In Silico Study of Perisbivalvin, Apioside and Pelargonidine 3-Sambubioside on PTGS2 Receptors

Abstract

Inflammation is a normal protective response to tissue injury that involves various physiological processes in the body. Perisbivalvin, apioside, and pelargonidine 3-sambubioside are anthocyanin compounds found in magenta plants. The purpose of this study was to obtain a candidate for a new compound as an anti-inflammatory agent targeting the PTGS2 receptor before in vivo testing. Molecular docking in silico with PDB code 5IKR was carried out by optimizing 2 and 3-dimensional chemical structures, method validation, and docking between perisbivalvin compounds and the comparison compound mefenamic acid. The results obtained were docking perisbivalvin -7.63 kcal/mol, apioside -0.77 kcal/mol, and pelargonidine -5.74 kcal/mol, while the bond energy of the comparison compound was -7.52 kcal/mol through hydrogen bonding interactions with amino acids TYR 385A and SER 530A. The prediction results of the test compounds and comparison compounds were classified as class 4 toxicities. Perisbivalvin compounds have anti-inflammatory potential because they can bind to the PTGS2 protein.

Keywords: Perisbivalvin, Antiinflammatory, PTGS2, In Silico.

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Kajian *In Silico* Senyawa Perisbivalvin, Apioside dan Pelargonidine 3-Sambubioside terhadap Reseptor PTGS2

Abstrak

Inflamasi adalah suatu respon protektif normal terhadap cedera jaringan yang melibatkan berbagai proses fisiologis dalam tubuh. Perisbivalvin, apioside dan pelargonidine 3-sambubioside merupakan senyawa antosianin yang terdapat pada tanaman magenta. Tujuan penelitian ini adalah untuk mendapatkan kandidat senyawa baru sebagai antiinflamasi dengan target reseptor PTGS2 sebelum dilakukan uji *in vivo*. *Molecular docking* secara *in silico* dengan kode PDB 5IKR dilakukan dengan optomasi struktur kimia 2 dan 3 dimensi, validasi metode serta docking antara senyawa perisbivalvin dan senyawa pembanding yaitu asam mefenamat. Diperoleh hasil *docking* perisbivalvin -7.63 kkal/mol, apioside -0.77 kkal/mol dan pelargonidine -5.74 kkal/mol, sedangkan energi ikatan senyawa pembanding sebesar -7.52 kkal/mol melalui ikatan hidrogen asam amino TYR 385A dan SER 530A. Hasil prediksi senyawa uji dan senyawa pembanding berada pada toksisitas kelas 4. Senyawa perisbivalvin berpotensi sebagai antiinflamasi karena mampu berikatan dengan protein PTGS2.

Kata Kunci: Perisbivalvin, Antiinflamasi, PTGS2, *In Silico*

1. Introduction

Inflammation is a symptom of a disease that often occurs in Indonesia. According to the 2018 Basic Health Research Data, the prevalence of joint diseases and dental and oral problems in Indonesia has increased significantly. Swollen gums and joint pain are diseases that involve inflammatory reactions. [1,2]

Inflammation is a normal protective response to tissue injury that involves various physiological processes in the body including enzyme activation, mediator release, diapedesis, or movement of white blood cells through capillaries to areas of inflammation, cell migration, tissue damage, and repair.[3] The main signs of tissue inflammation are the presence of a tumor (swelling), calor (heat), rubor (redness), and dolor (pain).[4] Swelling is caused by the accumulation of fluid, heat and redness are caused by increased blood flow, and pain is caused by the release of various compounds that stimulate painful nerves. Local inflammation involves bradykinin, a prostaglandin that induces vasodilation and increased vascular permeability.[5]

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of drugs with analgesic, antipyretic, and anti-inflammatory properties. NSAIDs work by inhibiting the synthesis of prostaglandins, which block both types of cyclooxygenase (COX), thereby reducing the production of prostaglandins.[6] Prostaglandins are hormones that arise when there is inflammation in the internal organs of humans. There are two isoforms in COX, namely COX-1 and COX-2.[7] COX-2 is an enzyme that catalyzes the biosynthesis of prostaglandins from arachidonic acid and is induced in inflamed cells by cytokines, endotoxins, and growth factors.[8] Mefenamic acid is one of the most widely used NSAIDs on the market. Mefenamic acid 2-[(2,3-dimethyl phenyl)amino]benzoic acid with the molecular formula C15H15NO2 is a benzoic acid that has an amine group attached to the benzene moiety.[9] Research written by Idacahyati et al. (2019), mentions that mefenamic acid has unwanted side effects such as gastrointestinal disturbances such as dyspepsia, diarrhea, constipation, nausea, vomiting, and gastritis. Therefore, it is necessary to develop herbal-based medicines, that can minimize unwanted side effects.[10]

Perisbivalvin, apioside, and pelargonidin 3-sambubioside are some of the anthocyanin compounds found in magenta plants (Peristrophe bivalvis (L.) Merr).[11] Priska et al. (2018) said that anthocyanins function as antidiabetic, anti-hypoglycemic, antihypertensive, anticancer, and anti-inflammatory.[12] In the development of new drugs, it is trial and error without a clear design, it can give less than optimal results.[13]

In silico testing is a method of drug development that uses a computer developed to predict pharmacological or physiological processes. If the 3D structure of the target protein has been obtained, the method that can be used is a structure-based drug design (SBDD) for example molecular docking.[14] The method has been developed and is widely used for the development of pharmacological hypotheses and testing the molecular structure design and biological activity based on systematic and rational reasoning.[15] The purpose of this study was to obtain candidate new compounds that are predicted to have anti-inflammatory activity with the target of the Prostaglandin Synthase-2 (PTGS2) receptor before in vivo testing so that it can be an alternative source of drug raw materials.

2. Methods

2.1. Materials

The research material used is using macromolecules as receptors obtained through the Protein Data Bank (PDB) website which can be accessed via http://www.rcsb.org/structure/5ikr with PDB ID 5IKR. Mefenamic acid as a comparison

drug as well as perisbivalvin compounds, apioside, and pelargonidine 3-sambubioside obtained a two-dimensional structure using the MarvinSketch Version 20.13 2020 program from ChemAxon®, while the three-dimensional structure image using the UCSF Chimera Version 1.14 Build 42094 program.

2.2. Instrument

ASUS A409UA-BV3511T computer set with Intel CORE i3 processor, 4GB RAM, 512GB SSD storage, Windows 10 (64 bit) equipped with AutoDockTools-1.5.6 program, MarvinSketch Version 20.13 2020 from ChemAxon®, Marvin Sketch, to determine the ADME, obtained through the Predicting Small-Molecule Pharmacokinetic and Toxicity Properties using Graph-Based Signatures (pkCSM) http://structure.bioc.cam.ac.uk/pkcsm.

2.3. Procedure

2.3.1.2-dimensional chemical structure

The 2-dimensional structure of perisbivalvin, apioside, and pelargonidine 3-sambubioside compounds were optimized using the MarvinSketch Version 20.13 2020 program. The optimization was performed using computational methods and saved in (*.pdb) and (*.mol2) formats.

2.3.2.3- dimensional chemical structure

Protein preparation was carried out using the UCSF Chimera Version 1.14 Build 42094 program. Compounds in the form of a three-dimensional structure were saved in the format (*.mol2).

2.3.3.Molecular docking method validation

Before docking the test compound, it was necessary to validate the Root Molecular Square Docking (RMSD) of the Prostaglandin Synthase 2 (PTGS2) receptor with the original ligand in the PDB code 5IKR. The method validation parameter was Root Mean Square Deviation (RMSD). The acceptable RMSD is 2.0 Å.[16]

2.3.4.Molecular docking of PTGS2 receptors

Before carrying out molecular docking, there are preparation steps for ligands and macromolecules as well as docking simulations using the Autodock program. The optimized perisbivalvin, apioside, and pelargonidine 3-sambubioside compounds were docked on the PTGS2 protein which had its native ligand removed using the Autodock application with a docking procedure. The results of the analysis show the conformation of the compound bond in the protein with the value of binding energy and hydrogen bonding.

2.3.5.Physicochemical parameters

The physicochemical properties of perisbivalvin, apioside, and pelargonidine 3-sambubioside were predicted using the pkCSM website and Lipinski's Five Law results from compounds consisting of LogP, molecular weight, num, H-bond donor, and H-bond acceptor. The physicochemical parameters were obtained by entering the file in the SMILES format on the pKCSM web. If the selected prediction mode is ADMET, the predicted data will be derived from the properties of absorption, distribution, metabolism, excretion, and toxicity of the compound. In addition to the properties of ADMET, data on Lima Lipinski compounds were also obtained, which can be seen in the molecular properties section in the form of molecular weight, num. H-bond acceptor, num. H-bond donor and Log P.[17]

2.3.6.Data analysis

Molecular docking revealed the formation of hydrogen bonds and bond energies. The bond energy was used to determine the strength of the bonds between the ligands and macromolecules. The lower the

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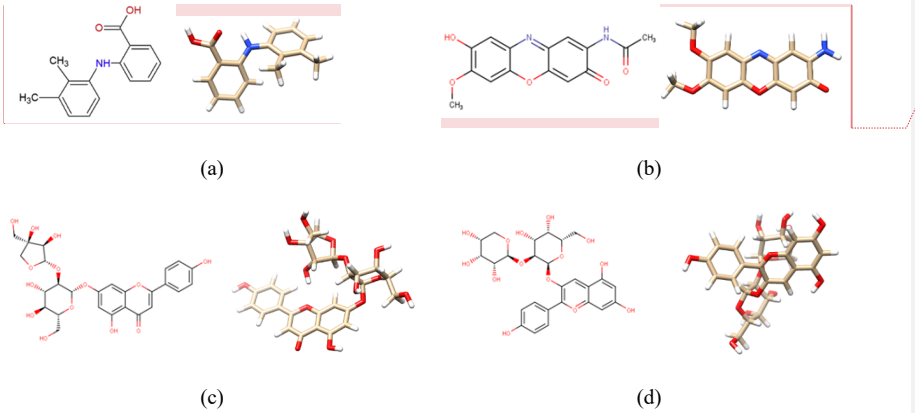
bond energy value, the stronger is the bond stability. The type of hydrogen bond formed was used to analyze the interaction mechanism.[18]

3. Results

Two-dimensional chemical structure images of perisbivalvin, apioside, pelargonidine 3-sambubioside, and mefenamic acid as comparison compounds were obtained using the MarvinSketch Version 19.25 2020 application from ChemAxon® and then saved in SDF format. A three-dimensional structure was created using UCSF Chimera Version 1.14 Build 42094 saved in the mol2 format. The results of the visualization of the two-dimensional and three-dimensional structures of the test compounds and comparison compounds are shown in Figure 1.



(a) (b) (c) (d)

Figure 1. The Structure of (a) *2-[(2,3-dimethylphenyl)amino]benzoic acid* (Mefenamic Acid) by Boudiombo & Jacobs (2018), (b) Perisbivalvin, (c) Apioside, and (d) Pelargonidine 3-sambubioside

The molecular docking parameter in this study was the Docking score obtained from the Autodock program using the PTGS2 receptor with PDB code 5IKR which has a ligand 2 - ((2,3-dimethyl phenyl) amino) as an anti-inflammatory. In molecular docking validation, it was analyzed based on the Root Mean Square Deviation (RMSD) value of the crystal structure of the original ligand from PDB 5IKR with redocked ligands, obtained RMSD of 0.43 Å (Figure 2). The results of determining the activity parameters of the test compounds and comparison compounds are shown in Table 1.

Table 1. Docking Results of Mefenamic Acid, Perisbivalvin, Apioside, and Pelargonidine 3-sambubioside

Compound Name	Docking Score (kcal/mol)	Hydrogen Bond
Asam mefenamat	-7.52	Tyr 385A, Ser 530A
Perisbivalvin	-7.63	Tyr 385A, Arg 120A
Apioside	-0.77	Arg 120A
Pelargonidine 3-sambubioside	-5.74	Arg 120, Ser 353A, Gln 192A, Ala 527A

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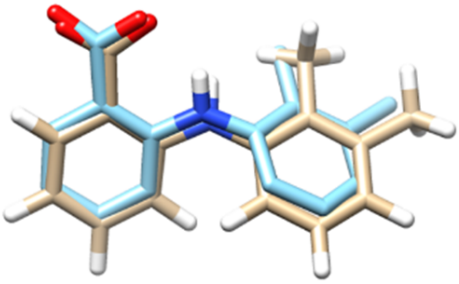

Figure 2. Crystal Structure of 5IKR Original Ligand (brown) with Redocked Ligand (blue) with RMSD value of 0.49 Å

Toxicity parameters (LD_{50}) were obtained through the Predicting Small-Molecule Pharmacokinetic and Toxicity Properties program using Graph-Based Signatures (pKCSM). The results of determining the toxicity parameters of the test compounds and comparison compounds are shown in Table 2.

Table 2. Toxicity Prediction of Mefenamic Acid, Perisbivalvin, Apioside, and Pelargonidine 3-sambubioside

Compound Name	Toxicity Parameters LD_{50} (mg/kg)	Class
Mefenamic acid	595,50	4
Perisbivalvin	715,543	4
Apioside	1.628,571	4
Pelargonidine 3-sambubioside	1.616,776	4

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To determine the physicochemical properties of a ligand when it crosses cell membranes in the body, the Lipinski test was carried out.[24] The results of the analysis with Lipinski's Five Laws are shown in Table 3.

Table 3. Physicochemical Properties of Mefenamic Acid, Perisbivalvin, Apioside, and Pelargonidine 3-sambubioside

Compound Name	Log P <5	MW <500	Donor H Bond <5	H-binding acceptor <10
Mefenamic acid	3,74	335,87	2	2
Perisbivalvin	1,8922	272,26	1	6
Apioside	-1,4852	564,496	8	14
Pelargonidin 3-sambubioside	-0,8603	565,504	9	13

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Note: LogP: Log of fat/water partition coefficient should be < 5; MW: Molecular weight should be <500; Donor H Bond: Donor -H bond expressed by the number of O-H and N-H groups <5; H acceptor bond: -H acceptor bond expressed by the number of O and N atoms < 10.[24]

4. Discussion

In silico methods are used to computationally predict drug design. This method has the advantages of being more efficient, saving time, and minimizing the isolation of inactive compounds.[19] In this study, an in silico test was carried out which required a two-dimensional and three-dimensional structure of the test compound, namely perisbivalvin, apioside, pelargonidine 3-sambubioside, and mefenamic acid as comparison compounds (Figure 1). The Autodock Tools application was used for method validation through the redocking process (Figure 2). The redocking process obtained the RMSD value and binding energy using the molecular docking method. The criterion for the best RMSD value is less than 2.0 Å; thus it has good validity and reliability. The smaller the RMSD value, the closer the docked natural ligand position to the crystallographic natural ligand. The RMSD value on the crystal structure of the original ligand from PDB 5IKR with the redocked ligand, obtained a value of 0.43 Å the results are declared valid.[20,21]

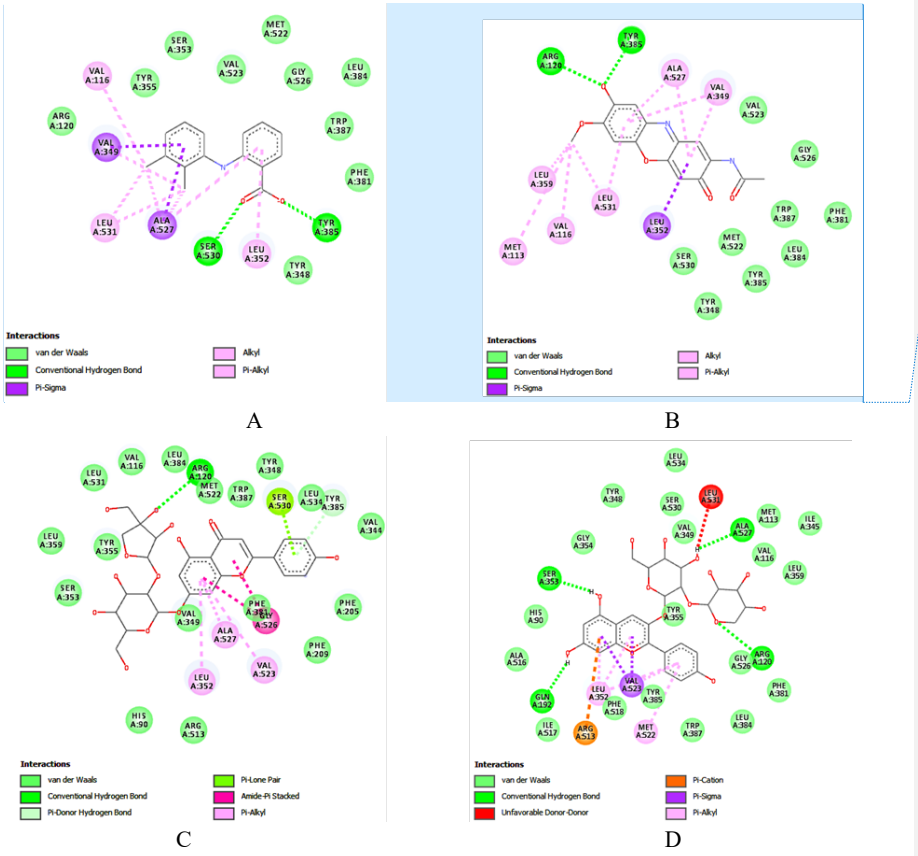

Figure 3. Visualization of (a) Comparison Compound Interaction with PTGS2, (b) Perisbivalvin with PTGS2, (c) Apioside with PTGS2, and (d) Pelargonidine 3-sambubioside with PTGS2

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The results of PTGS2 docking between perisbivalvin, apioside, and pelargonidine 3-sambubioside, and mefenamic acid showed that the bond energy between the test compound and PTGS2 was negative. The lower the Docking Score value the better the biological activity produced because the energy required by the compound to bind to the receptor is lower and the bond becomes stable. In the three test compounds, perisbivalvin had the best docking score of -7.63 kcal/mol compared to apioside and pelargonidine 3-sambubioside compounds. This shows that the potency of perisbivalvin compounds in binding to the active site of PTGS2 is stronger than that of the other test compounds and the comparison compound mefenamic acid which only has a docking score of -7.52 kcal/mol (Table 1). Perisbivalvin compounds can bind to PTGS2 through the formation of hydrogen bonds in the amino acid TYR 385A. The TYR 385A bond is the same hydrogen bond between mefenamic acid and PTGS2. Interaction between the comparison compound and the test compound against the PTGS2 receptor is shown in Figure 3.

Toxicity parameters (LD_{50}) were obtained through the website Predicting Small-Molecule Pharmacokinetic and Toxicity Properties using Graph-Based Signatures (pKCSM). LD_{50} is the amount of a given compound that can cause the death of 50% of the experimental animal group.[22] The results of the toxicity parameters (Table 2.) reported that the LD_{50} value of the perisbivalvin compound was 715,543 mg/kg, apioside had an LD_{50} value of 1,628,571 mg/kg, pelargonidine 3-sambubioside had an LD_{50} value of 1,616,776 mg/kg and the comparison compound mefenamic acid had an LD_{50} value of 1,616,776 mg/kg. LD_{50} value 595.50 mg/kg. All test compounds were classified as toxicity class 4 ($300 < LD_{50}$ 2000). Perisbivalvin, apioside and pelargonidine 3-sambubioside compounds have a better LD_{50} value than mefenamic acid. According to the toxicity class tabulation in the study by Kesuma et al. (2018), toxicity was relatively low in toxicity class 4. The test compounds perisbivalvin, apioside, and pelargonidine 3-sambubioside were predicted to be safer than the comparison compound mefenamic acid.[23]

The structure-activity relationship with docking only focuses on the compatibility of the bond between the drug and the receptor, so it is necessary to observe the lipophilic nature of the drug compound. Apioside has a molecular weight of 564.496 and pelargonidine 3-sambubioside has a molecular weight of 565.504. Molecular weights over 500 Da cannot diffuse across the cell membrane.[17,24] Perisbivalvin compound has a molecular weight of 500 which is 272.26 so it can be estimated that it has good penetration power and is easy to absorb compared to mefenamic acid which has a molecular weight of 335.87 and other test compounds.[25]

5. Conclusion

From these results, it can be concluded that perisbivalvin has an affinity for PTGS2 protein with a bond energy of -7.63 kcal/mol and has the same hydrogen bond as the comparison compound, TYR 385A. Perisbivalvin has a lower toxicity than the comparison compound. The value of the molecular weight of perisbivalvin compounds is 272.26 which is said to be able to penetrate cell membranes, so that perisbivalvin compounds are predicted to be candidates for new compounds that have anti-inflammatory activity.

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Naskah

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