the drug Indomethacin (IMN), this compound is proven to have interactions with the target protein. The pharmacokinetic properties of the 2,3-epoxydasqualene compound have good absorption ability, are distributed easily, metabolized by CYP3A4 substrates, are well excreted in the kidney, and have low toxicity. The active compound derived from saponins from soursop leaves (*Annona Muricata* L.), namely 2,3-epoxydasqualene, is predicted to be a potential anti-inflammatory drug candidate.
Keywords: *Annona Muricata* L.; Molecular Docking; Flavonoids; Saponin; Anti-inflammatory

1. INTRODUCTION

Utilization of treatment from natural ingredients such as soursop leaves is very likely to be an alternative candidate considering the potential and efficacy of its active chemical compounds which are quite a lot and have been used traditionally for a long time. (Soekaryo, 2016). Inflammation is usually treated using steroid class anti-inflammatory drugs (AIS) and non-steroidal anti-inflammatory drugs (NSAIDs) (Setyopuspito, 2017). The place where inflammation takes place, is characterized by elevated levels of the enzyme cyclooxygenase-2 (COX-2) which is an enzyme that is induced in cells that are experiencing inflammation (Fauziah & Mayora, 2020). Bioactive compounds such as tannins, flavonoids, polyphenols, *Annonaceuous acetogenius*, and saponins are abundant in soursop leaves. The content of soursop leaf extract such as flavonoids, saponins, alkaloids, and tannins function as anti-inflammatory (Asmiati, 2020).

Another class of NSAIDs work by inhibiting cyclooxygenase-2. One of the selective drugs that works to inhibit cyclooxygenase-2 is Indomethacin. Some of the chemical compounds contained in the soursop plant cannot be ascertained for their effectiveness as anti-inflammatories in inhibiting cyclooxygenase-2. (Zahra & Carolia, 2017). In silico studies were developed to reduce expensive costs and reduce the length of time required to obtain active compounds used as anti-inflammatory. In an in silico study, we were able to predict the computational biological effects of soursop leaves in the search for new drugs. One of the in silico methods used is molecular docking (Meilinawati, 2020).

2. METHODS

2.1 Tools and Materials

The tools used are: the computer hardware used is a Lenovo-0I0RP53Q Laptop with an AMD A9-9425 Radeon R5 processor, 5 Compute Cores 2c+3g, 4GB RAM, Windows 10 Home Single Language 64-bit operating system, x64-based processor.

The software used is YASARA, PLANTS, PDB, Discovery Studio Visualizer, Marvin Sketch, SwissADME.

The materials used in this study were saponin derivative test compounds, namely beta-amyrine, asiaticoside, 2,3 epoxidesqualen, gypsogenin, glyciretinic acid, annoionol A, annoionol B, annoionol C, annoionoside and a flavonoid derivative test compound, namely apigenin-6-C-glucoside, argentinine, catechin, daidzein, epicatechin, gallocatechin, genistein, glycitein, homoorientin, isoferulic acid, kaempferol, quercetin, quercetin-3-O-glucoside, robinetine, tangeretin, rutin and indomethacin drug with PDB ID code: 4COX as native ligands and receptors.

2.2 Analysis of Drug-like Properties (Druglikeness)

Analysis of similarity with the drug was carried out using the SwissADME program. The Lipinski rule which included the molecular weight of the compound, the value of the log P partition coefficient, the number of hydrogen bond donors, and the number of hydrogen bond acceptors.

2.3 Receptor and Native Ligand Preparation

Separation was carried out using YASARA software and hydrogen atoms were also added for optimization.

2.4 Ligand Preparation of Test Compounds

Saponin test compound ligands from soursop leaves (*Annona muricata* Linn.) were optimized using the Marvinsketch application and protonated with a pH of 7.4.

2.5 Redocking

Docking validation was carried out using the redocking method using the native ligand on the receptor which was downloaded from the Protein Data Bank with PDB ID code: 4COX. The parameter used to assess validity is the RMSD value which is used to determine the result of redocking between the native ligand and the re-docking result.

2.6 Docking of Test Compound Ligands Against Receptors

Determination of the conformation of the docked ligand is carried out by selecting the conformation of the ligand that has the lowest binding energy selected in the bestranking file. Then remove the water and add hydrogen.

2.7 Analysis and Visualization of Docking Results

To carry out this test, it is done by opening the YASARA application then input protein then input ligand then click joint and make it an object, save it in.

2.8 Pharmacokinetic Predictions

The prediction profile of ADMET shows a variety of absorption, distribution, metabolism, excretion and toxicity profiles.

3. RESULTS AND DISCUSSION

Considering pharmacokinetic aspects is very important when designing a drug because it is impossible to interact with the target if it cannot reach the target, so a rule was found, the five Lipinski rules or what is called the rule of five or Lipinski's Rule. Drugs that are able to reach the target when administered orally must meet the following requirements molecular weight

less than 500 dalton (g/mol), the number of hydrogen bond donor groups (Hydrogen Bond Donor) is not more than 5, the number of hydrogen bond acceptor groups (Hydrogen Bond Acceptor) is not more than 10, P log value less than 5, molar refractivity between 40-130.

Table 1. Prediction Results of Lipinski's Rules of Five Active Compounds Derived from Saponins and Flavonoids from Soursop Leaf Plants

Compound	Chemical Derivatives	Molecular Formula	MW	Log P	HBD	HBA	Mr	Desc
SAPONIN	Beta-Amyrine	$C_{30}H_{50}O$	426,72 g/mol	8,17	1	1	134,88	Yes
	Asiaticoside	$C_{48}H_{78}O_{19}$	959,12 g/mol	-1,03	12	19	234,82	No
	2,3-Epoxydasqualene	$C_{30}H_{50}O$	426,72 g/mol	9,82	0	1	142,96	Yes
	Gypsogenin	$C_{30}H_{46}O_4$	470,68 g/mol	6,41	2	4	142,96	Yes
	Annoionol A	$C_{13}H_{26}O_3$	230,34 g/mol	1,55	3	3	65,72	Yes
	Annoionol B	$C_{13}H_{24}O_4$	244,33 g/mol	0,44	4	4	66,44	Yes
	Annoionol C	$C_{13}H_{20}O_3$	224,30 g/mol	1,84	1	3	62,17	Yes
FLAVONOID	Apigenin-6-C-Glucoside	$C_{12}H_{20}O_{10}$	432,38 g/mol	1,94	7	10	106,61	Yes
	Argentinine	$C_{19}H_{21}NO_2$	295,38 g/mol	3,23	1	3	92,25	Yes
	Catechin	$C_{15}H_{14}O_6$	290,27 g/mol	1,47	5	6	74,33	Yes
	Daidzein	$C_{15}H_{10}O_4$	254,24 g/mol	1,77	2	4	71,97	Yes
	Epicatechin	$C_{15}H_{14}O_6$	290,27 g/mol	1,47	5	6	74,33	Yes
	Gallocatechin	$C_{15}H_{14}O_7$	306,27 g/mol	0,98	6	7	76,36	Yes
	Genistein	$C_{15}H_{10}O_5$	270,24 g/mol	1,91	3	5	73,99	Yes
	Glycitein	$C_{16}H_{12}O_5$	284,26 g/mol	2,36	2	5	78,46	Yes
	Homoorientin	$C_{21}H_{20}O_{11}$	448,38 g/mol	2,12	8	11	108,63	No
	Isoferulic Acid	$C_{10}H_{10}O_4$	194,18 g/mol	1,79	2	4	51,63	Yes
	Kaempferol	$C_{15}H_{10}O_6$	286,24 g/mol	1,70	4	6	76,01	Yes
	Quercetin	$C_{15}H_{10}O_7$	302,24 g/mol	1,63	5	7	78,03	Yes
	Quercetin-3-O-Glucoside	$C_{21}H_{20}O_{12}$	464,38 g/mol	2,11	8	12	110,16	No
	Robinetin	$C_{15}H_{10}O_7$	302,24 g/mol	1,00	5	7	78,03	Yes
	Rutin	$C_{27}H_{30}O_{16}$	610,52 g/mol	1,58	10	16	141,38	No
	Tangeretin	$C_{20}H_{20}O_7$	372,37 g/mol	3,71	0	7	100,38	Yes

Yes: No deviation; No: There is a deviation; MW: Molecular Weight; HBD: Number of H Bond Donors; HBA: Number of H bond acceptors; MR: Molar Refractivity

Table 1 shows the results of Lipinski's Rule of Five from derivatives of saponins and flavonoids. 19 derivatives of the active compound (6 derivatives of saponin compounds and 13 derivatives of flavonoid compounds) indicated “yes”, meaning that the compound complied

with Lipinski's Rule of Five. means that it is not in accordance with Lipinski's Rule of Five so that molecular docking is not carried out (docking process).

The downloaded protein structure is cyclooxygenase-2 (COX-2) with PDB code ID: 4COX obtained from X-ray diffraction with a resolution of 2.90 Å.

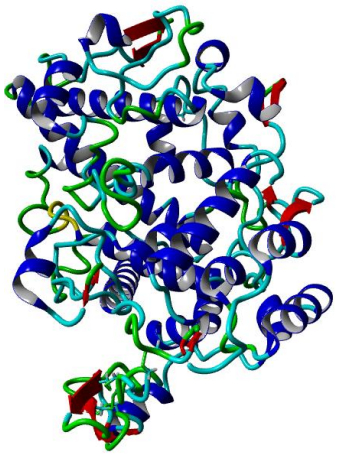

Figure 1. Cyclooxygenase-2 (COX-2) Protein Preparation

Native ligand was prepared using the YASARA application by isolating the native ligand that was already present in the protein, namely indomethacin (IMN).

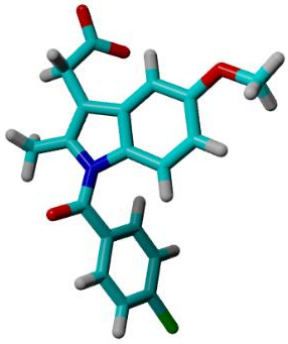

Figure 2. Indomethacin (IMN) Native Ligand Preparation

The ligands to be tested consisted of 6 saponin derivatives and 13 flavonoid derivatives from soursop leaves (*Annona muricata* Linn.). After the native ligand preparation, the ligand preparation process was carried out. The ligand used was copied from the Canonical SMILES code from Pubchem via the site https://pubchem.ncbi.nlm.nih.gov/ and pasted the code into the MarvinSketch application, converted the structure to 2D and then saved in the .mrv file format named ligand2D. Then reopen the "ligand2D" file and change the conformation using MarvinSketch with 10 conformations.

The validation of the docking method was carried out by re-docking between the native ligand and the prepared protein. The docking method is said to be valid if the RMSD value is 2Å, which means that the docking parameters used are valid so that the docking method can be used for docking the test compounds. (Sari & Pratiwi, 2020).

Assessment of the validation is based on Root Mean Square Deviation (RMSD), which shows the difference in coordinate positions between the two ligands, namely the crystal complex ligand and the re-docking ligand. The RMSD value obtained in this study was

1.1583Å, this figure indicates that the docking method using the PLANTS software has acceptable precision and accuracy (Manalu *et al*., 2021).

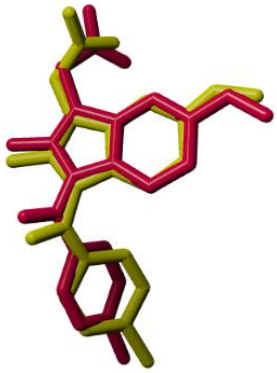

Figure 3. Docking Validation with RMSD Value of 1.1583Å

The increasingly negative docking score of the derivatives of flavonoids and saponins indicates a good degree of stability between the target protein and the ligand, so that the bonds formed are stronger. The docking scores obtained provided information that the active compounds from saponin and flavonoid derivatives of soursop (*Annona muricata* L.) leaves tested could be potential candidates for anti-inflammatory drugs or not.

Table 2. Docking Score Results

Native Ligand		
Compound	**Score Docking**	
4COX (IMN)	-106.541	
Test Ligand		
Name of Compound	**Derived Compounds**	**Score Docking**
2,3-epoxydasqualene	Saponin	-120.208
Epicatechin	Flavonoid	-93.2677
Catechin	Flavonoid	-93.2497
Gallocatechin	Flavonoid	-91.575
Robinetin	Flavonoid	-84.5963
Quercetin	Flavonoid	-84.3779
Kaempferol	Flavonoid	-83.0697
Glycitein	Flavonoid	-79.1277
Genistein	Flavonoid	-78.4242
Isoferulic Acid	Flavonoid	-77.7373
Daidzein	Flavonoid	-75.6103
Annoionol A	Saponin	-75.5868
Annoionol C	Saponin	-72.4081
Argentinine	Flavonoid	-71.1661
Annoionol B	Saponin	-70.813
Apigenin-6-C-Glucoside	Flavonoid	-66.459
Gypsogenin	Saponin	-46.3947
Beta-Amyrine	Saponin	-44.3843
Tangeretine	Flavonoid	-42.975

Table 2 shows the docking results in the form of docking scores on 20 ligands, 1 of which is a native ligand (4COX). Of the 19 ligands tested, 1 ligand received a more negative docking score than the native ligand, namely 2.3 epoxydasqualene, which means that the compound exhibits high bond stability compared to the native ligand.

2,3-epoxydasqualene is known to inhibit proinflammatory cytokine α (TNF-α) and chemokine C-C chemokine 2 (CCL2) in LPS stimulation using an in vitro inflammatory model. TNF-α helps recruit immune cells to sites of inflammation and thereby enhances the

inflammatory response. It has been previously reported that excess amounts of TNF-α play a pathological role in several diseases including inflammatory bowel disease, rheumatoid arthritis, and asthma (Sasaki et al., 2020).

The result of this visualization is the interaction of amino acid residues with ligands. The interaction of the amino acids involved allows contact between the ligand and the protein so that it has inhibitory activity. The binding site is the area of binding of the protein to the ligand which will affect the conformation and function of the protein. (Sari & Pratiwi, 2020).

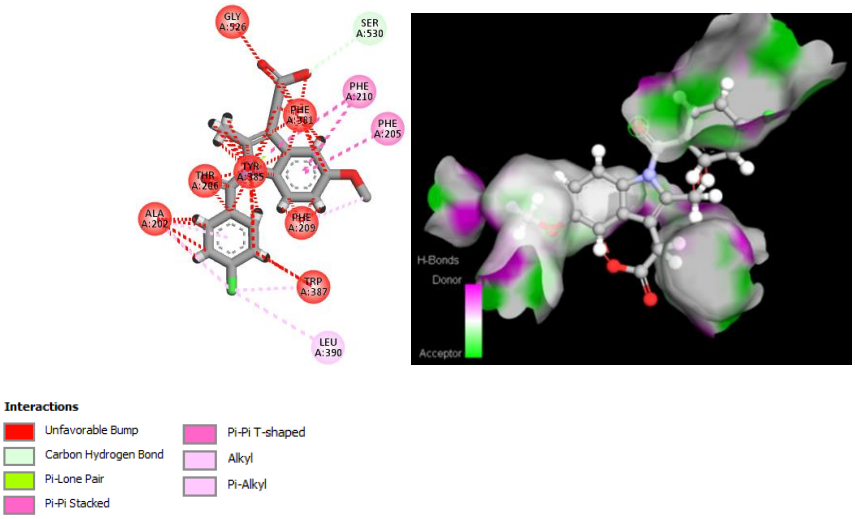

Figure 4. 2D and 3D Visualization of Interaction Between Protein and Drug Indomethacin

Based on the binding results between the comparator drug (Indomethachin) and the receptor, there are 11 amino acid residues that bind, namely GLY526, PHE381, TYR385, THR206, ALA202, PHE209. TRP387, PHE210, SER530, PHE205, LEU390. These results can be used as a reference to compare the amino acid residues that bind to the test ligand, namely 2,3-epoxydasqualene.

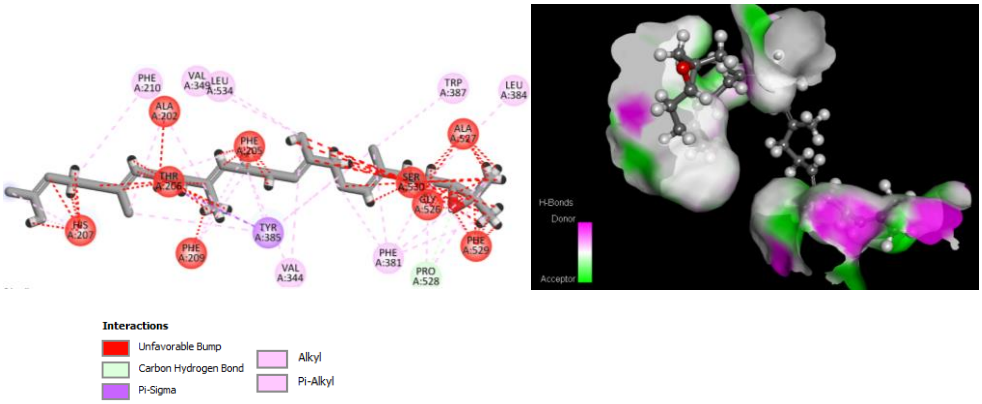

Figure 5. Visualization of Interaction Between Protein and Ligand 2,3-epoxydasqualene in 2D and 3D

The interaction between protein and 2,3-epoxydasqualene compounds produces 18 linked amino acid residues, namely PHE210, VAL349, LEU534, VAL344, PHE381, TRP387, LEU384, HIS207, ALA202, THR206, PHE209, PHE205, ALA527, SER530, GLY526, PHE52, TYR385, PRO528. The results of this visualization show several similarities in amino acid residues, namely SER530, PHE210, PHE205, PHE381, TYR385, THR206, ALA202, PHE209, and TRP387. The amino acid residues show that the 2,3-epoxydasqualene compound

has a binding position that is almost similar to the comparator drug (Indomethacin). Therefore, it can be concluded that the 2,3-epoxydasqualene compound has better inhibitory activity at the cyclooxygenase-2 (COX-2) receptor than the other test compounds derived from saponins and flavonoids from soursop leaves (*Annona muricata* L.).

It is important to know the pharmacokinetic prediction of a new drug because it is used to determine the presence of an active substance in the body which in turn will also determine its pharmacological activity. The following is a prediction table for the absorption, distribution, metabolism, excretion, and toxicity of 2,3-epoxydasqualene

Table 3. Absorption Prediction Using pkCSM Compound 2,3- Epoxydasqualene

Property	Model Name	Prediksi	Unit	Standard
Absorption	Water solubility	**-8.447**	Numeric (log mol/L)	<-6 (low)
	CaCO2 permeability	**1.176**	Numeric (log Papp in 10^{-6} cm/s)	>0,90 (high)
	Intestinal absorption (human)	**91.045**	Numeric (% Absorbed)	70%-100%
	Skin Permeability	**-3.181**	Numeric (log Kp)	>-2,5 Log Kp (low)
	P-glycoprotein substrate	**No**	Categorical (Yes/No)	-
	P-glycoprotein I inhibitor	**No**	Categorical (Yes/No)	-
	P-glycoprotein II inhibitor	**Yes**	Categorical (Yes/No)	-

The pharmacokinetic mechanism of a drug begins through the absorption process. Table 3 shows the predicted results of the absorption of the 2,3-epoxydasqualene compound which was determined through the pkCSM website at https://biosig.lab.uq.edu.au/. In the table above, compound 2.3 epoxydasqualene has a good absorption value of 91.045%. The permeability of CaCO2 monolayer cells is often used as an in vitro model of the intestinal mucosa so that it can predict the absorption of drugs administered orally (Abdullah et al., 2021).

Skin permeability is very influential in drug delivery through the skin. The 2,3-epoxydasqualene compound has a high skin permeability because a compound is considered to have a relatively low skin permeability if it has a logKp > -2.5 cm/hour and has a high permeability if the logKp value is <-2.5 cm/hour (Abdullah et al., 2021). On the P-glycoprotein substrate in the absorption stage, there is a statement "No", which means that the 2,3 epoxydasqualene compound is not absorbed through the substrate. Likewise for P-glycoprotein I inhibitors, it is not absorbed by these inhibitors. Whereas in P-glycoprotein II the compound 2,3-epoxydasqualene is absorbed in the inhibitor.

Table 4. Distribution Prediction Using pkCSM Compounds 2,3 Epoxydasqualene

Property	Model Name	Prediksi	Unit	Standard
Distribution	VDss (human)	**0.422**	Numeric (log L/kg)	Low:0,71 L/kg (log VDss <-0,15)
	Fraction unbound (human)	**0**	Numeric (Fu)	-

	BBB permeability	**0.894**	Numeric (log BB)	Easy: >0,3
	CNS permeability	**-1.464**	Numeric (log PS)	Can pass: >-2

VDSs is the theoretical volume that the total drug dose is uniformly distributed to provide the same concentration as in blood plasma. The higher the VD, the more drug is distributed at the same concentration as in the blood plasma. The efficacy of a given drug can be affected by the degree to which the drug binds to proteins in the blood, because the more drug that is bound, the less efficiently it can pass through the cell membrane or diffusion membrane. The human brain is protected from exogenous compounds through the blood-brain barrier.

Blood to brain permeability was measured in vivo in animal models as the logBW, the logarithmic ratio of brain plasma drug concentration. If a compound has a logBB >0.3 it is considered to cross the blood-brain barrier easily while molecules with a logBB -2 are considered to be able to penetrate the central nervous system , while compounds with logPS. (Abdullah et al., 2021).

Table 5. Metabolism Prediction Using pkCSM Compound 2,3 Epoxydasqualene

Property	Model Name	Prediksi	Unit
Metabolism	CYP2D6 substrate	**No**	Categorical (Yes/No)
	CYP3A4 substrate	**Yes**	Categorical (Yes/No)
	CYP1A2 inhibitior	**No**	Categorical (Yes/No)
	CYP2C19 inhibitior	**No**	Categorical (Yes/No)
	CYP2C9 inhibitior	**No**	Categorical (Yes/No)
	CYP2D6 inhibitior	**No**	Categorical (Yes/No)
	CYP3A4 inhibitior	**No**	Categorical (Yes/No)

In the pharmacokinetic process, after the drug goes through the distribution phase, the drug will go through the metabolic phase. Metabolism is a chemical process in which the drug will be changed in the body to form a metabolite. The inhibitor that plays a role in this process is cytochrome P450. Cytochrome P450 is an important enzyme in the body and is mainly found in the liver. Cytochrome P450 oxidizes xenobiotics to inactivate drug compounds. It is necessary to assess the ability of the compound to inhibit cytochrome P450. Cytochrome has several isoform models consisting of several substrate compounds CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. Compounds that are substrates indicate that these compounds can be metabolized by CYP3A4, these compounds are not affected by metabolism in the presence of CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4 inhibitors.

Table 6. Excretion Prediction Using pkCSM Compound 2,3 Epoxydasqualene

Property	Model Name	Prediksi	Unit
Excretion	*Total Clearance*	**1.396**	*Numeric* (log ml/min/kg)
	Renal OCT2 substrate	***No***	*Categorical (Yes/No)*

At this stage, the values of Total Clearance and Renal Organic Cation Transporter2 will be predicted. Organic cation transporter 2 is a renal uptake transporter that plays an important role in the movement and clearance of drugs and endogenous compounds in the kidney. Drug clearance is measured by a proportional constant total CL and is the result of a combination of hepatic clearance and renal clearance. The total clearance yield of the 2,3-epoxydasqualene compound was 1.396.

Table 7. Toxicity Prediction Using pkCSM Compound 2,3 Epoxydasqualene

Property	Model Name	Prediksi	Unit
Toxicity	*AMES toxicity*	***No***	*Categorical (Yes/No)*
	Max. tolerated dose (human)	**-0.319**	*Numeric* (log mg/kg/day)
	hERG I inhibitor	***No***	*Categorical (Yes/No)*
	hERG II inhibitor	***Yes***	*Categorical (Yes/No)*
	Oral Rat Acute Toxicity (LD50)	**1.622**	*Numeric* (mol/kg)
	Oral Rat Chronic Toxicity (LOAEL)	**0.714**	*Numeric* (log mg/kg bw/day)
	Hepatotoxicity	***No***	*Categorical (Yes/No)*
	Skin Sensitisation	***No***	*Categorical (Yes/No)*
	T.Pyriformis toxicity	**0.623**	*Numeric* (log ug/L)
	Minnow toxicity	**-3.029**	*Numeric* (log mM)

Prediction of compound toxicity is an important parameter besides pharmacokinetic prediction. The parameters used are the AMES test, LD50, hepatotoxicity, and skin sensitization. In the AMES test, this compound did not cause toxicity to bacteria, nor did it cause hepatotoxicity and skin sensitization. And the result of the LD50 test for the 2,3-epoxydasqualene compound is 1,622 mol/kg.

4. CONCLUSION

As many as 6 derivatives of saponin compounds and 13 derivatives of flavonoid compounds from soursop leaves (Annona muricata Linn.) have drug-like properties (druglikeness) because they comply with Lipinski's Rule of Five. Compound 2,3-epoxydasqualene has the best protein docking score (PDB ID: 4COX) compared to Indomethacin (IMN). The pharmacokinetic properties of the 2,3-epoxydasqualene compound are very good, to be used as candidates for

new drug compounds with good pharmacokinetic properties such as absorption, namely low water solubility with a value of -8.447 mol/L, high CaCO2 permeability with a value of 1.176, absorption ability in the intestine good with a value of 91.045%, high skin permeability with a value of -3.181 log Kp, low VDSs distribution with a value of 0.422 L/kg, easy permeability of the blood-brain barrier with a value of 0.894 log BW, no fraction bound to serum protein, and the CNS permeability value is -1.464 which means it can penetrate the central nervous system, is metabolized by CYP3A4, the compound is not affected by metabolism in the presence of CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4 inhibitors, then the excretion stage of the 2,3-epoxydasqualene compound is not an OCT2 substrate and The total clearance of 2,3-epoxydasqualene is 1.396 and has low toxicity.

5. ACKNOWLEDGMENT

The author would like to thank Muhammadiyah University of Magelang

6. CONFLICT OF INTEREST

The author declares that there no competing conflicts of interest.

7. REFERENCES

Abdullah, S. S., Putra, P. P., Antasionasti, I., Rundengan, G., Suoth, E. J., Abdullah, R. P. I., & Abdullah, F. (2021). Analisis Sifat Fisikokimia, Farmakokinetik Dan Toksikologi Pada Pericarpium Pala (Myristica Fragransa) Secara Artificial Intelligence. *Chemistry Progress*, *14*(2), 81. https://doi.org/10.35799/cp.14.2.2021.37112

Asmiati. (2020). *Efektivitas Ekstrak Daun Sirsak (Annona Muricata L) Terhadap Kadar IL-10 pada Mammae Tikus Betina Sprague Dawley yang Diinduksi Staphylococcus Aureus*. *11*(1), 74–81.

Fauziah, F., & Mayora, S. A. (2020). Aktivitas Anti-inflamasi dan Daya Hambat Siklooksigenase-2 Ekstrak Etanol Daun Tembelekan (Lantana camara L .). *Jurnal Farmasi Higea*, *Vol. 12*(No. 1), 32–39.

Komarudin, A. D. P., Purnama, M. F. G., Purnama, M. F. G., Sari, A. Y., Rizka Sahila, E. N. M., & Izzati, A. (2021). Studi In Silico Senyawa Tanaman Nerium Oleander Terhadap Stat-3 Pada Kanker Payudara. *Jurnal Farmasi Udayana*, *10*(2), 149. https://doi.org/10.24843/jfu.2021.v10.i02.p07

Manalu, R. T., Meheda, I. O., & Octaviani, C. (2021). Inhibition of HMG-CoA Reductase Activity from Active Compounds of Ginger (Zingiber officinale): In-Silico Study. *Jurnal Farmasi Etam (JFE)*, *1*(1), 32–38. https://doi.org/10.52841/jfe.v1i1.177

Meilinawati, D. (2020). *Virtual Screening Senyawa Agonis β2 Adrenergik Sebagai Kandidat Bronkodilator Berbasis Pharmacophore Modeling Dan Molecular Docking*. *09*, 1–23.

Sari, I. W., & Pratiwi, D. (2020). *Studi Molecular Docking Senyawa Flavonoid Herba Kumis Kucing (Orthosiphon Stamineus B) Pada Reseptor A-Glukosidase Sebagai Antidiabetes Tipe 2*. *VII*(2), 54–60. https://doi.org/10.47653

Sasaki, K., Inami, Y., Tominaga, K., Kigoshi, H., Arimura, T., & Isoda, H. (2020). Synthesis of 2-(2-Hydroxyethoxy)-3-hydroxysqualene and Characterization of Its Anti-Inflammatory Effects. *BioMed Research International*, *2020*. https://doi.org/10.1155/2020/9584567

Setyopuspito, A. (2017). Uji Efektivitas Antiinflamasi Ekstrak Etanol Daun Srikaya (Annona Squamosa. L) Terhadap Edema Kaki Tikus Putih Jantan Galur Wistar. *Jurnal Ilmiah Farmasi*, *13*(1), 8–14. https://doi.org/10.20885/jif.vol13.iss1.art2

Soekaryo. (2016). *Uji Inhibisi Enzim Siklooksigenase-2 (COX-2) dari Ekstrak Daun Sirsak (Annona muricata Linn.) Sebagai Antiinflamasi*. *2*, 485–492.

Zahra, A. P., & Carolia, N. (2017). Obat Anti-inflamasi Non-steroid (OAINS): Gastroprotektif vs Kardiotoksik. *Majority*, *6*.