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Study Of Molecular Docking On Compounds With Potential As Anti-Inflammatory

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ABSTRACT

Inflammation is a protective response caused by damage to certain tissues. Anti-inflammatory is a substance or drug used to treat redness, increased body temperature, swelling, pain and loss of function of an organ. Steroid and non-steroidal anti-inflammatory drugs have many side effects, so studies are needed to develop new drugs to minimize side effects and improve therapeutic effects. The method used is literature review from journals and articles obtained from Google Scholar in 15 journals. The purpose of the literature review is to find out the study of the development of new drugs from several compounds that have potential as anti-inflammatories. Secondary metabolites that have potential as anti-inflammatory include essential oils, flavonoids, alkaloids, terpenoids, and anthocyanins. Secondary metabolites will interact with the cyclooxygenase (COX) enzyme which is the main mediator of inflammation. The results obtained from the 15 compounds contain these secondary metabolites so they have the potential as anti-inflammatory.

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1. INTRODUCTION

The process of producing a protective physiological response to injured tissue through physical trauma, chemicals, and microbiological agents infection. The biological healing step occurs when the immune system fights infection caused by microbes, then is calmed by pain according to the area of inflammation and heals the tissue. Whereas in pathological conditions, there are more antigens or foreign substances in an inflammatory state, so that these conditions may damage tissues or organs of the body (Nurtamin et al., 2018).

Inflammation is closely related to arachidonic acid as a mediator of inflammation. Arachidonic acid has cyclooxygenase enzymes one and two, namely COX-1 and COX-2. This enzyme has the same mechanism of action to create an inflammatory response, but when it occurs in excess it will affect the development of dangerous diseases such as cancer. However, when it is inhibited by an anti-inflammatory drug, it will have a greater effect on COX-2 by 75% compared to COX-1 by 25%. This is because COX-2 plays a greater role in the inflammatory process than COX-1 (Desai et al., 2018). However, when synthetic anti-inflammatory drugs are consumed continuously, they cause irritation and increase the risk of gastric ulceration (Tanto, 2014).

Plants in Indonesia are one of the steps of alternative medicine for healing inflammation. There are many secondary metabolites in it, but from several journals it is known that they have anti-inflammatory potential including flavonoids, essential oils, alkaloids, terpenoids, and anthocyanins.

These secondary metabolites specifically work to inhibit the cyclooxygenase (COX) enzyme. This test has only been known in-vitro, not yet known through in-silico research. This type of in-silico research is a method that is carried out computationally in the form of pharmacological or physiological compounds (Suherman et al., 2020). Aims to find out whether these compounds have the potential or not to become new drugs that can be consumed by the public.

The method used is molecular docking, which is a method to match the receptor with the ligand in three dimensions. This process is done computationally through specially made software such as Autodock 4.2, Autodock Vina, ChemDraw, Discovery Studio Visualizer, Pymol, and others. Molecular docking results must first pay attention to its validation by looking at RMSD values that are less than 2 Å. In addition, in the end result you can see the bond free energy, the formation of hydrogen bonds, and the number of interactions with amino acid residues. Thus, based on the description that has been described in this study, we would like to discuss the potential of plants in Indonesia as new anti-inflammatory drugs through a molecular docking process.

2. METHOD

The method used in compiling this journal review is a literature review with sources taken from https://scholar.google.com/andhttps://www.google.co.id/. Journals, articles, and guidelines that are selected as references for a maximum of 10 years previously. In addition, other criteria use the keywords molecular docking, anti-inflammatory, COX-1 and COX-2. After getting 20 journals that almost met these criteria, there were only 15 journals that really fit the topic and theme raised.

3. RESULTS AND DISCUSSION

Table 1. Results

No	Citation	Application	Receptors	Ligand	Results
1.	Muhammad Noor Rezki et al, 2022	*Software*Autodock Tools; Avogadro software and Swiss PDB; Discovery Studio Visualizer software; PyMOL.	COX-2	myricetin; tricetin; quercetin	The best docking value (free binding energy (ΔG)) came from myricetin of -8.62 kcal/mol, followed by tricetin of -8.53 kcal/mol and quercetin of -8.32 kcal/mol.
2.	Diyan Sakti Purwanto, Iin Suhesti; 2021	AutoDock Vina; PyMOL; Chimeras	COX-2	Aglycone kurkuligoside phenolic compound a	The curculigoside a aglycone compound has a large free bond energy value (4.8 kcal/mol).
3.	Kamiel Roesman Bachtiar et al; 2021	ChemDraw Ultra 8.0; Marvin Sketches 5.2.5.; Molegro Molecular Viewer; AutoDock Tools 1.5.6; Discovery Studio 2016.	COX-1	phenylmethylene compounds; α-Phellandrene; Sabinenes; α.-Terpinene; Terpine-4ol	Phenylmethylene compounds can bind and have stable interactions with COX-1 receptors (anti-inflammatory) with a ΔG value of -6.94 kcal/mol.
4.	Diyan Sakti Purwanto et al; 2021	AutoDock 4.2; Biovia Discovery Studio	COX-2	quercetin compounds	The quercetin compound has a large free bond energy value (-10.6 kcal/mol).

		Visualizers; Ligplot 4.5.3; MGL Tools; Autodock vina; Chinera; CommandWindow.			
5.	Meilia Suherman et al; 2020	Windows 10 Home Operating System, LigandScout® 4.3; MarvinSketch®; ChemDraw® Ultra 12.0; Chem3D® Pro 12.0; Autodock Tools®;D Studio 3.5 Visualizer®; Data Proteins Bank; PubChem; DUD-E; Pre-ADMET.	COX-2	Celecoxib and its compounds compounds from Tamarindus indica (L)	Linalool has a bond free energy (ΔG) value of -9.21 kcal/mol, lower than its natural ligand, Celecoxib (-7.98 kcal/mol).
6.	Atim Febry Masul et al; 2018	PyRx; PyMol; Pubchem; GDP; PoseView	COX-1	Umuhengerin; Lantaden A; Lantaden B; icterogenin,	The Ikterogenin compound has an RMSD value of 41.1 Å and a binding affinity value of -8.8 and the Umuhengerin compound has an RMSD value of 1.61 Å and a binding affinity value of -8.0.
7.	Lusi Thenois, Noer Komari; 2022	Operating System Windows 8 pro 64-bit; Chimera -1.15-win64; Autodock Tools® 1.5.6; Autodock 4.2 VMD 1.9.2; Discovery Studio 2021 Client; Protein DataBank; PubChem; Swiss ADME; pkCSM; Lipinski filter	TNF-α	querceti compounds	The quercetin compound has a bond free energy value (ΔG) of -8.55 kcal/mol.
8.	Dina Ahsana et al; 2021	Autodock 4.2.6, energy minimization of ligand-protein using Avogadro and Swiss PDB Viewer software. Discovery Studio VisuaSwitzerland; PyMOL; pkCSM.	COX-2	31 flavonoid compounds; celecoxib; ligand native SC-558	Some of the test compounds for the flavonoids had the best ΔG docking values derived from Epicatechin-3-O-Gallate of -9.31 kcal/mol, followed by Gallocatechin of -8.97 kcal/mol and Tamarixetin -8.83 kcal/mol .

9.	Khoirotul Ummah et al; 2020	Microsoft Surface Laptop 2 core i5 with Windows 10 Home; Discovery Studio Client 4.1; Autodock 4.2; Autodock Vina; PyMOL; LigPlot.	COX-1; COX-2	Vanylyl methyl ketone compound	The vanylyl methyl ketone compound has a bond free energy (ΔG) value of -5.9 kcal/mol for the COX-1 enzyme and -6.2 for COX-2.
10.	Ruslin et al; 2020	ChemDraw Professional 15.0; HyperChem 8.0; Open Babel Graphical User Interface (Obabel GUI); AutoDock; Discovery Studio Visualizer (DSV).	COX-2	Leonurine compounds and their derivatives	The lowest binding energy value of the receptor-ligand (ΔG) is best for derivative 11, which is -7.95 kcal/mol.
11.	NMP Susanti et al; 2019	Windows 7 (64 bit) includes the program Hyperchem 8; Autodock 4.2; Chimeras 1.10.1.	ERK1; ERK2; JNK; JNK2; p38MAPK	Compound Terpinen 4-ol	The binding energy of terpinen-4-ol with the proteins ERK1, ERK2, JNK1, JNK2, and p38MAPK respectively is -5.12 Kcal/mol; -5.24 Kcal/mol; -5.08 Kcal/mol; -5.88 Kcal/mol; and -4.99 Kcal/mol.
12.	Gede NH C , I Made AP W; 2021	Windows 10 64 specifications bit includes the AutoDock Tools 1.5.6 program; Chimera 1.11.1; HyperChem 8.	Nf-kB	Kaempferol compound	The bond energy formed between kaempferol and NF-κB protein is -7.85 kcal/mol.
13.	Susanti et al; 2018	Windows 7 64 bit and programs Autodock 4.2 on Windows OS; Chimeras 1.10.1; HyperChem 8.	Nf-kB	Cyanidin and Peonidin compounds	Bond energy between cyanidin and peonidin with NF-4% protein—EHUWXUXW -7.92 kcal/mol and -7.86 kcal/mol respectively.
14.	Erma Yunita et al; 2019	The Linux operating system and supporting applications used are YASARA; Pymol; MarvinSketch.	1EQH; 3PGH; 6CO	Quercetin compounds	Quercetin is able to interact with 1EQH, 3PGH, and 6COX where their respective docking scores are -77.6195; -75.1344; and -82.2454.
15.	Deden I. Dinata et al; 2014	Chem draw software, hyperchem	COX-1; COX-2	Xanthorrhizol compounds	Xanthorrhizol docking results with COX-1 enzyme, namely bond

	software, PDB viewer, PDB (Protein Data Bank), ArgusLab, Autodock 4.	free energy of -8.75 and with COX-2 enzyme of -10.11

Based on research that has been conducted by(Susanti et al., 2019). The structure of terpinen-4-ol was drawn and optimized with the Hyperchem 8 program using a semi-empirical calculation method on the AM1 model (Austin model 1). The protein was prepared by separating the native ligand from the protein structure using the Chimera 1.10.1 program and the respective protein structures without native ligand and native ligand structures were generated separately. The validity of the molecular docking method is by docking the native ligand on the target protein using the Autodock 4.2 program with the semirigid method, which regulates the macromolecule to be rigid so that there is no change in the shape of the binding site during the redocking process, while the ligand to be docked is docking is flexible. As a result of redocking, it is known that the native ligand binding energy with ERK1, ERK2, JNK1, JNK2, and p38MAPK respectively -14.98 Kcal/mol; -5.97 Kcal/mol; -8.80 Kcal/mol; -15.21 Kcal/mol; and -10.24 Kcal/mol. Terpinen-4-ol has potential as an anti-inflammatory in atherosclerosis molecularly because it has affinity for the proteins ERK1, ERK2, JNK1, JNK2, and p38MAPK with binding energy values of 5.12, respectively; -5.24; -5.08; -5.88; -4.99; -4.89 kcal/mol, so it can inhibit ERK1, ERK2, JNK1, JNK2, and p38MAPK proteins.

Based on research conducted by(Beny et al., 2020)Design and design of leonurine derived compounds using ChemDraw Professional 15.0. The validation stage was carried out using the AutoDock Tools software. Molecular docking was performed with leonurin ligand and its derivatives, and ibuprofen to COX-2 protein using AutoDock 4.2. The results of molecular docking were visualized using the Discovery Studio Visualizer to see the hydrogen bond interactions and the hydrogen bond distances that occur between the ligand and the receptor. the best results were obtained for the 11-derivative ligand with a ΔG value of -7.95 kcal/mol and forming hydrogen bond interactions with 5 amino acid residues including: Tyr936 (O), Asn933 (O).

Based on research that has been conducted by(Ummah et al., 2020)that the preparation of enzyme and ligand molecules was carried out using Discovery Studio Client 4.1 software. to replace the ligand in PDB format and remove water molecules attached to COX-1 and COX-2 enzymes. The next preparation was carried out using the Autodock 4.2 program. Molecular docking of the synthesized compound (vanylyl methyl ketone) was performed using the Autodock Vina program and then analyzed using PyMOL and LigPlot. The results of the molecular docking simulation show that compound 1 (vanylyl methyl ketone) can interact with the active site of the COX-1 enzyme through 4 hydrogen bonds, namely between the ketone group in compound 1 and the hydrogen in Gln92 with a bond distance of 2.90 Å and oxygen in the methoxy hydrogen bonds with Thr199 (2.99 Å). . Based on a comparison of the results of inhibition of compound 1 against COX-1 and COX-2, it can be seen that vanylyl methyl ketone also has a higher inhibitor selectivity for COX-2 enzymes compared to COX-1. This selectivity is evidenced by the affinity value of the binding energy on the COX-2 enzyme which is lower than that of COX-1. Transformation of the olefin group in the eugenol compound into a ketone group (vanilyl methyl ketone) can increase its activity as an anti-inflammatory and selectivity for its inhibition of the COX-2 enzyme.

Based on research that has been conducted by(Suherman et al., 2020)The 3LN1 protein complex was separated between macromolecules and ligands using the Discovery Studio Visualizer® program. The ligands were first redrawn using the ChemDraw® Ultra 12.0 program and energy minimized using the Chem3D® Pro 12.0 program. Molecular docking method validation was carried out by redocking between default ligands from the target receptors downloaded from the protein data bank website using the Autodock Tools software. After all the docking settings are complete, running can be done using Autogrid4 and Autodock4. Based on the data generated, there is an interaction between the natural ligand of Celecoxib and the receptor which produces 8 amino acid residues namely ILE503, PHE504, ARG499, GLN178, HIS75, SER339, TYR 371 and ARG106. The test compound with lower energy

than the comparator drug, namely Linalool, showed 1 hydrogen bond with the TYR371 amino acid residue. linalool has been shown to be non-mutagenic, but carcinogenic, so further modification is needed to eliminate its carcinogenic properties. This shows that Linalool has potential as a COX-2 selective anti-inflammatory compared to other tamarind active compounds.

Based on research that has been conducted by(Bachtiar et al., 2021)In carrying out molecular docking of the anti-inflammatory activity test of compounds in the essential oil of bangle rhizome (Zingiber purpureum roxb), the PreADMET program was carried out which was accessed at http://preadmet.bmdrc.org/. The docking process was carried out using the AutoDockTools 1.5.6 software by entering the value of the Autogrid parameter, where the grid was made to cover all active protein surface pockets. The free energy value (ΔG) of the bangle rhizome essential oil compound which has the smallest hydrogen bonds is the Phenylmethylene compound with a ΔG value of -6.94 kcal/mol and a Ki value of 8.20 µM. The free energy value (ΔG) of ibuprofen is -8.38 kcal/mol with a Ki value of 0.71 µM, so that the affinity of ibuprofen for COX-1 is higher than that of the phenylmethylene compound. This shows that ibuprofen is predicted to have the best stable interaction with COX-1, which indicates that ibuprofen is more potent as an anti-inflammatory drug than Phenylmethylene. there are similarities in the hydrogen bonds that occur in the selected compounds Phenylmethylene and ibuprofen namely Arg120 and Tyr355, while the similarities in the hydrophobic bonds are Ser353. The similarity of hydrogen bonding and hydrophobic bonding indicates the level of solubility of the drug in the cell membrane and is predicted to bind well to the receptor site like the drug ibuprofen.

Based on research that has been conducted by(Rezki et al., 2022)in carrying out molecular docking of secondary metabolites in watermelon (Citrullus lanatus) which have the potential as anti-inflammatories, the software used in this study is Autodock 4.2 as software for docking, the process of minimizing ligand energy, comparator compounds, test compounds using Avogadro and Swiss software PDB, for visualization of protein and ligand interactions using Discovery Studio Visualizer and PyMOL software, for screening Lipinski's rules of five using the SCFBio website, while the pkCSM website is used to make ADMET predictions. From the docking results, the strongest bond free energy (ΔG) was obtained, namely the native ligand SC-558 with a value of -11.28 kcal/mol and the comparator compound Celecoxib of -10.37 kcal/mol. The constant value of inhibition can also be used as a reference or comparison in conducting in vitro tests (IC50). the smaller the distance between the hydrogen bonds formed, the stronger and more stable the hydrogen bonds will be to bind to proteins, so that the SC-558 compound produces better COX-2 inhibitory activity. In the three best test compounds, namely myricetin, tricetin, and quercetin, it was found that the formation of GLN (glutamine) 192 and PHE (phenylalanine) 518 amino acid residues was the same as the natural ligand compound SC-558 and the test compound celecoxib so that the compounds myricetin, tricetin, and Quercetin forms strong bonds at GLN (glutamine) 192 and PHE (phenylalanine) 518 residues. the smaller the distance between the hydrogen bonds formed, the stronger and more stable the hydrogen bonds will be to bind to proteins, so that the SC-558 compound produces better COX-2 inhibitory activity. In the three best test compounds, namely myricetin, tricetin, and quercetin, it was found that the formation of GLN (glutamine) 192 and PHE (phenylalanine) 518 amino acid residues was the same as the natural ligand compound SC-558 and the test compound celecoxib so that the compounds myricetin, tricetin, and Quercetin forms strong bonds at GLN (glutamine) 192 and PHE (phenylalanine) 518 residues. the smaller the distance between the hydrogen bonds formed, the stronger and more stable the hydrogen bonds will be to bind to proteins, so that the SC-558 compound produces better COX-2 inhibitory activity. In the three best test compounds, namely myricetin, tricetin, and quercetin, it was found that the formation of GLN (glutamine) 192 and PHE (phenylalanine) 518 amino acid residues was the same as the natural ligand compound SC-558 and the test compound celecoxib so that the compounds myricetin, tricetin, and Quercetin forms strong bonds at GLN (glutamine) 192 and PHE (phenylalanine) 518 residues.

Based on research that has been carried out by (Purwanto & Suhesti., 2021) in carrying out molecular docking of phenolic basil leaves (Ocimum basilicum L.) the software used is the AutoDock Vina application, and PyMOL. The docking results show that the phenolic test compound can interact with 6COX cyclooxygenase-2. Ligand-receptor interactions occur because of hydrogen bonds, Van der

Waals bonds and or electrostatic interactions. In cyclooxygenase-2, hydrogen bonds are formed on amino acid residues in phenolics. Oxygen from the test compound forms two hydrogen bonds with O and H atoms that have a bond distance, while the ligand-receptor interaction occurs between one N atom and C. Bond free energy (ΔG) indicates the stability of the interaction (bond) of the ligand with cyclooxygenase-2 on the binding site. The greater the free energy value, the more stable the ligand bond with the receptor. The curculigoside a aglycone compound has a large free bond energy value (4.8 kcal/mol). These results indicate that phenolic compounds have good affinity for the 6COX cyclooxygenase-2I receptor.

Based on research that has been conducted by(Candra & Wijaya, 2021)in carrying out molecular docking of kaempferol with the programs used, namely AutoDock Tools 1.5.6, Chimera 1.11.1. This study shows that kaempferol has an affinity because it is able to produce hydrogen bonds with NF-κB protein. Kaempferol with NF-κB protein of -7.85 kcal/mol can form hydrogen bonds on the amino acid residues LEU472 and SER476. The affinity that occurs between kaempferol for NF-κB protein can inhibit the transcription of pro-inflammatory genes so that the formation of atherosclerotic plaques on the walls of blood vessels can be inhibited.

Based on research that has been conducted by(Saputra, 2018)in carrying out the molecular docking of cyanidin and peonidin with the programs used, namely Autodock 4.2 on Windows OS, Chimera 1.10.1, and HyperChem 8. Based on the bond energy values obtained, it shows that cyanidin and peonidin compounds have potential activity as anti-atherosclerosis because they have affinity and form hydrogen bonding with NF-4% protein, NDWDQ \DQJ that occurs between cyanidin and peonidin with NF-4% PDPSX PHQJKDPEDW protein transcription of proinflammatory genes and smooth muscle migration so that the formation of atherosclerotic plaques on blood vessel walls can be inhibited.

Based on research that has been conducted by(Yunita et al., 2019)in carrying out molecular docking of the potential of tamarind leaves (Tamarindus indica L.) with the program used, namely PLANTS. The docking results showed that Quercetin was able to interact with 1EQH, 3PGH, and 6COX where the docking scores were -77.6195; -75.1344; and -82.2454, while the Aspirin docking results were -69.8784; -75.2421; and - 72.0884. Quercetin has the potential as a better anti-inflammatory compared to Aspirin but has a higher risk of causing stomach ulcers than Aspirin.

Based on research that has been conducted by(Masula et al., 2018)in carrying out molecular docking of secondary metabolites (Lantana camara) with the programs used, namely PyRx software, PyMol software, Pubchem (compound database), PDB (Protein Data Bank), and PoseView (https://proteinsplus.zbh.uni-hamburg.de/).

Based on the docking results it was concluded that the Ikterogenin compound and the Umuhengerin compound were the most effective compounds in the anti-inflammatory process, the Ikterogenin compound had an RMSD value of 41.1 Å and a binding affinity value of -8.8 and the Umuhengerin compound had an RMSD value of 1.61 Å and a binding affinity value of affinity -8.0. This shows that the Umuhengerin compound has a percentage similarity to the target protein because it has a smaller RMSD value compared to the Ikterogenin compound. However, the Ikterogenin compound has a stronger and more efficient hydrogen bond than the Umuhengerin compound because of the lowest binding affinity value.

Based on research that has been conducted by(Purwanto et al., 2021)the molecular process of docking the anti-inflammatory potential of quercetin in Moringa leaves (Moringa oleifera L.) with the program used, namely Autodock-Vina. The results obtained are the value of the binding affinity (kcal/mol) of the ligand to the protein. The Ligplot+ program was used to visualize the 3D conformation of the molecule and the ligand-protein interactions. The device used is an ASUS notebook with Windows 10 64-bit specifications. Based on molecular docking, quercetin has potential activity as an anti-inflammatory because it has an affinity and forms in-silico Cox 6 hydrogen bonds and was tested further with in vitro activity to obtain results as an anti-inflammatory.

Based on research that has been conducted by(Ahsana et al., 2021)who have carried out molecular docking of flavonoid compounds in samples of guava leaves (Psidium Guajava L.) using the Autodock4 docking software program with the semiflexible method and the Lamarckian Genetic Algorithm (LGA). Research on flavonoid compounds on ID:6COX protein as a COX-2 inhibitor using

molecular docking obtained the best free bond energy (ΔG) from the results of flavonoid compounds with a high value of -9.31 kcal/mol derived from Epicatechin-3-O- Gallate, has potential activity as a COX-2 inhibitor and the amino acid residues that are most involved in research are SER 353, TYR 385, SER 530, ARG 120, and GLN 192.

Based on research conducted by(Scientiae & Docking, 2022)in carrying out the molecular docking of quercetin compounds from eggplant (Solanum torwum Swartz) using the program used, namely Autodock-Vina. The compound quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) has the potential as an anti-inflammatory drug as a TNF-protein inhibitor with an LD_{50} value of 2.471; with a bioavailability value of 0.55; does not have skin hepatotoxicity and sensitization properties and passes the Lipinski test. Test compound 8 (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) has potential as an anti-inflammatory drug on TNF-protein with a ΔG value of -8.55 kcal/mold an interacts with amino acid residues ILE^{155}, TRY^{59}; GLY^{121}; GLN^{61}; TYR^{151}; VAL^{123}; LEU^{157}; ILE^{58}; GLY^{122}; $SER^{6^{\circ}}$; $LEU^{12^{\circ}}$; LEU^{157}.$\alpha\alpha$

4. CONCLUSION

All of the compounds used contain secondary metabolites of flavonoids, alkaloids, essential oils, terpenoids and anthocyanins so that they have potential as anti-inflammatories and are suitable for use as candidates for discovery and design of new drug development.

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