

HARIYANTI-Molecular Docking Study of Lemon (*Citrus limon* (Linn) Burm. f) Flavonoid Derivatives Compound in Receptor Cyclooxygenase-1 (COX-1) as Antiplatelet in Ischaemic Stroke Disease

by Hariyanti Uploaded By Mas'ud Syaiful

Submission date: 31-Mar-2023 08:18AM (UTC+0700)

Submission ID: 2051541763

File name: Rizky_scite_press_Scite_press_-_Hariyanti_Hariyanti.pdf (1.57M)

Word count: 3614

Character count: 19462

Molecular Docking Study of Lemon (*Citrus limon* (Linn) Burm. f) Flavonoid Derivatives Compound in Receptor Cyclooxygenase-1 (COX-1) as Antiplatelet in Ischaemic Stroke Disease

Rizky Arcinthy Rachmania*, Hariyanti, Nurul Rochmah

Faculty of Pharmacy and Science, Universitas Muhammadiyah Prof. DR. HAMKA (UHAMKA)
Islamic Center, Jl. Delima II/IV Perumnas Klender, Jakarta Timur, 13460, Telp. (021) 8611070

Keywords: *Citrus limon*, COX-1, flavonoid derivatives, antiplatelet, docking.

Abstract: Lemon (*Citrus limon* (Linn) Burm. f) is a plant that has efficacy as antiplatelet. Flavonoids in lemon potentially obstruct COX-1 (Cyclooxygenase-1) receptor which has an important role in increasing thromboxane A₂ the process of ischaemic stroke. This research aims at looking for flavonoids activity from citrus lemon which is expected to be the antiplatelet drug candidates. The method used in this research was the molecular docking method using Autodock Vina and Pymol software programs. The results showed that the value of ΔG binding affinity Aspirin as the standard ligand was -6,5 kcal/mol and lemon flavonoid derivatives that have the lowest ΔG binding affinity value was on Neohesperidin -15,4 kcal/mol and Rutin -15,3 kcal/mol. This research shows that Neohesperidin and Rutin in lemon can be used as drug candidate of antiplatelet in ischaemic stroke disease.

1 INTRODUCTION

Stroke is the third most common disease after heart disease and cancer. According to the World Health Organization (WHO), the definition of stroke is a rapidly growing clinical sign of focal (or global) brain dysfunction, with symptoms that last for 24 hours or more, can cause death, with no cause other than vascular. Stroke is characterized by a sudden loss of blood circulation to the brain area resulting in a neurological deficit (Gund *et al.*, 2013). In general, strokes are classified as ischaemic and hemorrhagic. Ischaemic stroke is an ischaemic brain tissue arising from a blockage in the cervical vascular blood vessels or brain tissue hyperfusion by various factors such as atherothrombosis, embolism or hemodynamic instability (Chung and Caplan, 2007).

Stroke is the third leading cause of death in the United States and Britain after heart disease and cancer, and the main cause of adult disability. In the United States, more than 160,000 adult Americans die of strokes every year. In Europe, around 650,000 people died from strokes. In the United States, people who report strokes over 65 years (Gund *et al.*, 2013). According to the latest data from Riset Kesehatan Dasar in 2013, the number of stroke

patients in Indonesia in 2013 based on the diagnosis of Health Workers is estimated to be 1,236,825 people (7.0 ‰), whereas based on diagnosis symptoms are estimated as many as 2,137,941 people (12.1 ‰) (Balitbang, 2013).

Antiplatelet therapy is an important long-term treatment for all patients at risk of atherothrombosis such as ischaemic stroke. A comparison of some antiplatelet drugs statistically indicated a significant difference in outcomes (Shinohara *et al.*, 2010). Strong platelet function inhibitors have been developed in recent years with different drug-action mechanisms, because when combined the effects are additive or even synergistic (Ringleb *et al.*, 2011). These antiplatelet drugs are classified into several groups based on their mechanism of action, namely inhibition of prostaglandin synthesis (aspirin), inhibition of ADP-induced platelet aggregation (clopidogrel, prasugrel, ticlopidine), and blockade of the receptor glycoprotein IIb/IIIa in platelets (abciximab, tirofiban, and eptifibatid) (Ringleb *et al.*, 2011). However, these drugs can cause serious side effects for users such as gastrointestinal bleeding, leukopenia, and thrombocytopenia (Ringleb *et al.*, 2011). Because of the side effects of

these drugs, herbal medicine is also an option for patients.

Indonesia has a wealth of herbs, one of which is lemon (*Citrus limon* (Linn) Burm F.). One of the compounds in lemon that is thought to be potential as an antiplatelet is flavonoids. Based on studies that have been conducted, lemon plants are known to have activity as an anticoagulant and antiplatelet *in vitro/in vivo* (Riaz *et al.*, 2014). Flavonoids are one type of antioxidant that can inhibit adhesion, aggregation and platelet secretion (Retnaningsih *et al.* 2007). The ability of flavonoids to inhibit platelet aggregation is caused by the flavonoid inhibiting the metabolism of arachidonic acid by cyclooxygenase enzyme, thus reducing the amount of thromboxane A₂ (TXA₂) production and platelet aggregate production causing blood vessel blockage (Middleton *et al.*, 2000).

Cyclooxygenase (COX) is a functional enzyme bound to the membrane acting to catalyze two important stages in the formation of prostanoid, cyclooxygenation, and peroxidation reaction. The cyclooxygenation reaction stage is the stage at which COX conducts a cyclization process and the addition of two oxygen molecules to arachidonic acid to form prostaglandin G₂ (PGG₂). The peroxidation stage is the reduction stage of PGG₂ into an unstable endoperoxide compound called prostaglandin H₂ (PGH₂). There are two main isoforms of the cyclooxygenase enzyme, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is expressed continuously and has a function as a regulator of homeostasis in the function of protecting the gastric mucosa, maintaining platelet integrity, and maintaining the function of renal perfusion. COX-2 plays a role in pathologies such as inflammation, pain, and cancer (Claria, 2003).

Molecular docking is a device that can be used to study the interactions that occur from a molecular complex. Molecular docking helps in studying drug or ligand interactions with receptors or proteins. Molecular docking is conducted by identifying the corresponding active site of the receptor/protein, obtaining the best geometry of the receptor ligand and calculating the interaction energy of each different ligand for designing a more effective ligand. To perform molecular docking, the first thing required is a three-dimensional structure of ligand and receptor. Virtual screening is a computational technique in the design of new computer-based drugs (*in silico*) to identify the structures most likely to bind to a targeted drug, usually a protein or enzyme receptor (Mukesh and Rakesh, 2011).

21

2 MATERIALS AND METHODS

2.1 Materials

The tool used in this research was hardware and software. Hardware performances were equipped with AMD E1-2100 APU with Radeon™ HD Graphics CPU GHz processor, 2GB RAM, and Microsoft Windows 7 Ultimate 64-bit operating system, 24-inch Hp® Monitor, and Bolt® modem for internet access. The software programs were equipped with the MGL Tools 1.5.6 Package consisting of Autodock Vina, Autodock Tools, Pymol (DeLano Scientific LLC.), Discovery Studio 4.5 Client, CLC Drug Discovery Workbench 2.5, Chem office 2010, Protein Data Bank (<http://www.rcsb.org/pdb>).

The material used as the 3D structure of the platelet receptor that was downloaded from Protein Data Bank which has formatted .pdb, i.e. prostaglandin H₂ synthase-1 (PDB ID: 1CQE) and 3D structure used was flavonoid derived compound among others were eriocitrin, hesperidin, neohesperidin, diosmin, rutin, luteolin, nobiletin, sinensetin, and tangeritin (Molina *et al.*, 2010).

2.2 Methods

Preparation of Prostaglandin H₂ Synthase-1 (COX-1) structure was conducted by downloading the COX-1 receptor macromolecule from the Protein Data Bank from <http://www.rcsb.org/pdb> formatted from .pdb website to .pdb. Cavity must be determined to find the residues in the receptor. The cavity determination was performed using the offline CLC Drug Discovery Workbench 2.5 software that was downloaded from <http://www.clebio.com/products/cle-drug-discovery-workbench/>. Receptor macromolecules were separated from solvents and ligands or non-standard residues. The separation of macromolecules from unnecessary molecules was done using the Discovery Studio 4.0 program. The result of the separation was saved in .pdb format. The design of the ligand structure of the flavonoid derived compound consists of eriocitrin, hesperidin, neohesperidin, diosmin, rutin, luteolin, nobiletin, sinensetin, and tangeritin were downloaded from the PubChem site (<http://pubchem.ncbi.nlm.nih.gov/>).

The docking file preparation was conducted by using Autodock Tools that was optimized by setting the number of action torsion and converting the format to .pdbqt. While the receptor preparation was being conducted by adding hydrogen polar, the grid

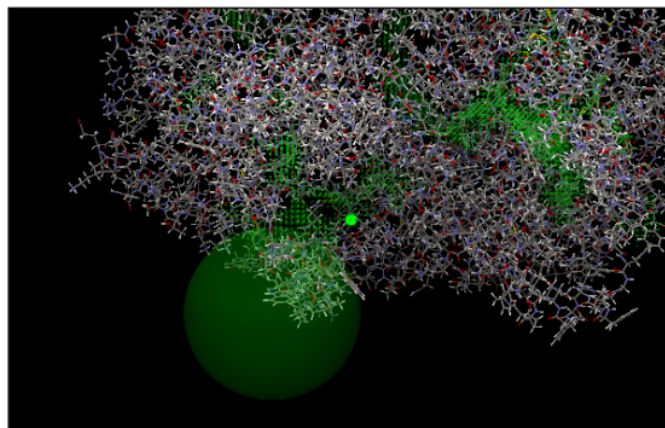


Figure1: Results of COX-1 receptor site binding detection (CLC Drug Discovery Software). Description: Areas marked with green spots are cavity areas. The area in the white circle is the actual cavity as a binding site on the COX-1 receptor.

box was set to know the position of the binding site and the format was changed to .pdbqt. This file was saved in a single folder in the C: drive on the computer. Molecular Docking Process was conducted using Autodock Vina. Ligands and receptor that were already in drive C: copied and converted in the form of notepad were saved with a conf.txt name, Autodock Vina was executed with command prompt program.

Molecular docking analysis was done by looking at the free energy value of binding docking results, viewed at the output in log.txt format. The selected ligand-receptor complex was the complex which has the lowest free binding energy value for further analysis. The interaction between receptor and ligand can be observed in Pymol software

3 RESULTS AND DISCUSSION

The macromolecule that was used as the docking target was the Cyclooxygenase-1 enzyme (COX-1). COX-1 was downloaded from the Protein Data Bank. The PDB ID of COX-1 used was 1CQE which has been used as a reference in predicting antiplatelet activity based on previous research (Wu *et al.*, 2007). 1CQE consisted of 580 amino acid residues. The 1CQE structure was downloaded from the RCSB site with the format .pdb. Cyclooxygenase-1 (COX-1) downloaded from the RCSB must be cleaned using the offline Discovery Studio 4.5 software because the receptor on RCSB is holoprotein, which contains many ligands in the

receptor. The reason for the cleansing was to remove the original disturbing ligands and water attached to the receptor to speed up the docking process.

Molecular docking is carried out on the specific region of the target protein, which is to be a binding site. The location of this site is based on the ligand or cofactor position co-crystallized with the structure of the target protein, or the position of the amino acids known for the binding position.

To get the cyclooxygenase-1 receptor inhibitory effect, it must first recognize the residues that form cavity and pocket in the target (receptor). The cavity is a substance that is owned by the receptor. A pocket is a space inside the cavity as access to the bond between the ligand and the receptor, resulting in the expected effect. Cavity search was carried out using the CLC Drug Discovery Workbench 2.5 software located at the site <http://www.clcbio.com/products/clc-drug-discovery-workbench/> (Glaab 2015). CLC Drug Discovery Workbench 2.5 is a software managed by CLC Bio A QIAGEN Company. This software can detect bindings on receptors through the programs provided.

Usually, more than one cavity is found in the target receptor. Therefore, it was necessary to evaluate the cavity to see the possibility of a cavity being a binding site that actually used the CLC Drug Discovery Workbench 2.5 software. In the search for COX-1 cavity receptors, many cavities were detected in the COX-1 receptor regions (Figure 1). It was necessary to do cavity evaluation by setting a binding site on the Drug Discovery

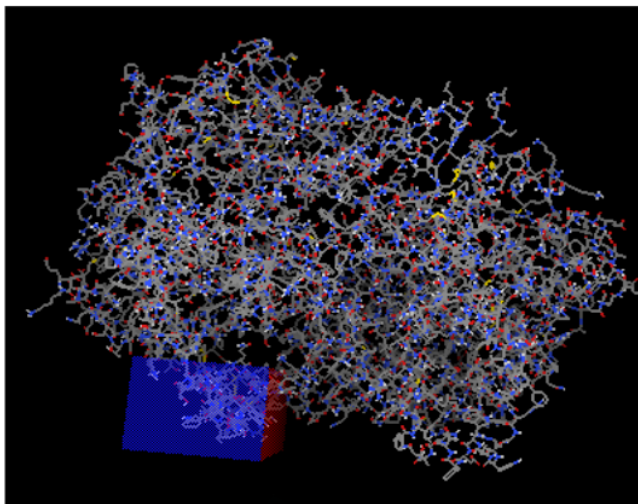


Figure 2: Results of COX-1 receptor site binding detection (CLC Drug Discovery Software And Autodock Tools). Description: The area in the blue box is the actual cavity as a binding site on the COX-1 receptor.

Workbench 2.5 CLC work program. After cavity evaluation, the COX-1 receptor area that had been detected by cavity showed a more specific area that described the actual cavity as a binding site (Figure 1). This area is the place where interactions between amino acid residues and receptors and ligands will be used as the grid box area. The selection of cavity binding pocket by CLC drug design based on the largest pocket size (Li *et al.*, 2008) and more open and compact pockets have good properties for drug binding (Cheng *et al.*, 2007). Ligands, receptor, and Autodock Vina software was saved in a folder located on drive C: windows in the vina folder. The destination was saved in one folder so that the docking process can be carried out through the command prompt. The command prompt is a command line interface based program with written work orders. At the receptor, the grid box must be determined according to the results of the cavity binding pocket from CLC Drug Design which was set in the offline software of Autodock Tools. The grid box used for ICQE in the oriented docking process was at the center_x coordinate = 28,453; center_y = 7.271; center_z = 195.072, grid size 56 x 40 x 122Å with a spacing of 0.375Å (Figure 2). Analysis of results in molecular docking includes values of ΔG binding affinity and Root Mean Square Deviation (RMSD). Molecular docking was conducted to see the complex conformation of the receptor-the docked ligand with Autodock Vina.

Determination of ligand conformation can be seen from the results that come out in the command prompt program which will be selected one of the best out of nine conformations out of the docking results by using Autodock Vina. The docking result was the value of ΔG binding affinity (kcal/mol) for one ligand. Affinity binding is a docking parameter using Autodock Vina. The smaller the value of the ΔG binding affinity, the affinity between the receptor - the ligand will be higher and otherwise, the greater the value of ΔG binding affinity, the affinity between receptor-ligand complex will be lower (Rachmania *et al.*, 2015).

Table 1: Results of standard ligand docking (Aspirin), lemon plant ligand with COX-1 receptor (ICQE) using Autodock Vina Software.

Ligands	ΔG Binding Affinity (kcal/mol)	RMSD (Å)
Aspirin	-6.5	0
Neohesperidin	-15.4	0
Rutin	-15.3	0
Eriocitrin	-14.9	0
Hesperidin	-14.7	0
Diosmin	-14.1	0
Luteolin	-10.0	0
Nobiletin	-9.5	0
Sinensetin	-9.5	0
Tangeritin	-9.5	0

Table 2: The distance of amino acid bond and residue, ligand functional group between Aspirin, Neohesperidin, and Rutin with COX-1 Receptor (1CQE) using PyMol Software.

Ligands	The Distance of hydrogen bond (Å)	Amino Acid Residue Binding	Functional groups binding
Aspirin	2,8	Cys ⁴¹	-O
	3,4	Cys ⁴¹	-O
Neohesperidin	3,0	Arg ⁴⁶⁹	-OH
	3,1	Arg ⁴⁶⁹	-OH
	3,5	Gln ⁴⁴	-O
	3,3	Cys ⁴¹	-OH
	3,4	Cys ⁴¹	-OH
	3,2	Lys ⁴⁶⁸	-OH
Rutin	3,4	Lys ⁴⁶⁸	-OH
	2,3	Glu ⁴⁶⁵	-OH
	3,0	Glu ⁴⁶⁵	-OH
	2,8	Asp ¹³⁵	-OH
	3,2	Asp ¹³⁵	-OH
	3,2	Gly ⁴⁵	-OH
	3,4	Gly ⁴⁵	-OH
	2,6	Cys ⁴¹	-O
	3,2	His ⁴³	-OH

Based on table 1, it can be seen that of the ten ligands that were analyzed, the lowest values of ΔG binding affinity in lemon are neohesperidin -15.4 kcal/mol and rutin -15.3 kcal/mol. The ΔG binding value of affinity aspirin as a standard ligand is -6.5 kcal/mol. These values suggest that neohesperidin and rutin ligands have better affinity than aspirin and have antiplatelet potency. RMSD is the value used to determine whether the prediction of the bond mode is successful and important for validating the

docking program with a fault value of $\leq 2\text{\AA}$. With increasing deviations, the greater the error of predicting the ligand interaction with receptors (Brooijmans, 2009). The RMSD value obtained from the docking of each ligand in the best conformation is 0. This is caused by Vina compared the value of each conformation with its best conformation value.

The interaction between the receptor and the ligand resulted in the distance between the bonds



Figure 3. Residue contact between Neohesperidin and 1CQE receptor (Software Pymol)

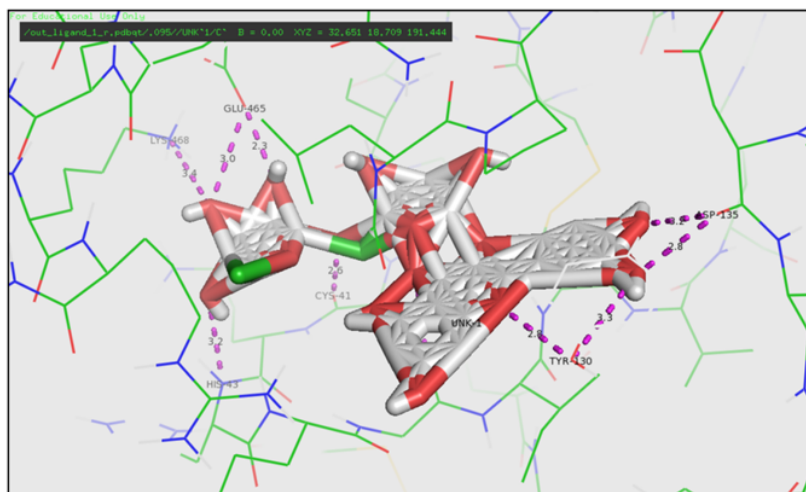


Figure 4: Residual contact between Rutin ligand with 1cqe receptor (Software Pymol)

and the bonded amino acid residues. Hydrogen bonding is a bond that can occur by involving the interaction of hydrogen atoms bonded covalently with electronegative atoms such as Fluorine (F), Nitrogen (N), Oxygen (O) (Glowacki *et al.*, 2013). Table 2 shows distances, amino acids and binding groups that illustrate the interaction between ligands/drugs with COX-1 receptors. The interaction between aspirin as a standard drug against the COX-1 receptor shows the presence of hydrogen bonds from the -O group at Cys41 residues. For ligands having the lowest ΔG binding affinity values, neohesperidin and rutin, show that hydrogen bonds are formed from the -O and -OH groups to the Arg469, Gln44, Cys41, and Lys468 residues in neohesperidin (Figure 3). The hydrogen bonds are formed from the -O and -OH groups to the residues Glu465, Cys41, Gly45, Asp135, Lys468, and His43 on the rutin (Figure 4). Hydrogen bonds may occur between intermolecular and intramolecular, a good range of hydrogen bonds at 2.5-3.5 Å (Syahputra *et al.*, 2014). The hydrogen bond distance that occurs between amino acids residues in the COX-1 receptor and neohesperidin and the rutin is a good hydrogen bond because it is in the range 2.5-3.5 Å. So from the results of the *in silico* analysis using molecular docking method, it can be concluded that neohesperidin and rutin compounds in lemon are predicted to have potential as antiplatelet ischaemic in stroke.

4 CONCLUSIONS

The flavonoid derived compounds found in lemon (*Citrus limon* (Linn) Burm f) ie neohesperidin and rutin result values of ΔG binding affinity (kcal/mol), i.e. -15.4 kcal/mol and -15.3 kcal/mol. These numbers are lower compared with aspirin comparative drugs that has a value of ΔG binding affinity -6.5 kcal/mol. neohesperidin and rutin compounds have a better affinity than aspirin so that it can be used as an antiplatelet candidate in ischaemic stroke disease.

REFERENCES

- Balitbang Kemenkes RI. 2013. *Riset Kesehatan Dasar (RISKESDAS)*. Balitbang Kemenkes RI. Jakarta.
- Brooijmans N. 2009. Docking Methods, Ligand Design and Validating Data Sets in The Structural Genomics Era. *Structural Bioinformatics Second Edition*. Wiley Interscience. New York. 645-646.
- Claria J. 2003. Cyclooxygenase-2 Biology. *Current Pharmaceutical Design*. 9 (27): 2177-2190.
- Cheng, A. C., Coleman, R. G., Smyth, K. T., Cao, Q., Soulard, P., Caffrey, D. R., Salzberg, A. C., and Huang, E. S. 2007. Structure-based maximal affinity model predicts small-molecule druggability. *Nat Biotechnol*, 25(1):71--75.
- Chung CS, Caplan LR. 2007. Neurovascular Disorder. Dalam: Christopher G, Goetz MD (eds). 2007.

- Textbook of Clinical Neurology 3rd edition*. Saunders Company. Philadelphia. 874 – 885.
- Glaab E. 2015. Building A Virtual Ligand Screening Pipeline Using Free Software. *Briefing in Bioinformatics*. 17 (2): 352-356
- Glowacki ED, Vladu MI, Bauer S. 2013. Hydrogen Bonds in Molecular Solid From Biological Systems to Organic Electronics. *Journal of Material Chemistry*. (1): 3742-3753.
- Gund, BM, Jagtap, PN, Ingale, VB, Patil, RY. 2013. Stroke: A Brain Attack. *IOSR Journal of Pharmacy*. 3(8): 01-23.
- Li, B., Turuvekere, S., Agrawal, M., La, D., Ramani, K., and Kihara, D. 2008. Characterization of local geometry of protein surfaces with the visibility criterion. *Proteins*, 71(2):670--683.
- Middleton E, Kandaswami C, Theoharides TC. 2000. The Effects of Plant Flavonoids on Mammalian Cells. *Pharmacological Reviews*. 52(4): 673-751.
- Molina EG, Perles RD, Moreno DA, Viguera CG. 2010. Natural Bioactive Compounds of *Citrus limon* for Food and Health. *Journal of Pharmaceutical and Biomedical Analysis*. 51: 327-345.
- Mukesh B, Rakesh K. 2011. Molecular Docking: A Review. *International Journal of Research in Ayurveda and Pharmacy*. 2(6): 1746-1751.
- Rachmania, RA, Supandi, Larasati, OA. 2015. Analisis In-Silico Senyawa Diterpenoid Lakton Herba Sambiloto (*Andrographis paniculata* Nees) pada Reseptor Alpha-Glucosidase Sebagai Antidiabetes Tipe II. *Pharmacy*. 12(02): 210-222.
- Retnaningsih CH, Setiawan A, Sumardi. 2011. Potensi Antiplatelet Kacang Koro (*Mucuna pruriens* L) dari Fraksi Heksan dibandingkan dengan Aspirin pada Tikus Hiperkolesterolemia. *Seri Kajian Ilmiah*. 14 (1): 80-86.
- Riaz A, Khan RA, Mirza T. 2014. In vitro/In Vivo Effect of (*Citrus Limon* L. Burm. f.) Juice on Blood Parameters, Coagulation And Anticoagulation Factors in Rabbits. *Journal of Pharmaceutical Sciences*. 27(4): 907-915.
- Ringleb, PA, Bousser, MG, Ford, G, Bath, P, Brainin, M, Caso, V, Cervera, A, Chamorro, Al, Cordonnier, C, Csiba, L. 2011. *Ischaemic Stroke and Transient Ischaemic Attack*. European Handbook of Neurological Management, Second Edition, Volume 1, Second Edition.
- Syahputra, G, Ambarsari, L, Sumaryada, T. 2014. Simulasi Docking Kurkumin Enol, Bismetoksikurkumin dan Analognya Sebagai Inhibitor Enzim12-Lipoksigenase. *Jurnal Biofisika*. 10(1): 55-67.
- Shinohara Y, Katayama Y, Uchiyama S, Yamaguchi T, Handa S, Matsuoka K, Ohashi Y, Tanahashi N, Yamamoto H, Genka C, Kitagawa Y, Kusuoka H, Nishimaru K, Tsushima M, Koretsune Y, Sawada T, Hamada C. 2010. Cilostazol for Prevention of Secondary Stroke (CSPS 2): An Aspirin-Controlled, Double-Blind, Randomised Non-Inferiority Trial. *The Lancet Neurology*. 9(10): 959-968.
- Wu CM, Wu SC, Chung WJ, Lin HC, Chen KT, Chen YC, Hsu MF, Yang JM, Wang JP, Lin CN. 2007. Antiplatelet Effect and Selective Binding to Cyclooxygenase (COX) by Molecular Docking Analysis of Flavonoids and Lignans. *International Journal of Molecular Sciences*. 8: 830-841.

HARIYANTI-Molecular Docking Study of Lemon (Citrus limon (Linn) Burm. f) Flavonoid Derivatives Compound in Receptor Cyclooxygenase-1 (COX-1) as Antiplatelet in Ischaemic Stroke Disease

ORIGINALITY REPORT

19%

SIMILARITY INDEX

15%

INTERNET SOURCES

10%

PUBLICATIONS

5%

STUDENT PAPERS

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet Source	5%
2	jamu.journal.ipb.ac.id Internet Source	1%
3	Daniel Jamrozik, Weronika Borymska, Ilona Kaczmarczyk-Żebrowska. "Hibiscus sabdariffa in Diabetes Prevention and Treatment—Does It Work? An Evidence-Based Review", Foods, 2022 Publication	1%
4	www.researchgate.net Internet Source	1%
5	Felipe Alves de Almeida, Uelinton Manoel Pinto, Maria Cristina Dantas Vanetti. "Novel insights from molecular docking of SdiA from Salmonella Enteritidis and Escherichia coli with quorum sensing and quorum quenching molecules", Microbial Pathogenesis, 2016	1%

6	journal.portalgaruda.org Internet Source	1 %
7	Kholis Amalia Nofianti, Juni Ekowati. "o-Hydroxycinnamic derivatives as prospective anti-platelet candidates: in silico pharmacokinetic screening and evaluation of their binding sites on COX-1 and P2Y12 receptors", Journal of Basic and Clinical Physiology and Pharmacology, 2019 Publication	1 %
8	accesspharmacy.com Internet Source	1 %
9	resources.qiagenbioinformatics.com Internet Source	1 %
10	kb.osu.edu Internet Source	1 %
11	www.scitepress.org Internet Source	1 %
12	pdfs.semanticscholar.org Internet Source	1 %
13	Submitted to University of Kent at Canterbury Student Paper	<1 %
14	www.hindawi.com Internet Source	<1 %

15	Submitted to University of Nottingham Student Paper	<1 %
16	www.dovepress.com Internet Source	<1 %
17	www.igi-global.com Internet Source	<1 %
18	Kamel Mahmoud Hewedi, Mohie El Din Tharwat Mohamed, Mohammed Awad Yousef Abo Sleem. "PRE HOSPITAL AND IN HOSPITAL DELAYS AFTER THE ONSET OF ACUTE ISCHEMIC STROKE IN A SAMPLE OF EGYPTIAN PATIENTS", Al-Azhar Medical Journal, 2019 Publication	<1 %
19	linux-hardware.org Internet Source	<1 %
20	oup.silverchair-cdn.com Internet Source	<1 %
21	repository.hkbu.edu.hk Internet Source	<1 %
22	"Computational Drug Discovery and Design", Springer Science and Business Media LLC, 2018 Publication	<1 %
23	Meiby Fernández-Rojas, Lyanne Rodríguez, Andrés Trostchansky, Eduardo Fuentes.	<1 %

"Regulation of platelet function by natural bioactive compounds", Food Bioscience, 2022

Publication

24

Nur Iszakiyah, Byba Melda Suhita, Sandu Siyoto. "Anxiety, Self Concept and Meaning of Life Patients Post Stroke Earning Age", JOURNAL FOR QUALITY IN PUBLIC HEALTH, 2019

Publication

<1 %

25

Tumilaar Sefren Geiner, Fatimawali Fatimawali, Niode Nurdjannah Jane, Effendi Yunus et al. "The potential of leaf extract of Pangium edule Reinw as HIV-1 protease inhibitor: A computational biology approach", Journal of Applied Pharmaceutical Science, 2020

Publication

<1 %

Exclude quotes Off

Exclude matches Off

Exclude bibliography On