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IN SILLICO STUDY OF ACTIVE COMPOUNDS OF RAMANIA LEAF EXTRACTS (Bouea macrophylla Griffth) ON PROTEIN KINASE C-β

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Abstract

Background: Traumatic Dental Injury (TDI) causes injury to the teeth and tissues around the oral cavity. A total of 17.2% incidence of TDI in children and adolescents under the age of 18 years, in permanent teeth TDI as much as 15.2%. TDI will cause an inflammatory process that will increase the immune response. PKC-β is a conventional type of PKC isoform. Prolonged PKC-β activation is associated with impaired NF-κB activation by TNF-α. PKC-β has been shown to reduce the activity of NF-κB. PKC has a clear role in several cellular functions and diseases, making PKC isoenzymes a very promising target for drug development. TDI can be treated with herbal medicine therapy, one of the plants that can be used as medicinal plants is ramania (Bouea macrophylla Griffith). Objective : To analyze the binding of the active compound of BMG leaf extract to the expression of PKC-β as an anti-inflammatory with the in sillico method. Methods: This research is computationally based with the in sillico method. This research uses molecular docking analysis of the protein X-Ray diffreaction results from the Protein Data Bank (PDB) ID web. The Docking process is carried out using Autodock Vina which is integrated in the PyRx application and visualized using the Biovia Discovery Studio application. Conclusion : The methyl ricinoleate compound in BMG is the most potent inhibitor of Protein Kinase C-β and has the potential as an anti-inflammatory of the 10 BMG leaf extract compounds studied

1. INTRODUCTION

Traumatic Dental Injury (TDI) is a risk factor in an individual's life (Khan & Jindal, 2022). TDI causes injury to the teeth and tissues around the oral cavity (Lam, 2016). The WHO classification of TDI consists of trauma to the periodontal tissues, pulp and hard tissues of the teeth, supporting bones, to the gingiva and oral mucosa with seven types of tooth fracture, six types of luxation, eight types of damage to the supporting bone and three types of damage to the oral mucosa or gingiva (Zaleckiene et al., 2014). The prevalence of TDI differs between geographic areas. According to the meta-analysis of Azami-Aghdash *et al* (2015) children and adolescents aged 18 years and under have a TDI prevalence of 17.2%. Petti *et al* (2015) stated that the prevalence of TDI was 15.2% in permanent teeth (Majewski et al., 2013).
TDI will cause an inflammatory process that will increase the immune response. Central inflammatory mediator in the form of *Nuclear factor kappa B* (NF-κB) will be activated and deregulated in various inflammatory diseases. NF-κB can be activated by activated Protein Kinase C (PKC) to stimulate pro-inflammatory genes to release inflammatory mediators, such *as Interleukin 1 Beta* (IL-1β) and *tumor necrosis factor alpha* (TNF-α) (Izzi et al., 2012; Shita, 2015). PKC-β is a conventional type of PKC isoform. Prolonged PKC-β activation is associated with impaired NF-κB activation by TNF-α(Alleboina et al., 2020). PKC-β has been shown to reduce the activity of NF-κB. PKC has a clear role in several cellular functions and diseases, making PKC isoenzymes a very promising target for drug development (Leppänen et al., 2014; Liu et al., 2017; Robertson et al., 2007).

Prompt and appropriate treatment of TDI can result in long-term survival of the tooth (Majewski et al., 2013). TDI can be treated with herbal medicine therapy. Herbal therapy is a drug solution with ingredients that are relatively easy to obtain and have harmless side effects. One of the plants that can be efficacious as medicine is BMG which comes from Kalimantan. BMG has leaves with secondary metabolites such as flavonoids, phenols, tannins, saponins, terpenoids, steroids (Rahman et al., 2017; Rizkia et al., 2021; Sukalingam, 2018).
Research by Nguyen *et al*, (2020) stated that BMG leaves have several active compounds that function as antioxidants and anti-inflammatory, including *2-Methyl-cis-7,8-epoxynonadecane*; *Caryophyllene*; *Hexadecanoic acid, ethyl ester*; *Humulene*; *Oxiraneundecanoic acid, 3-pentyl-, methyl ester, trans-*; *Phytol*; *Retinol, acetate*; *Squalene*; Vitamin E; *γ-himachalene* (Nguyen et al., 2020). The reaction between the active compounds of BMG must be known, one of which is the in sillico method.

The in silico test can describe experiments performed with the help of a computer. One of the in sillico processes is molecular docking which is the key to molecular biology and drug design methods using numerical aids. Docking can be used to perform virtual screening of large compound databases, classify results and propose structural hypotheses about how ligands inhibit targets, which is very important in primary optimization (Aziz et al., 2016; Dona et al., 2019; Setiawan dan Istyastono, 2015). Based on the description above, an in sillico study with molecular docking technique can be carried out to determine the potential of BMG extract as an anti-inflammatory based on PKC-β interactions, determine the test compound binding and interactions that can be formed, and predict the orientation and binding affinity of the active

compound from the BMG extract (Ngurah et al., 2021).

2. EXPERIMENTAL SECTION

2.1 Ingredient

Three-dimensional structure of protein kinase-c βII (2I0E) and comparison protein phospholipase C (7NXE) downloaded from the Protein Data Bank website (http://www.rcsb.org/pdb/) using the .pdb format. Three-dimensional structure of the active compound of BMG leaf extract, namely: 2-*Methyl-cis-7,8-epoxynonadecane* (*Pristanal*) (CID 537313); *Caryophyllene* (CID 5281515); *Hexadecanoic acid, ethyl ester* (*Palmitic acid*) (CID 21859); *Humulene* (CID 5281520); *Oxiraneundecanoic acid, 3-pentyl-, methyl ester, trans-* (*Methyl ricinoleate*) (CID 22821244); *Phytol* (CID 5280435); *Retinol, acetate* (CID 638034); *Squalene* (CID 638072); Vitamin E (CID 14985); *γ-himachalene* (CID 577062) dan *Ruboxistaurin mesylate* (CID 153999) which were downloaded from the PubChem website (http://www.pubchem.org/) using SDF. format.

Figure 1. BMG plant leaves (Taufiqurrahman I)

2.2 Tool

Laptop that has Microsoft Windows 10 operating system. Protein Data Bank (PDB) Website ID (https://www.rcsb.org) to download protein data. Pubchem website (https://pubchem.ncbi.nlm.nih.gov/) to download the active compound. The PyRx app includes Vina's AutoDock for validation and docking. Biovia Discovery Studio application to remove docked ligands and other impurities. pkCSM website (http://biosig.unimelb.edu.au/pkcsm/) and molinspiration (https://www.molinspiration.com/cgi-bin/properties) to predict the pharmacokinetic properties of the active compound of BMG leaf extract and the comparative ligand compound.

3. Research methods

3.1 *Protein and ligand preparation*

Protein Kinase c-βII (PKC-βII) and phospholipase C (PLC) were cleaned of water molecules and residues using the Biovia Discovery Studio application. The downloaded ligands were minimized using the PyRx application on the open babel menu.

3.2 *Validation*

The validation process for the docking method was carried out by re-docking PKC-βII with its natural ligand, C27 H28 N4 O2 (CID 11963533). The results are said to be valid if the RMSD (Root Mean Square Deviation) value < 2. The results of the PKC-β protein validation process

obtained an RMSD value of 0 which means the docking parameter is valid and can be used to dock a compound.

3.3 *Docking and visualization*

The docking process is carried out using the PyRx application version 0.8 using the AutoDock vina menu. The docking results are then visualized using the Biovia Discovery Studio version 21 application.

3.4 *Prediction of drug-likness, pharmacokinetics, and toxicity*

*Drug-likness*carried out based on Lipinski's rule of 5 to determine the similarity of the drug with the active compound. Pharmacokinetics and toxicity predictions were made through the pkCSM website (http://biosig.unimelb.edu.au/pkcsm/) and the molinspiration website (https://www.molinspiration.com/cgi-bin/properties).

4. RESULTS AND DISCUSSION

Table 1. Results of docking PKC-β with the active compounds of BMG leaf extract and Ruboxistaurin

Ligand	Binding Affinity	Amino Residue	Category
Pristanal	-5,8	THR404	Hydrogen
		*PHE353, *LEU348, *VAL356, *VAL356, *ALA369, *ALA369, LYS371, MET420, VAL423, *MET473, ALA483, ALA483, *LEU348, TYR422	Hydrophobic
Caryophyllene	-7,6	*PHE353, *VAL356, MET420, ALA483	Hydrophobic
Palmitic acid	-5,9	PHE485, GLU390	Hydrogen
		*VAL356, *VAL356, *ALA369, *ALA369, VAL423, MET420, *LEU348, *PHE353, *PHE353	Hydrophobic
Humulene	-7,5	*VAL356, ALA483	Hydrophobic
Methyl ricinoleate	-6,3	VAL356, THR404	Hydrogen
		*VAL356, *VAL356, LYS371, MET420, ALA483, *PHE353, *PHE353	Hydrophobic
Phytol	-5,8	*VAL356, *VAL356, *ALA369, *ALA369, LYS371, ALA483, LYS371, MET420	Hydrophobic
Retinol, acetate	-7,8	TYR422, TYR422	Hydrogen
		*LEU348, *VAL356, *VAL356, *ALA369, *ALA369, VAL423, *MET473, *PHE353*	Hydrophobic
Squalene	-7	*PHE353, *LEU348, *VAL356, *ALA369, MET420, ALA483, ALA483, *LEU348, TYR422	Hydrophobic
Vitamin E	-7,9	*PHE353, *VAL356, *VAL356, *VAL356, *ALA369, LYS371, MET420, ALA483, LYS371, *LEU348	Hydrophobic
γ-himachalene	-8,1	*PHE353, *VAL356, *VAL356, *ALA369, *PHE353	Hydrophobic
Ruboxistaurin	-9,1	LEU348	Hydrogen

	PHE353, VAL356, LEU348,N NALA369, MET473	Hydrophobic

***Figure* 2. a. Result 3D structure *docking of PKC-β with* Methyl ricinoleate. *b. 2D structure of PKC-β docking with* Methyl ricinoleate.**

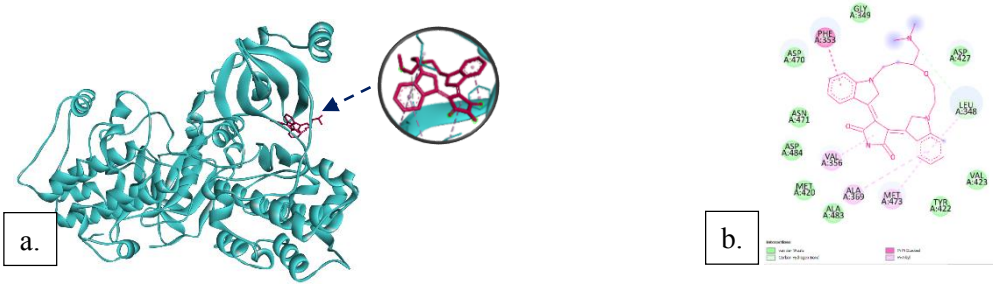

***Figure* 3. 1a. 3D structure of PKC-β docking with *Ruboxistaurin*. b. 2D structure of PKC-β docking with *Ruboxistaurin*.**

Table 2. The results of PLC-PKC-β docking with the active compounds of BMG leaf extract and Ruboxistaurin

Ligand	Binding Affinity	Amino Residue	Category
Pristanal	-3,5	ARG609	Hydrogen
		ARG609, PHE591	Hydrophobic
Caryophyllene	-5,3	ARG609, PH591	Hydrophobic
Palmitic acid	-3,9	ARG586, ARG586, THR590, THR596, SER588	Hydrogen
		ARG609, PHE591, HIS607	Hydrophobic
Humulene	-5,5	ARG609, PHE591	Hydrophobic
Methyl ricinoleate	-4,5	GLU730, GLU730	Hydrogen
		LYS743, *PHE731, *TYR740, HIS744	Hydrophobic
Phytol	-4,9	ARG5860, THR596, THR590	Hydrogen
		CYS608, CYS608, ARG609, ARG609, LEU623, LEU644, LEU623, LEU644, PHE591	Hydrophobic
Retinol, acetate	-5,1	GLN659	Hydrogen
		LYS549, PRO658, ALA662, ALA662	Hydrophobic
Squalene	-4,7	LYS743, *PHE731, *PHE731, *TYR740, *TYR740, *TYR740, *TYR740,	Hydrophobic
Vitamin E	-5,8	ARG562, THR590	Hydrogen
		ARG562	Electrostatic
		CYS608, CYS608, ARG609, ARG609, LEU623, PHE591	Hydrophobic
γ-himachalene	-5,5	ALA760, LYS763, ILE764, TYR754	Hydrophobic
Ruboxistaurin	-7,2	ASP732, ASP736, H-O	Hydrogen
		TYR740, TYR740, PHE731, TYR740	Hydrophobic

***Figure* 4. a. Result 3D structure docking PLC with results of docking PKC-β with *Methyl ricinoleate*. b. 2D structure of PLC docking results with PKC-β docking results with *Methyl ricinoleate*.**

***Figure* 5. a. Result 3D structure PLC docking with PKC-β docking results with *Ruboxistaurin*. b. 2D structure of PLC docking results with PKC-β docking results with *Ruboxistaurin*.**

Binding affinity is a measure of a compound's ability to bind to a receptor. The smaller the binding affinity value, the stronger and more stable the bond, and vice versa (Pantsar & Poso, 2018; Supriyanto et al., 2020).

This study showed that docking PKC-β with 10 active compounds of BMG leaf extract and a comparison ligand (*Ruboxistaurin*) resulted in a binding affinity that varied from -5.8 kcal/mol to -9.1 kcal/mol. It is known that the strongest interaction is in the PKC-β-*Ruboxistaurin* bond (comparison ligand) with a value of -9.1 kcal/mol, while the strongest bond of BMG leaf extract is -himachalene bond with a value of -8.1 kcal/mol. The weakest bonds were PKC-β-*Pristanal* and PKC-β-*Phytol* bonds with a value of -5.8 kcal/mol.

The results of protein to protein docking found that the highest binding affinity value was in the comparison ligand binding, namely PLC-(PKC-β-*Ruboxistaurin*) with a value of -7.2 kcal/mol. Whereasthe lowest value was found in the PLC-(PKC-β-*Pristanal*) bond with a value of -3.5 kcal/mol. It is known that the 10 active compounds of BMG leaf extract that have been tested for protein to protein have less stable bonds compared to their comparison ligands (*Ruboxistaurin*) because it has a higher binding affinity value.

Hydrogen bonding is a bond to consider when searching for active sites, especially since hydrogen bonding is the most important contributor to the structural stability of a protein. This is due to the fact that proteins are made of NH and OH groups that can donate hydrogen bonds and other groups that will accept them. Thus, hydrogen bonding helps in the specificity of the protein-ligand interaction stabilizing the ligand in the binding pocket (Ami Fini Faqiha et al., 2022; Dhorajiwala et al., 2019).

The results of docking PKC-β with 10 active compounds of BMG leaf extract and the comparison ligand (*Ruboxistaurin*) which has the most hydrogen bonds are owned by three bonds, namely the PKC-β-*Palmitic acid* bond (at residues PHE485 and GLU390), PKC-β- *Methyl ricinoleate* (at residues VAL423 and THR404), and PKC-β-*Retinol Acetate* (at residues TYR422 at a distance of 2.85162 and 3.03661Å). In the results of protein-to-protein docking, the most hydrogen bonds were in the PLC-(PKC-β-*Palmitic acid*) bond as many as 5 hydrogen bonds at residues ARG586 (3.17751Å and 3.04531Å), THR590, THR596, and SER588. The ligand-receptor bond will be more stable the more the number of hydrogen bonds, because hydrogen bonds affect the stability of the structure of a protein (Rena et al., 2022). The smaller the hydrogen bond distance, the stronger the bond will be and not easily separated (Pratama & Nashihah, 2021). The results of visual docking of PKC-β bonds with 10 active compounds of BMG leaf extract seen the same amino acid residue interactions as the comparison ligand (*Ruboxistaurin*). The similarity of interactions with the comparison ligand allows for the same biological activity as the comparison ligand (Prasetiawati et al., 2021). The amino residue bonds that have the most similarities with the comparison ligand are found in the PKC-β-*Palmitic acid* (at PHE485 and GLU390) residues, PKC-β-*Methyl ricinoleate* (at the VAL423 and THR404) residues, and PKC-β-*Retinol Acetate* (at residues VAL423 and THR404). at residue TYR422 at a distance of 2.85162 and 3.03661).

Table 3. Lipinski's Rule of Five test on the active compound of BMG leaf extract and the comparative ligand *Ruboxistaurin*

Ligand	**MW (g/mol)**	**Log P**	**HBA**	**HBD**	**TPSA Å**	**nviolations**
Pristanal	296.539	6.8911	1	0	12.53	1
Caryophyllene	204.357	4.7252	0	0	0	0
Palmitic acid	284.484	6.1884	1	1	37.30	1
Humulene	204.357	5.0354	0	0	0	1
Methyl ricinoleate	312.494	5.5673	2	1	46.53	1
Phytol	296.539	6.3641	1	1	20.23	1
Retinol, acetate	328.496	6.0811	2	0	26.30	1
Squalene	410.73	10.605	0	0	0	1
Vitamin E	430.717	8.84026	2	1	29.46	1
γ-himachalene	204.357	4.7252	0	0	0	0
Ruboxistaurin	468.557	3.5137	6	1	72,27	0

MW : Molecular Weight (<500); HBA : Hydrogen Bond Acceptors (<10); HBD : Hydrogen Bond Donor (< 5); LogP : partition coefficient 5; TPSA : Topological Polar Surface Area; Nviolations : number of violations of lipinski's rules

Table 4. Predictive test of pharmacokinetic properties and toxicity of active compounds of BMG leaf extract and *Ruboxistaurin*

ligand	HIA (%)	Caco-2 (10^{-6} cm/s)	VDss (Log L/kg)	CYP2D6 Inhibitor	Total Clearance	AMES Toxicity	Hepatotoxicity	LD50 (mol/kg)	LOAEL (log mg/kg_bw/day)
Pristanal	91.808	1.226	0.406	No	1.631	No	No	1.40	0.991
Caryophyllene	94.845	1.423	0.652	No	1.088	No	No	1.61	1.416
Palmitic acid	91.462	1.572	-0.578	No	1.678	No	No	1.42	3.313
Humulene	94.682	1.421	0.505	No	1.282	No	No	1.76	1.336
Methyl ricinoleate	91.956	1.57	-0.509	No	1.615	No	No	1.57	2.701
Phytol	90.71	1.515	0.468	No	1.686	No	No	1.60	1.043
Retinol, acetate	94.33	1.188	0.408	No	1.503	No	Yes	1.67	2.276
Squalene	90.341	1.216	0.411	No	1.791	No	No	1.84	0.946
Vitamin E	89.782	1.345	0.709	No	0.794	No	No	2.07	1.987
γ-himachalene	94.556	1.418	0.648	No	1.093	No	No	1.68	1.346
Ruboxistaurin	94.291	0.918	0.584	No	0.719	Yes	Yes	2.381	1.576

4.1 Pharmacokinetics

Human Intestinal Absorption (HIA) and permeability of Caco-2 cells were studied to predict drug absorption (Prasetiawati et al., 2021). The results of the pharmacokinetic prediction test showed that the 10 active compounds of BMG leaf extract and *Ruboxistaurin* tested had a percentage above 89%. The absorption is said to be good if the absorption value is >80%, while the absorption is bad if the absorption value is <30% (Maslikah et al., 2019). Caco-2 was used to predict the gastrointestinal permeability of drugs. Based on the nature of the human small intestine, this model expresses enterocytes, transporters, cytochrome P450 enzymes and microvilli. The active compounds of leaf extract BMG and *Ruboxistaurin* have high Caco-2 permeability because they have log Papp values above $0{,}9^{-6}$ cm/s (Yeni & Rachmania, 2022; Zackria et al., 2022).

Volume of distribution (VDSS) is the volume of drug dose needed to be distributed homogeneously at a balanced level in blood plasma, the higher the volume of distribution, it means that more compounds are distributed compared to blood plasma in the body(Purwanto et al., 2021; Wahyuningsih et al., 2022). Based on pkCSM predictions, the Log VD value <-0.15 means that the volume of distribution of the compound is low, and is said to be high if >0.45 (Firdausy et al., 2020; Kirtishanti et al., 2020). **Table 3**.The prediction results show that the VDss ranges from -0.578 L/kg to 0.709 L/kg, the compound *Methyl ricinoleate* and *Retinol*, acetate has a low VDss value.

Cytochrome P450 (CYP450) is an important detoxifying enzyme in the body found in the liver and is responsible for many drugs. Cytochrome P450 inhibitors can affect drug metabolism, so it is necessary to evaluate whether a compound can affect CYP450 which in this study is represented by the isoform of cytochrome P2D6 (CYP2D6) (Ekowati et al., 2018; Sugiharto et al., 2021). The active compound of ramania leaf extract and the comparison ligand tested in this study did not have inhibitory power against CYP450, so that the pharmacokinetic predictions were enzymatic and not hepatotoxic(Sugiharto et al., 2021; Utami et al., 2022).

Excretion prediction value*total clearance*can be performed using CLTOT (a combination of hepatic clearance and renal clearance)(Krihariyani et al., 2021). Result of prediction*total clearance*of the active compound of ramania leaf extract and the comparison ligand ranged from 0.719 log mL/minute/kg to 1.791 mL/minute/kg where the comparison ligand had a value of*total clearance*the smallest, so that *Ruboxistaurin* as a comparison ligand is the slowest to be excreted from the body.

4.2 Toxicology

Determining the toxicity present in a compound is done by using the Ames toxicity test, this test has been widely used to measure the mutagenic potential of a compound using bacteria. The mutagenicity of a compound that can act as a carcinogen shows a positive result(Purwanto et al., 2021). **Table 4**. Shows the results of all tested BMG leaf extract compounds that are neither mutagenic nor carcinogenic, except for Ruboxistaurin (comparison ligand). It was also known in the hepatotoxicity test that all BMG leaf extract compounds were not hepatotoxic, except for *retinol acetate* and *Ruboxistaurin* compounds which were known to be hepatotoxic.

Prediction of toxicity for drug-like molecules is an important parameter for calculating the total tolerability before being administered to animal and human models. The compounds tested using pkCSM predictions showed acute and chronic lethal doses as Oral Rate Acute Toxicity (LD50) and Oral Rate Chronic Toxicity (LOAEL) (**Table 4**.) (Bharadwaj et al., 2022; Simoben et al., 2020). LD50 of compound *Methyl ricinoleate* worth1.57 mol/kg which is smaller than the comparison ligand *Ruboxistaurin* with value 2,381 moles/kg. In contrast to the results of nLOAEL value, where compound *Methyl ricinoleate* higher by value 2,701 log mg/kg_bb/day, compared to*Ruboxistaurin*(comparison ligand) which is worth 1,576 log mg/kg_bb/day.

The results of the Molecular docking study showed that 10 active compounds of BMG extract were potential candidates for anti-inflammatory drugs. Methyl ricinoleate compound is a compound that shows the best affinity compared to 9 other compounds. Methyl ricinoloeate compounds work in anti-inflammatory processes by inhibiting the activity of PKC-β, thereby inhibiting the activation of the NF-κB pathway which results in reduced pro-inflammatory mediators such as Nitric Oxide (NO), inducible Nitric Oxide Synthase (iNOS), Prostaglandin E2 (PGE2), cyclooxygenase-2 (COX-2), and cytokines, such as Tumor necrosis factor alpha (TNF-α) (Da-Silva et al., 2019; Martin-Perez et al., 2019, 2021).

COMPETING INTERESTS

The author has no competing interests to declare.

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References

[1] Khan, M. K., and Jindal, M. K., 2022, Multilayer Perceptron to Assess the Impact of Anatomical Risk Factors on Traumatic Dental Injuries : An Advanced Statistical Approach of Artificial Intelligence in Dental Traumatology, *J. Orofac. Sci.*, 14 (1), 28–34.
[2] Lam, R., 2016, Epidemiology and outcomes of traumatic dental injuries: A review of the literature, *Aust. Dent. J.*, 61, 4–20.
[3] Zaleckiene, V., Peciuliene, V., Brukiene, V., and Drukteinis, S., 2014, Traumatic dental injuries: etiology, prevalence and possible outcomes, *Stomatologija*, 16 (1), 7–14.
[4] Majewski, M., Kostrzewska, E. P., and Ziółkowska, D. S., 2013, Traumatic dental injuries – practical management guide, 216–218.
[5] Izzi, V., Masuelli, L., Tresoldi, I., Sacchetti, P., Modesti, A., Galvano, F., and Bei, R., 2012, The effects of dietary flavonoids on the regulation of redox inflammatory networks, *Front. Biosci.*, 17 (7), 2396–2418.
[6] Shita, A. D. P., 2015, Perubahan Level TNF-α dan IL-1 pada Kondisi Diabetes Mellitus, *Pros. Dent. Sci. Meet. II, Fak. Kedokt. Gigi, Univ. JEMBER*, (1), 1–7.
[7] Alleboina, S., Wong, T., Singh, M. V., and Dokun, A. O., 2020, Feature article: Inhibition of protein kinase C beta phosphorylation activates nuclear factor-kappa B and improves postischemic recovery in type 1 diabetes, *Exp. Biol. Med.*, 245 (9), 785–796.
[8] Leppänen, T., Tuominen, R. K., and Moilanen, E., 2014, Protein kinase C and its inhibitors in the regulation of inflammation: Inducible nitric oxide synthase as an example, *Basic Clin. Pharmacol. Toxicol.*, 114 (1), 37–43.
[9] Liu, T., Zhang, L., Joo, D., and Sun, S. C., 2017, NF-κB signaling in inflammation, *Signal Transduct. Target. Ther.*, 2 (March), .
[10] Robertson, M. J., Kahl, B. S., Vose, J. M., De Vos, S., Laughlin, M., Flynn, P. J., Rowland, K., Cruz, J. C., Goldberg, S. L., Musib, L., Darstein, C., Enas, N., Kutok, J. L., Aster, J. C., Neuberg, D., Savage, K. J., LaCasce, A., Thornton, D., Slapak, C. A., and Shipp, M. A., 2007, Phase II study of enzastaurin, a protein kinase C beta inhibitor, in patients with relapsed or refractory diffuse large B-cell lymphoma, *J. Clin. Oncol.*, 25 (13), 1741–1746.
[11] Rahma, A., Taufiqurrahman, I., and Edyson, 2017, PERBEDAAN TOTAL FLAVONOID ANTARA METODE MASERASI DENGAN SOKLETASI PADA EKSTRAK DAUN RAMANIA (Bouea macrophylla Griff), *Dentino J. Kedokt. gigi*, 1 (1), 22–27.
[12] Rizkia, D., Taufiqurrahman, I., and Dewi, R. K., 2021, THE EFFECT OF RAMANIA LEAF (Bouea macrophylla Griff) EXTRACT GEL ON COLLAGEN FIBERS DENSITY IN INCISIONAL WOUND OF MALE WISTAR RATS, *Dentino J. Kedokt. Gigi*, 6 (1), 96.
[13] Sukalingam, K., 2018, Preliminary phytochemical analysis and in vitro antioxidant properties of Malaysian 'Kundang' (Bouea macrophylla Griffith), *Trends Pyhtochemical Res.*, 43 (6), 261–266.
[14] Nguyen, N. H., Nguyen, T. T., Ma, P. C., Ta, Q. T. H., Duong, T. H., and Vo, V. G., 2020, Potential antimicrobial and anticancer activities of an ethanol extract from bouea macrophylla, *Molecules*, 25 (8), .
[15] Dona, R., Frimayanti, N., Ikhtiarudin, I., Iskandar, B., Maulana, F., and Silalahi, N. T., 2019, Studi

In Silico, Sintesis, dan Uji Sitotoksik Senyawa P-Metoksi Kalkon terhadap Sel Kanker Payudara MCF-7, *J. Sains Farm. Klin.*, 6 (3), 243.
[16] Aziz, F. K., Nukitasari, C., Oktavianingrum, F. A., Aryati, L. W., and Santoso, B., 2016, Hasil In Silico Senyawa Z12501572, Z00321025, SCB5631028 dan SCB13970547 dibandingkan Turunan Zerumbon terhadap Human Liver Glycogen Phosphorylase (1l5Q) sebagai Antidiabetes, *J. Kim. Val.*, 2 (2), 120–124.
[17] Setiawan dan Istyastono, 2015, UJI IN SILICO SENYAWA 2,6-DIHIDROKSIANTRAQUINON SEBAGAI LIGAN PADA RESEPTOR ESTROGEN ALFA Felicia Fraulein Setiawan *) , Enade Perdana Istyastono Fakultas Farmasi, Universitas Sanata Dharma, Yogyakarta, *J. Farm. Sains dan Komunitas*, 12 (2), 76–79.
[18] Ngurah, G., Candra, H., Adnyana, I. M., and Wijaya, P., 2021, Molecular Docking Kaempferol sebagai Antiinflamasi pada Aterosklerosis secara In Silico Molecular Docking Kaempferol as Anti-Inflammatory in Atherosclerosis in Silico, 7 (1), 13–18.
[19] Pantsar, T., and Poso, A., 2018, Binding affinity via docking: Fact and fiction, *Molecules*, 23 (8), 1DUMMY.
[20] Supriyanto, S., Rifa'i, M., Yunianta, Y., and Widjanarko, S. B., 2020, Potential Use of Compounds from Neem Leaves (Azadirachta indica Juss) as PPARg and ERa Inhibitors to Control Breast Cancer Cell Growth In Silico Model, *Alchemy*, 8 (1), 18–22.
[21] Dhorajiwala, T. M., Halder, S. T., and Samant, L., 2019, Comparative in silico molecular docking analysis of l-threonine-3-dehydrogenase, a protein target against African trypanosomiasis using selected phytochemicals, *J. Appl. Biotechnol. Reports*, 6 (3), 101–108.
[22] Ami Fini Faqiha, Indrawijaya, Y. Y. A., Suryadinata, A., Amiruddin, M., and Mutiah, R., 2022, Potensi Senyawa Nitazoxanide dan Arbidol sebagai Antivirus SARS-CoV-2 terhadap Reseptor NSP5 (7BQY dan 2GZ7) dan ACE2 (3D0G dan 1R4L), *J. Food Pharm. Sci.*, 5 (1), 570–583.
[23] Rena, S. R., Nurhidayah, N., and Rustan, R., 2022, Analisis Molecular Docking Senyawa Garcinia Mangostana L Sebagai Kandidat Anti SARS-CoV-2, *J. Fis. Unand*, 11 (1), 82–88.
[24] Pratama, R. R., and Nashihah, S., 2021, STUDI PENAMBATAN MOLEKULER SENYAWA FLAVONOID DAUN JAMBU BIJI (Psidium guajava L.) TERHADAP SARS-CoV-2 3CL PROTEASE, *Med. Sains J. Ilm. Kefarmasian*, 6 (1), 9–24.
[25] Prasetiawati, R., Suherman, M., Permana, B., and Rahmawati, R., 2021, Molecular Docking Study of Anthocyanidin Compounds Against Epidermal Growth Factor Receptor (EGFR) as Anti-Lung Cancer, *Indones. J. Pharm. Sci. Technol.*, 8 (1), 8.
[26] Maslikah, S. I., Amalia, A., and Afifah, S., 2019, Red betel apigenin compound (Piper crocatum Ruiz & Pav.) as an anti-inflammatory rheumatoid arthritis agent through virtual screening, *AIP Conf. Proc.*, 2120, .
[27] Yeni, Y., and Rachmania, R. A., 2022, The Prediction of Pharmacokinetic Properties of Compounds in Hemigraphis alternata (Burm . F .) T . Ander Leaves Using pkCSM, *Indones. J. Ch em*, 22 (4), 1081–1089.
[28] Zackria, A. A., Pattabiraman, R., Murthy, T. P. K., Kumar, S. B., Mathew, B. B., and Biju, V. G., 2022, Computational screening of natural compounds from Salvia plebeia R. Br. for inhibition of SARS-CoV-2 main protease, *Vegetos*, 35 (2), 345–359.
[29] Wahyuningsih, D., Purnomo, Y., and Tilaqza, A., 2022, In Silico Study of Pulutan (Urena lobata) Leaf Extract as Anti Inflammation and their ADME Prediction, *J. Trop. Pharm. Chem.*, 6 (1), 1–14.
[30] Purwanto, B. T., Hardjono, S., Widiandani, T., and Nasyanka, A. L., 2021, In Silico Study and ADMET prediction of N-(4-fluorophenylcarbamothioyl) Benzamide Derivatives as Cytotoxic Agents, *J. Hunan Univ. Sci.*, 48 (2), .
[31] Firdausy, A. F., Muti'ah, R., and Rahmawati, E. K., 2020, Predicting Pharmacokinetic Profiles of Sunflower's (Helianthus annuus L.) Active Compounds using in Silico Approach, *J. Islam. Med.*, 4 (1),

1–7.
[32] Kirtishanti, A., Siswandono, Hardjono, S., and Kesuma, D., 2020, Molecular Docking of Benzoylurea Derivatives as Potential Anti-Breast Cancer Agent and Its Admet Profiles, *J. Glob. Pharma Technol.*, 12 (6), 726–735.
[33] Ekowati, J., Diyah, N. W., Nofianti, K. A., Hamid, I. S., and Siswandono, 2018, Molecular docking of ferulic acid derivatives on P2Y12 receptor and their ADMET prediction, *J. Math. Fundam. Sci.*, 50 (2), 203–219.
[34] Sugiharto, M. I., Bintari, Y. R., and Damayanti, D. S., 2021, Mekanisme Senyawa Aktif Daun Sirsak (Annona muricata Linn.) Sebagai Anti Diabetes : Studi In Silico, *J. Kedokt. Komunitas*, 9 (2), 1–13.
[35] Utami, J. P., Kurnianingsih, N., and Faisal, M. R., 2022, An in Silico Study of the Cathepsin L Inhibitory Activity of Bioactive Compounds in Stachytarpheta jamaicensis as a Covid-19 Drug Therapy, *Makara J. Sci.*, 26 (1), 25–36.
[36] Krihariyani, D., Haryanto, E., and Sasongkowati, R., 2021, In Silico Analysis of Antiviral Activity and Pharmacokinetic Prediction of Brazilein Sappan Wood (Caesalpinia sappan L.) Against SARS-CoV-2 Spike Glycoproteins, *Indones. J. Med. Lab. Sci. Technol.*, 3 (1), 26–37.
[37] Bharadwaj, K. K., Ahmad, I., Pati, S., Ghosh, A., Sarkar, T., Rabha, B., Patel, H., Baishya, D., Edinur, H. A., Abdul Kari, Z., Ahmad Mohd Zain, M. R., and Wan Rosli, W. I., 2022, Potent Bioactive Compounds From Seaweed Waste to Combat Cancer Through Bioinformatics Investigation, *Front. Nutr.*, 9 (April), 1–16.
[38] Simoben, C. V., Qaseem, A., Moumbock, A. F. A., Telukunta, K. K., Günther, S., Sippl, W., and Ntie-Kang, F., 2020, Pharmacoinformatic Investigation of Medicinal Plants from East Africa, *Mol. Inform.*, 39 (11), 1–15.
[39] Da-Silva, C. F., Sousa, N. R. T., Amorim, I. H. F., Leite, B. G., Neves, K. R. T., Costa, J. G. M., Felipe, C. F. B., and De-Barros Viana, G. S., 2019, Antinociceptive and anti-inflammatory activities of a triterpene-rich fraction from himatanthus drasticus, *Brazilian J. Med. Biol. Res.*, 52 (5), 1–12.
[40] Martin-Perez, M., Ito, T. K., Grillo, A. S., Valente, A. S., Han, J., Entwisle, S. W., Huang, H. Z., Kim, D., Yajima, M., Kaeberlein, M., and Villen, J., 2019, Protein kinase C is a key target for attenuation of Leigh syndrome by rapamycin, *bioRxiv*, 562207.
[41] Martin-Perez, M., Anthony S. Grillo, Ito, T. K., Valente, A. S., Han, J., Entwisle, S. W., Huang, H. Z., Kim, D., Yajima, M., Kaeberlein, M., and Villén, J., 2021, PKC downregulation upon rapamycin treatment attenuates mitochondrial disease, *Nat Metab*, 176 (5), 139–148.