ANALYSIS OF POTENTIAL COMPOUNDS FROM JAVANESE GINSENG (*TALINUM PANICULATUM* GAERTN.) AND KELOR LEAVES (*MORINGA OLEIFERA*) AS THE ANTI-INFLAMMATION WITH MOLECULAR DOCKING METHOD

Syifa Farhatunnisa El-Baehaqi[1], Agniya Dwiputri Aminah[1], Firdayani[2]

Author information

[1]Department of Chemistry, Faculty of Mathematics and Natural Science, Bandung Institute of Technology (ITB).
[2] Research Center for Vaccine and Drugs, Research Organization for Health, National Research and Innovation Agency (BRIN)

***Correspondence:**

Syifa Farhatunnisa El-Baehaqi
E-mail:
syifaelbae@students.itb.ac.id

ABSTRACT

Inflammation is the immune system's response to noxious stimuli such as pathogens, damaged cells, toxic compounds, or radiation. It often causes pain or discomfort. In this study, the search for potential compounds as COX-2 inhibitors from Javanese Ginseng (*Talinum paniculatum* Gaertn.) and Moringa (*Moringa oleifera*) was carried out. The method used in this research was molecular docking by the Molegro Virtual Docker. Some assessments that have been done in this research are Rerank Score, H-bond interaction, and Lipinski Rule of Five. The result showed that COX-2 inhibitor compounds potential are Chlorogenic acid and Quercetin with the Rerank Score -112.802 and -95.8476, respectively. The results show that Chlorogenic acid and Quercetin have Rerank scores of -112.802 and -95.8476, respectively. Thus the two compounds can be predicted to have the potential as COX-2 inhibitors.

Keywords: Moringa oleifera, Talinum paniculatum, Molecular Docking, Anti-inflammation, Molegro Virtual Docker

ANALISIS SENYAWA POTENSIAL PADA GINSENG JAWA (*TALINUM PANICULATUM* GAERTN.) DAN DAUN KELOR (*MORINGA OLEIFERA*) SEBAGAI ANTI-INFLAMASI DENGAN METODE PENAMBATAN MOLEKUL (*MOLECULAR DOCKING*)

ABSTRAK

Inflamasi atau peradangan adalah respons sistem kekebalan tubuh terhadap rangsangan berbahaya seperti patogen, sel yang rusak, senyawa beracun, atau penyinaran. Seringkali inflamasi menyebabkan rasa sakit atau ketidaknyamanan. Tindakan terapeutik anti-inflamasi NSAID berkaitan dengan penghambatan COX-1 dan COX-2, tetapi penghambatan COX-1 biasanya menyebabkan efek samping seperti iritasi pada saluran cerna perut. Pada penelitian ini, dilakukan pencarian senyawa potensial sebagai inhibitor COX-2 dari senyawa bioaktif Ginseng Jawa (*Talinum paniculatum* Gaertn.) dan Daun Kelor (*Moringa oleifera*). Metode yang digunakan dalam penelitian ini adalah penambatan (*docking*) dengan Molegro Virtual Docker. Beberapa penilaian yang dilakukan dalam penelitian ini adalah Rerank Score, interaksi H-bond, dan *Lipinski Rule of Five*. Hasil penelitian menunjukkan bahwa Asam klorogenat dan Quercetin memiliki nilai *docking Rerank Score* paling negatif, *yaitu* -112.802 and -95.8476. Dengan demikian kedua senyawa tersebut diprediksi memiliki potensi sebagai inhibitor COX-2

INTRODUCTION

Inflammation is the response of the body's immunity system to noxious stimuli such as pathogens, damaged cells, toxic compounds, or irradiation. This inflammation process has occurred cause the central defense system building cytokines and mediators responsible for inflammation (Rao and Mishra, 1998; Joshi *et al*., 2019).

Anti-inflammatories nonsteroids (AINS) exist for pain relief and inflammation. It is classified into two big classes, nonselective that works to inhibit cyclooxygenase enzyme (COX-1 and COX-2), and selective AINS that work to inhibit COX-2 enzyme. COX has two active sites, the cyclooxygenase active site, and the peroxidase active site. However, COX-2 has the advantage of having a higher sensitivity to hydroperoxides than COX-1, so t it can work at lower concentrations of arachidonic acid than COX-1. (Sudewa & Budiarta, 2017).

This enzyme is constitutively expressed in many tissues such as the prostate, endothelium, brain, and renal medulla to overcome the infection, inflammation, cancer, and prodices prostanoids responsible for disease pathogenesis (Baek *et al*. 2021).

Some drugs such as COX-2 inhibitors have been widely circulated in the market, such as Prodigiosin, Cycloprodigiosin, Valdecoxib, Celecoxib, and Rofecoxib (Krishna *et al*. 2013). However, currently, only celecoxib is available in the market. Rofecoxib (Vioxx) and Valdecoxib (Bextra) were discontinued in 2003 and 2005 respectively, due to their increased risk of heart attack and stroke from long-term use (Annette 2021). The development of Prodigiosin and Cycloprodigiosin has not been too much, so the information obtained is minimal. In addition, to enrich knowledge and utilization of abundant natural resources in Indonesia, this research becomes a good thing to find out more benefits of plants that thrive in Indonesia, including Javanese ginseng and Moringa.

Moringa oleifera or Moringa is a plant that thrives in the tropics and subtropics, one of which is Indonesia. This plant is believed to have many benefits and activities, such as anti-anaphylactic, antiulcer, antithyroid, hepatoprotective, antitumor, antidiabetic, antioxidant, diuretics, antiurolithic, hypocholesterolemic, cardioprotective, anti-inflammatory, and many more (Alphonsine *et al.,* 2019). Part of these plants that has inflammatory effect are the root, bark, leaves, flowers, seeds, and stalks (Paikra *et al*., 2017).

Javanese ginseng or *Talinum paniculatum* is believed to have anti-inflammatory, antioxidant, antitumor, bactericidal, anti-viral, and anti-histamine effects (Lestario *et al.* 2009). Javanese Ginseng has essential ingredients such as saponins, alkaloids, tannins, flavonoids, pro-vitamin A, and other compounds that are physiologically able to improve circulation or blood circulation in the nervous system (Mahajan & Mehta 2007).

Drug manufacturing is usually done accidentally in a trial-and-error process with screening methods in vitro trials to measure the activity of large amounts of compounds against a target. This takes a lot of time and cost. Therefore, the structure of target 3D compounds that have been known to be simulated computationally so as not to take a lot of time and cost (Thomsen and Christensen 2006, Khayrani *et al.,* 2021).

The use of molecular docking is generally used by pharmaceutical and agrochemical companies. There are three main docking objectives: 1) prediction of bonding modes; 2) virtual screening; and 3) binding energy prediction. Another study stated that the information obtained from this method is about the complex's free energy and stability. However, the main objective of this method is to obtain information on the interaction of the ligand and its receptor with the optimal conformation. (Bortolato *et al.,* 2013, Dar & Mir, 2017)

This study was conducted following Moldock algorithm which is based on a new hybrid search called guided differential evolution that combines the differential evolution optimization technique with a cavity prediction algorithm. Alternatively, the algorithm provides a predictive search for cavities resulting in fast and accurate identification of potential binding modes (Thomsen & Christensen, 2006). This algorithm is believed to

have a higher docking accuracy because it is related to identifying the ligand-binding mode.

This study aims to determine the potential anti-inflammatory compounds from Moringa and Javanese ginseng. The collected compounds were then searched for the lowest energy form for docking and found the compound that had the best pose and complied with Lipinski's rules. In addition, research was conducted on several potential commercial compounds as anti-inflammatory agents.

MATERIALS AND METHODS

Hardware

The experiment was conducted using a computer withprocessor Intel(R) Core™ i5-2430M CPU @ 2.40 GHz, operating system 8 GB of RAM, the Windows 10 Pro, 64-bit operating system, and x64-based processor type system.

Software

The software used in this research included MarvinSketch 22.9.0 (ChemAxon, 2022) and trial version Molegro Virtual Docker 2019 7.0.0 (Thomsen & Christensen, 2006).

Molecular Structures and Energy Minimization

The X-ray crystallographic structure of COX-2 protein was obtained from the Protein Data Bank with the PDB ID: 5IKQ (https://www.rcsb.org/structure/5IKQ) at a resolution of 2.41 Å. The file was saved with the PDB file. When it was uploaded into Molegro Virtual Docker, the water molecules were removed from the protein molecule. The ligand molecules structure were drawn and minimized in MarvinSketch 22.9 and was done using dreading force field. This is done to help the docking program identify the bioactive conformer from the local minima (Kaushik *et al.,* 2014), then the minimized ligands were saved in mol2 format.

Molecular Docking Simulation

Molecular docking of compounds of javanese ginseng and moringa to the active site of the cyclooxygenase enzyme was carried out using Molegro Virtual Docker (MVD). This step was performed to find a cavity with a detection algorithm to detect the protein binding site as a potential area on the active site (Puspaningtyas *et al*., 2013).

To ensure that ligands docked using the docking software represent valid scores and accurate binding with the receptor, the MVD scoring algorithm had to be validated first (Kaushik *et al.,* 2014). This was done by docking one of the available ligands of the PDB ID: 5IKQ, namely JMS 602 [A] with protein A and JMS 602 [B] with protein B. This matching is done because each pair has its match at the corresponding coordinates.

After validation, docking pairs with an Root Mean Square Deviation (RMSD) value below 2 were selected and used for the screening process. The screening process was carried out by inputting molecules. The scoring function was Moldock Score [GRID] with the Grid Resolution 0.30 Å. This scoring function guided the differential evolution algorithm that combines the differential evolution optimization technique with a cavity prediction algorithm. The algorithm used was Moldock SE with 10 runs and 1500 maximum iteration.

Analysis of Lipinski Rule of 5 (Lipinski R05)

The rules are; both the H-bond donors and acceptors are less than 5, the molecular weight is less than 500, the calculated Log P is less than 5, and the molar refractivity should be between 40 to 130. If a compound fails the RO5, there is a high probability that oral activity problems will be encountered. In this study, the molecular weight of the ligand was determined from the Properties column provided by the Molegro Virtual Docker, while the Log P, H-Bond donor, H-Bond acceptor, and refractivity data were obtained using MarvinSketch.

RESULTS AND DISCUSSION

In this study, 5IKQ of RCSB PDB was used, which is the structure of meclofenamic acid (JMS 602) bound to humans COX-2 (Orlando & Malkowski, 2016). Before starting, a docking validation was carried out to validate the docking method on the software used compared to the position of the native ligand in the receptor that has been experimentally tested at the pocket ligand-binding site (Puspaningtyas *et al.,* 2013).

The molecular docking method was calculated on protein 5IKQ [A] with ligand JMS_60 [A], carried out at coordinates x: 21.60, y: 51.88, and z: 17.70 with the radius 15. This docking gave an RMSD value of 1.01. Protein 5IKQ [B] with ligand JMS_60 [B] that was carried out at coordinated x: 61.60, y: 51.88, and z: 17.70 gave the best RMSD value of 0.63702. The reposition between JMS 602 [B] and COX-2 chain B can be seen in **Figure 1**.

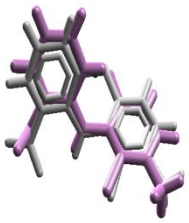


Figure 1. Redocking JMS-602 into COX-2 chain B with RMSD: 0.6

RMSD is an expression that shows the ratio in which the ligand atoms are compatible and symmetrical with their receptors. A good RMSD should show a value of less than 2 (Ramírez & Caballero, 2018; Thomsen & Christensen, 2006). This is because the position of the copy ligand after superimposition is getting closer to its position on the native ligand, so the method used will be more precise (Puspaningtyas *et al.,* 2013). In this study, the binding site of protein B was used to perform a docking simulation, which has an RMSD value of 0.63702.

Docking simulations were conducted on 82 compounds from Moringa and 22 from Javanese Ginseng. These results are sorted to find the best-ranking value and then compared with meclofenamic acid, which has a docking score of -82.6431. The value is different from the result of the previous study due to the program and the docking parameters that being used are different (Joshi *et al.,* 2019; Mardianingrum *et al.,* 2020).

The screening results obtained in this study showed that the best molecules based on their Rerank scores and Lipinski rules were Chlorogenic acid, Stigmasterol, Javaberine A, Heneicosanoic acid, and Quercetin with their Rerank scores –140.03, -144,829, -148.84, -128,887, and –112,732 respectively for Javanese Ginseng. The compounds that show the best scores from moringa are Quercetin-3-O-glucoside, δ-Tocopherol, 3-O-Caffeoylquinic acid, Neochlorogenic acid, and Astragalin with its Rerank scores -127,381, -122,439, -112,802, -111,209, and -110.067 respectively. Supposedly there is 4-(4'-O-Acetyl-alpha-L-rhamnopyranosyloxyl) benzyl glucosinolate in that sequence. However, due to the inability of the compound to fulfill the Lipinski Rule of Five, with a violation of 4, this compound can be declared unsuitable as a drug candidate. Lipinski rule is a rule commonly used in the medical world to determine whether a candidate drug has specific chemical and physical properties to make it an active drug for humans, or simply this rule can detect whether a chemical molecule can do absorption, distribution, and metabolism well or not. The Lipinski Rule describes molecular properties essential for the pharmacokinetics of drugs, including absorption, distribution, metabolism, and excretion (ADME). However, The Lipinski Rule rule cannot predict which compound is pharmacologically active, so that specific research is needed. These rules indicate which compounds have certain chemical and physical properties that will determine whether they are safe for medicine orally. If the conditions are not met, then it can be concluded that the drug candidate compounds are dangerous enough to be a drug. However, compounds that obey this rule are not necessarily drug-like compounds (Lipinski, 2004; DrugBank, 2022).

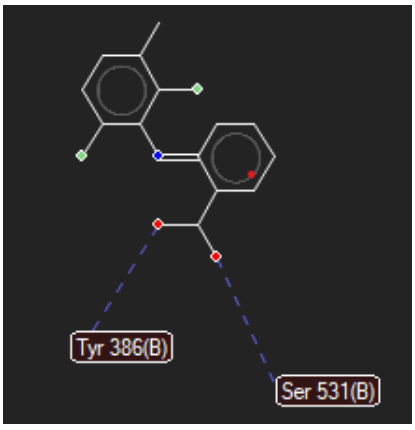


Figure 2. Native ligand (JMS 602_B) interaction

The scoring function has been used to identify the most energy-favorable ligand conformation to bind

the target. The more negative the ligand's binding energy to the target then, the more the ligand fits the target (Thomsen & Christensen, 2006). In addition, these compounds also have a more negative Rerank Score than JMS 602, so they are all available to be candidates for recommended drugs. However, not all of these molecules have adhered to the Lipinski RO5.

Figure 2 shows that the native ligands used in this study, namely JMS 602_B interact with two amino acids named Ser 531 and Tyr 386. The similarity of interaction formed in this research and the ligand native's interaction indicates that the ligand found is the potential to pose (Khayrani *et al.,* 2021). In addition, their Rerank score exceeds the negative value owned by the native ligand, which is -82.7761. It indicates that all compounds in **Table 1** can bind to COX-2 due to the more vital and stable bond to become a COX-2 inhibitor. However, the bond strength of a ligand can also be seen by how much it interacts with the hydrogen bond. This is because hydrogen bonds can significantly affect bond affinity (Khayrani *et al.,* 2021).

Table 1 shows the best five potential compounds data related to the ligands with the best Rerank Score and obeying the Lipinski RO5 with a maximum violation of 2. Due to the sorting, the best five compounds and the structures can be seen in **Table 2**.

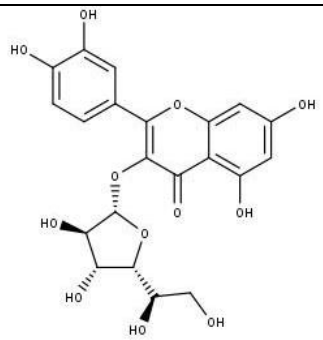
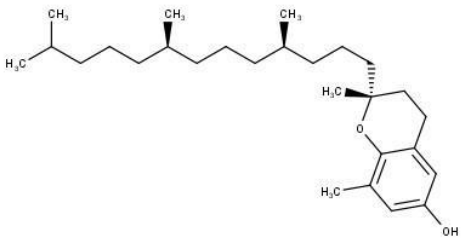
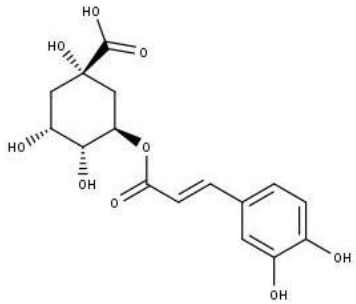
Table 1. The compounds that have the best Rerank Score

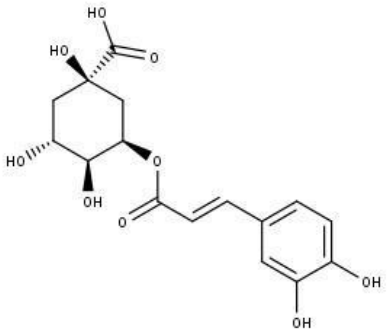
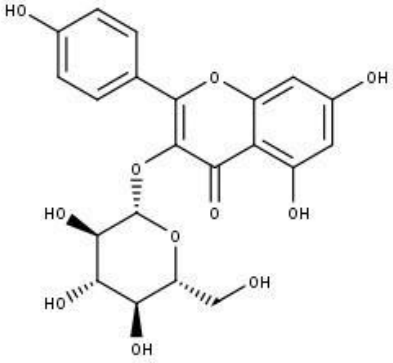
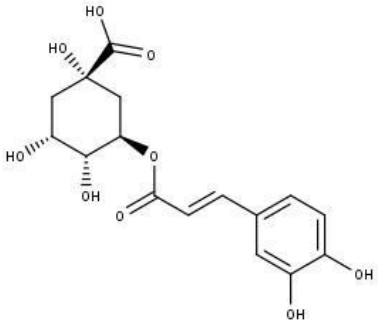
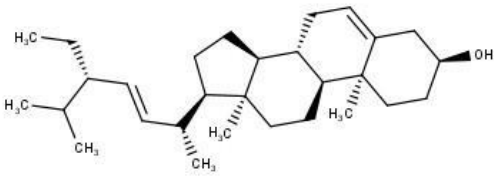
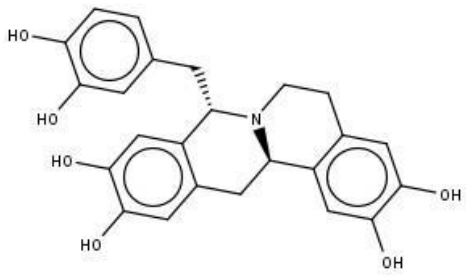
Ligand	Rerank Score	H-bond	H-bond Interactions	Violation of Lipinski Rules of Five
Moringa oleifera				
Quercetin-3-O-glucoside/ Chlorogenic acid	-127.381	-9.95075	Gln 193(B) Leu 353(B) His 90(B) Ser 354(B) Tyr 356(B) Met 523(B) **Tyr 386(B)**	2
δ-Tocopherol	-122.439	-3.3533	Lys 83(B) Tyr 356(B) Arg 121(B)	1
3-O-Caffeoylquinic acid	-112.802	-16.6686	His 90(B) Phe 519(B) Ile 518(B) Gln 193(B) Gly 527(B) Ala 528(B) Met 523(B) **Ser 531(B)** **Tyr 386(B)**	1
Neochlorogenic acid	-111.209	-6.12856	His 90(B) Gln 193(B) Leu 353(B) **Ser 531(B)** Val 524(B) Met 523(B)	1
Astragalin	-110.067	-3.9653	Gln 193(B) Met 523(B) **Ser 531(B)**	2
T. Paniculatum				
Chlorogenic acid	-127.381	-9.95075	Gln 193(B) Leu 353(B) His 90(B) Ser 354(B) Tyr 356(B)	2

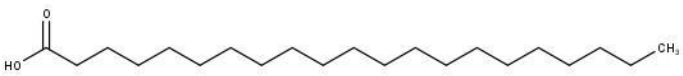
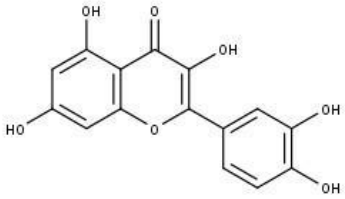
Ligand	Rerank Score	H-bond	H-bond Interactions	Violation of Lipinski Rules of Five
			Met 523(B) **Tyr 386(B)**	
Stigmasterol	-99.3001	-1.7085	Met 523(B)	2
Javaberine A	-97.8562	-10.7806	Arg 121(B) His 90(B) Ser 354(B) Leu 353(B) Gln 193(B) Gly 527(B)	1
Heneicosanoic acid	-96.7652	-2.5	Met 523(B)	1
Quercetin	-95.8476	-11.7605	Tyr 356(B) His 90(B) Ser 354(B) Ile 518(B) Phe 519(B) Gln 193(B) **Tyr 386(B)** **Ser 531(B)**	0

*Notes: Bold form shows that the amino acid also exists in JMS 602 [B] in. teractions

Table 2. Structures of the compounds that have the best Rerank Score and the violation of the Lipinski rule

No.	Compound	Structure	Reference
Moringa oleifera			
1	Quercetin-3-glucoside		(Singh and Sharma 2020)
2	δ-Tocopherol		(Leone *et al.* 2016)
3	3-O-Caffeoylquinic acid (Chlorogenic acid)		(Singh B 2020)

4	Neochlorogenic acid		(Singh B 2020)
5	Astragalin		(Singh B 2020)
Talinum paniculatum			
1	Chlorogenic Acid		(Kim 2016, Cerdeira *et al*. 2020)
2	Stigmasterol		(Cerdeira *et al.* 2020)
3	Javaberine A		

4	Heneicosanoic acid		(Perpétua *et al.* 2010, Shimoda *et al.* 2020)
5	Quercetin		(Kim 2016)

The interactions of these ligands are also presented. Moringa only presents 3-O-Caffeoylquinic acid, or in its trivial name is Chlorogenic acid, have the same interaction with native ligands, Tyr 386[B] and Ser 531[B]. The other ligands have only one interaction, like Quercetin-3-O-glucoside and δ-Tocopherol, whick have interactions with Tyr 386[B], and Neochlorogenic acid and Astragalin have interactions with Ser 531[B]. Javanese ginseng's result shows that Quercetin has interaction with Tyr 386[B] and Ser 531[B], Chlorogenic acid has interaction with Tyr 386[B]. Meanwhile , Javaberine A, and Heneicosanoic acid have interaction neither with Tyr 386[B] nor Ser 531. The entire compounds interaction can be shown in **Figures 3** to **12**.

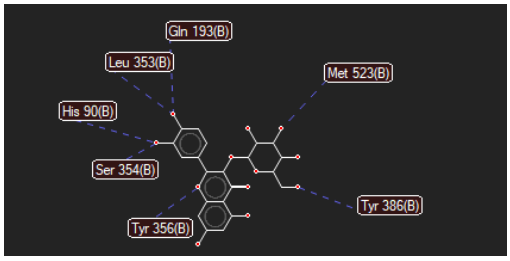


Figure 3. Quercetin-3-O-glucoside interaction

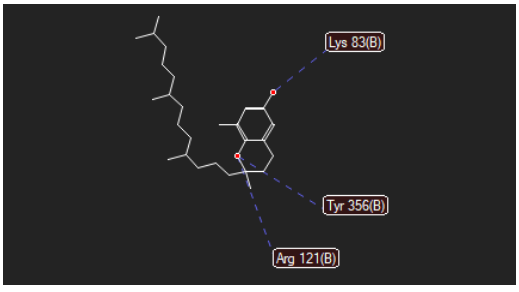


Figure 4. δ-Tocopherol interaction

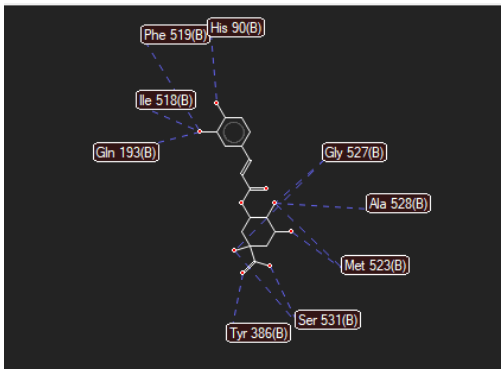


Figure 5. 3-O-Caffeoylquinic acid (Chlorogenic acid) in moringa interaction

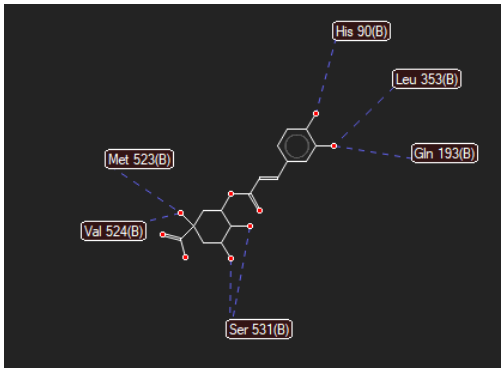


Figure 6. Neochlorogenic acid interaction

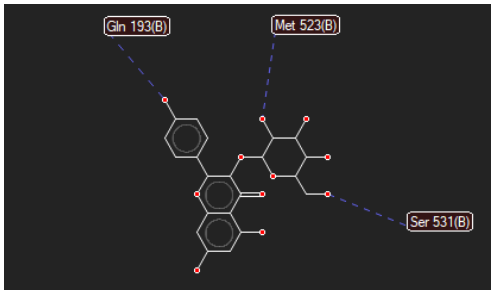


Figure 7. Astragalin interaction

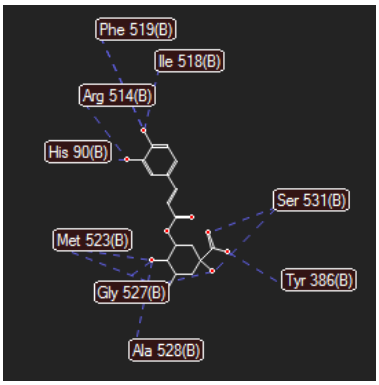


Figure 8. Chlorogenic acid in Javanese ginseng interaction

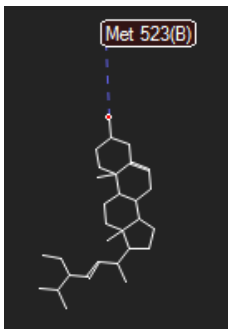


Figure 9. Stigmasterol interaction

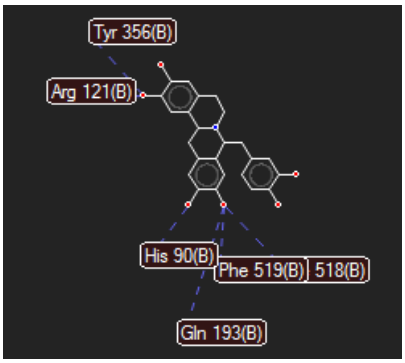


Figure 10. Javaberine A interaction

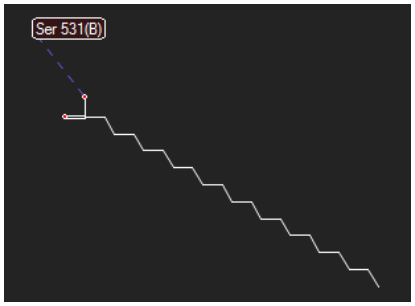


Figure 11. Heneicosanoic acid interaction

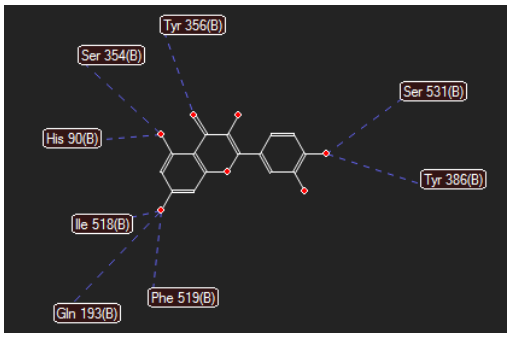


Figure 12. Quercetin interaction

Chlorogenic acid and Quercetin are recommended as compounds with anti-inflammatory effects. This does not mean that other compounds do not have anti-inflammatory effects. However, based on the results of docking the Lipinski RO5 and the molecular interactions, these two compounds become potential compounds for anti-inflammatory.

According to the literature, Chlorogenic acid in Moringa can be found in the leaves, while in Javanese ginseng, it can be found in the fruit (Ali & Abdrabou, 2015; Chung *et al.,* 2016). Quercetin in Javanese ginseng is mainly found in the leaves but in the primary root and root hairs. Quercetin can also be found there even though it is less than in the leaves (Kim, 2016).

This study also screened commercial compounds like Celecoxib, Prodigiosin, Cycloprodigiosin, Rofecoxib, and Valdecoxib. These commercial substances have been on the market because they have high anti-inflammatory effects. This study found that the five compounds had good Rerank Scores, and the best two from the five are Celecoxib and Prodigiosin. Celecoxib and Prodigiosin have a Rerank -119.597 and -114.37, respectively. Apart from that, these five compounds have a more negative Rerank Score value when compared to the native ligand JMS 602 [B], which is -82.7761. Entirely the data can be seen in **Table 3**. Despite that, the H-bond interactions of these five compounds are not familiar with native ligands, and even the Rerank scores show lower than several compounds in Moringa and Javanese Ginseng.

Table 3 . Docking result of commercial compounds as COX-2 inhibitors.

Ligand	Rerank Score	H-Bond	H-bond Interactions
Celecoxib	-119.597	-3.87867	Tyr 356 (B) Gln 193 (B) Ser 354 (B) Val 524 (B) Leu 353 (B) Arg 514 (B) His 90 (B) Phe 519 (B)
Prodigiosin	-114.37	0	Leu 353 (B) Phe 519 (B) Tyr 356 (B)
Rofecoxib	-10.9.152	-3.42973	Leu 353 (B) Val 524 (B) Gln 193 (B) Phe 519 (B) His 90 (B)
Valdecoxib	-108.736	-5.43277	Val 350 (B) Met 523 (B) Phe 519 (B) Arg 514 (B) His 90 (B) Ser 354 (B) Leu 353 (B) Gln 193 (B) Val 524 (B)
Cycloprodigiosin	-107.9	-1.76473	Val 524 (B) Phe 519 (B) Ala 517 (B) Ser 354 (B) Gln 193 (B) Leu 353 (B)

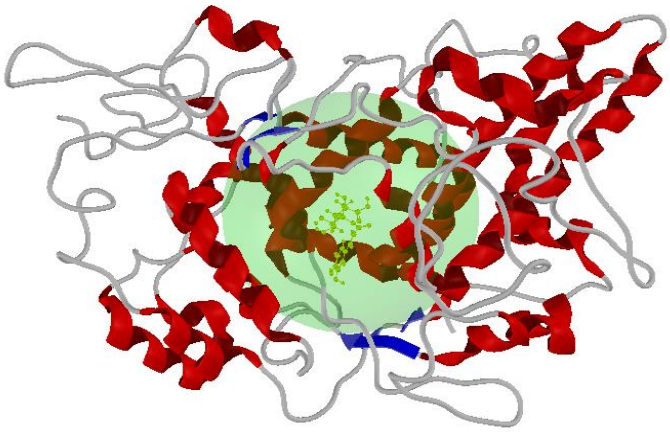


Figure 13. Chlorogenic acid (yellow) with the protein cavity

An overview of these two compounds entering the protein cavity can be seen in **Figures 13** and **14**. The figures show the protein drawn by the protein backbone and the potential compound that fits the cavity shown by the ball and stick.

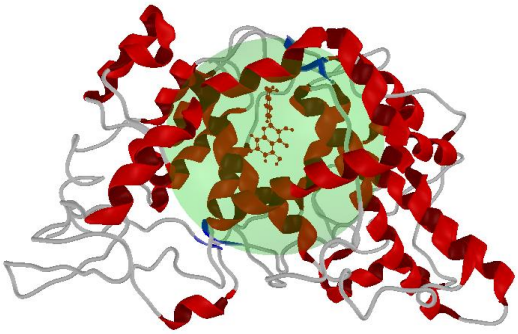


Figure 14. Quercetin (red) with the protein cavity

This study only directed that there are potential compounds *in Javanese ginseng and Moringa* for anti-inflammatory. Further in vitro and in vivo experiments areis needed to support the evidence on Moringa and Javanese Ginseng anti-inflammatory effects.

CONCLUSIONS

Docking on Moringa and Javanese Ginseng was carried out on 82 and 11 potential compounds, respectively. The results showed that 3-O-caffeoyl quinic acid, chlorogenic acid and quercetion from both moringa and javaness ginseng possess prospective inhibitory activity toward COX-2.

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