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Research Article

Interactions of Perisbivalvin, Apioside, and Pelargonidine 3-Sambubioside Against PTGS2 Receptors

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Abstract

Inflammation is a normal protective response to tissue injury and involves various physiological processes in the body. This study used the prostaglandin synthase 2 (PTGS2) receptor or cyclooxygenase-2 (COX-2) which contributes to prostaglandin synthesis and the regulation of inflammation, and its inhibition is associated with a reduced risk for several colon cancer. Perisbivalvin, apioside, and pelargonidin 3-sambubioside are anthocyanin compounds found in magenta plants. This study aimed to obtain a new candidate 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, conducting method validation, and docking between perisbivalvin compounds and the comparison compound mefenamic acid. The docking results showed that perisbivalvin at -7.63 kcal/mol, apioside at -0.77 kcal/mol, and pelargonidine at -5.74 kcal/mol, while the binding energy of the control compound was at -7.52 kcal/mol through hydrogen bonding interactions with amino acids of TYR385A and SER530A. The prediction results showed the experiment compounds compared to the control compounds were classified as class 4 toxicities. Perisbivalvin compounds are potentially anti-inflammatory because they can bind to the PTGS2 protein.

Keywords: anti-inflammatory, in silico, perisbivalvin, PTGS2

Interaksi dari 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. Penelitian ini menggunakan reseptor prostaglandin sintase 2 (PTGS2 atau siklooksigenase-2 (COX-2) yang memegang peran penting dalam sintesis prostaglandin dan telah terbukti memainkan peran kunci dalam regulasi peradangan, dan penghambatannya dikaitkan dengan penurunan risiko pada beberapa kanker usus besar. Perisbivalvin, apioside, dan pelargonidine 3-sambubioside merupakan senyawa antosianin yang terdapat pada tanaman magenta. Penelitian ini bertujuan untuk mendapatkan kandidat baru anti-inflamasi dengan target reseptor PTGS2 sebelum dilakukan uji *in vivo*. Penambatan molekul secara *in silico* dengan kode PDB 5IKR dilakukan dengan optimasi 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 TYR385A dan SER530A. Hasil prediksi senyawa uji dan senyawa pembanding berada pada toksisitas kelas 4. Senyawa perisbivalvin berpotensi sebagai anti-inflamasi karena mampu berikatan dengan protein PTGS2.

Kata Kunci: anti-inflamasi, *in silico*, perisbivalvin, PTGS2

1. Introduction

Inflammation is a symptom of a disease that often occurs in Indonesia. According to the Basic Health Research Data (2018), the prevalence of joint diseases and dental and oral problems in Indonesia has increased significantly. Inflammatory reactions take place for swollen gums and joint pain.[1,2]

Inflammation is a normal protective response to tissue injury and 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 a tumor (swelling), color, rubor (redness), and dolor (pain) that occur in the body.[4] Swelling is caused by the accumulation of fluid, heat and redness because of 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 increases vascular permeability.[5]

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of drugs with analgesic, antipyretic, and anti-inflammatory activities. 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 inflammation occurs 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 in the market. Mefenamic acid 2-[(2,3-dimethyl phenyl)amino]benzoic acid with the molecular formula $C_{15}H_{15}NO_2$ is a benzoic acid that has an amine group attached to the benzene moiety.[9] Research done by Idacahyati (2020) mentions that mefenamic acid has unwanted side effects for example gastrointestinal disturbances such as dyspepsia, diarrhea, constipation, nausea, vomiting, and gastritis. Therefore, it is necessary to develop alternative drugs, such as herbal-based medicine, that can minimize unwanted side effects.[10]

Perisbivalvin, apioside, and pelargonidin 3-sambubioside are the anthocyanin compounds found in magenta plants (*Peristrophe bivalvis* L. Merr).[11,26] Priska et al. (2018) stated that anthocyanins have antidiabetic, anti-hypoglycemic, antihypertensive, anticancer, and anti-inflammatory activities.[12] Trial and error experiments usually performed during new drugs development. These approaches can be more time consuming and costly and produce less optimal results.[13] So that, an appropriate aprroach is needed to obtain an optimum results with less time and cost.

In silico testing is a method of drug development that uses a computer to predict pharmacological or physiological processes. The 3D structure of the target protein obtained can be used to performed the structure-based drug design (SBDD) analysis such as molecular docking.[14] The method has been developed and widely used for the development of pharmacological hypotheses and testing of the molecular structure design and biological activity based on systematic and rational reasoning.[15]

This study used the prostaglandin synthase 2 (PTGS2) receptor, which has a native ligand that interacts with the amino acids Tyr385A and Ser530A through hydrogen bonds and Leu352A, Ala527A, Leu531A, Val349A, and Val116A through hydrophobic bonds. PTGS2 or cyclooxygenase-2 (COX-2) contributes to the regulation of inflammation, and its inhibition is associated with a reduced risk for several colon cancers.[16] PTGS or COX is an enzyme that plays an important role in the synthesis of prostaglandins. This enzyme has bifunctions. The initial function is the COX reaction converting arachidonic acid to prostaglandin G2. Furthermore, the peroxidase reaction converts prostaglandin G2 to prostaglandin H2. PTGS2 also plays a role in the synthesis of prostanoids in inflammation and mitogenesis. The purpose of this study was to obtain a candidate of a new compound that potentially has an anti-

inflammatory activity with the target of the PTGS2 receptor before *in vivo* testing and that can be an alternative source of drug raw materials.

2. Methods

2.1. Materials

The research material used was macromolecules as receptors obtained through the Protein Data Bank (PDB) accessed on http://www.rcsb.org/structure/5ikr with PDB ID 5IKR.[27] The two-dimensional chemical structures of mefenamic acid as a control drug as well as perisbivalvin compounds, apioside, and pelargonidin 3-sambubioside were obtained using the MarvinSketch Version 20.13 2020 program from ChemAxon®, while the three-dimensional chemical structures were captured using the UCSF Chimera Version 1.14 Build 42094 program.

2.2. Instrument

The research instruments were 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, used to determine the ADME through the predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures (pkCSM) accessible on http://structure.bioc.cam.ac.uk/pkcsm.

2.3. Procedures

2.3.1. Two-dimensional chemical structure

The two-dimensional structure of perisbivalvin, apioside, and pelargonidin 3-sambubioside were converted to a three-dimensional (3D) structure 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. Three-dimensional chemical structure

Protein preparation was carried out using the UCSF Chimera Version 1.14 Build 42094 program. Three-dimensional chemical structures of the compounds were captured and saved in the (*.mol2) format.

2.3.3. Validation of molecular docking method

Before docking the experiment compounds, it was necessary to validate the root molecular square docking (RMSD) of PTGS2 receptor with the original ligand in the PDB code 5IKR. The validation parameter was root mean square deviation (RMSD), and the acceptable RMSD was 2.0 Å.[17]

2.3.4. Molecular docking of PTGS2 receptors

Before carrying out molecular docking, there were preparation steps for ligands and macromolecules. Docking simulations were performed using the Autodock 4 program. The optimized perisbivalvin, apioside, and pelargonidin 3-sambubioside were docked on the PTGS2 protein which native ligand was removed using the Autodock tools through a docking procedure. The process started from removing of water molecules, residues, and native ligands. Then, the file was saved in (.pdbqt) format. The results of the analysis showed the conformation of the compound bond in the protein with the value of bond energy and hydrogen.

2.3.5. Physicochemical parameters

The physicochemical properties of perisbivalvin, apioside, and pelargonidin 3-sambubioside were predicted using the pkCSM website and Lipinski's rules of five results from compounds consisting of LogP, molecular weight, num, H-bond donor, and H-bond acceptor. The physicochemical properties were obtained by entering the file in the SMILES format on the pKCSM web. When the selected prediction mode was ADMET, the predicted data were derived from the properties of absorption, distribution, metabolism, excretion, and toxicity of the compounds. In addition to the properties of ADMET, data on Lipinski rules of five compounds were also obtained. They could be seen from the molecular properties e.g., molecular weight, H-bond acceptor, H-bond

donor, and Log P.[18]

2.3.6. Data analysis

Molecular docking revealed the formation of hydrogen bonds and bond energy. The hydrogen bond was used to analyze the interaction mechanism.[19] While the bond energy determined the strength of the bonds between the ligands and macromolecules. The lower the bond energy value, the stronger the bond stability.

3. Results

Two-dimensional chemical structures of perisbivalvin, apioside, pelargonidin 3-sambubioside, and mefenamic acid as a control compound were captured using the MarvinSketch Version 19.25 2020 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 visualization of the two-dimensional and three-dimensional structures of the experiment compounds and control compound is presented in Figure 1.

The molecular docking parameters in this study were obtained from the Autodock program using the PTGS2 receptor with PDB code 5IKR which had a ligand 2 - ((2,3-dimethyl phenyl) amino) as an anti-inflammatory agent. The molecular docking validation 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 at RMSD of 0.43 Å (Figure 2) of the activities between the experiment compounds and control compound are explained in Table 1.

Toxicity parameters (LD_{50}) were obtained through the predicting small-molecule pharmacokinetic and toxicity properties program using graph-based signatures (pKCSM). The toxicity parameters of the experiment compounds and control compound are demonstrated in Table 2.

To determine the physicochemical properties of a ligand crossing cell membranes in the body, the Lipinski test was carried out.[25] The analysis results with Lipinski's rules of five compounds are demonstrated in Table 3.

4. Discussion

In this study, *in silico* testing was carried out which required a two-dimensional and three-dimensional structure of the experiment compounds, namely perisbivalvin, apioside, pelargonidin 3-sambubioside, and a control compound mefenamic acid (Figure 1). The Autodock tool was used to validate a docking method through the redocking process (Figure 2). The redocking process obtain the RMSD value and binding energy through the

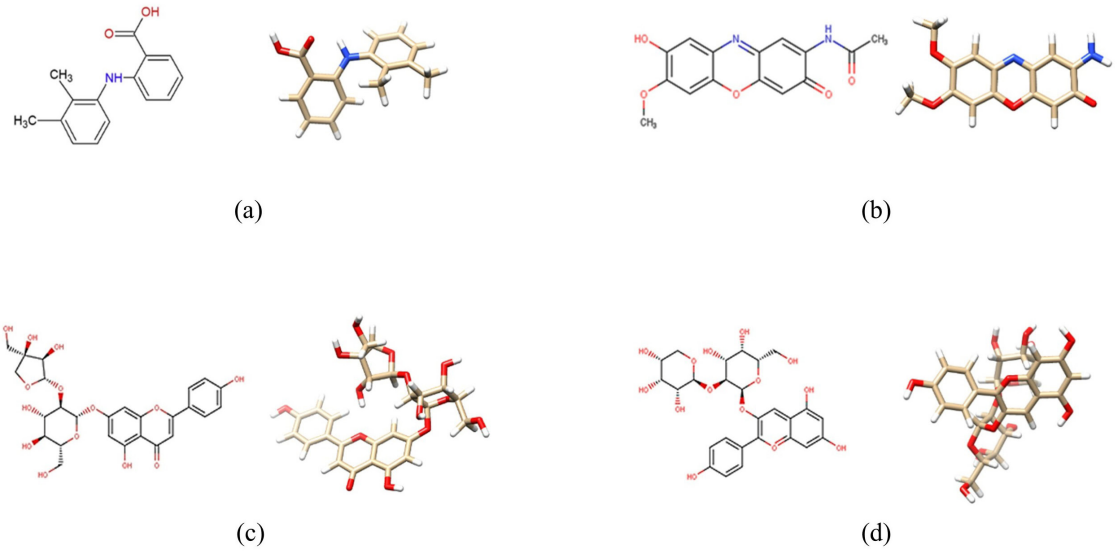

Figure 1. The Structure of (a) 2-[(2,3-dimethylphenyl) amino] benzoic acid (Mefenamic Acid) by Boudiombo & Jacobs (2018), (b) Perisbivalvin, (c) Apioside, and (d) Pelargonidine-3-sambubioside

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

Compound Name	Docking Score (kcal/mol)	Hydrogen Bond
Mefenamic acid	-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

molecular docking method. The criterion for the best RMSD value is less than 2.0 Å to have 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 was at 0.43 Å, thus declared valid.[21,22]

In silico methods were used to computationally predict a drug design, drug activity, and molecular target against a specific receptor. This method is more efficient, time-saving and optimal in minimizing the isolation of inactive compounds.[20]

The results of PTGS2 docking between perisbivalvin, apioside, and pelargonidin 3-sambubioside, and mefenamic acid showed that the bond energy between the experiment compounds and PTGS2 was negative. The lower the docking score, the better the biological activity. The energy required by the compounds to bind to the receptor was lower, and the bond became stable. In the three experiment compounds, perisbivalvin had the best docking score of -7.63 kcal/mol compared to apioside and pelargonidin 3-sambubioside. This showed that the potency of perisbivalvin in binding to the active site of PTGS2 was stronger than the other test compounds and the control compound, mefenamic acid, which only had a docking score of -7.52 kcal/mol (Table 1). Perisbivalvin can bind to PTGS2 through the formation of bond hydrogen in the amino acid TYR385A which was also a bond between mefenamic acid and PTGS2.[27] Interaction between the control compound and the experiment compounds against the PTGS2 receptor is illustrated in Figure 3.

Toxicity parameters (LD_{50}) were obtained through the predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures (pKCSM). LD_{50} is the number of compounds that can cause the death of 50% of the experimental animal group.[23] The results of the toxicity parameters (Table 2) reported that the LD_{50} values of the perisbivalvin, apioside, and pelargonidin 3-sambubioside were 715.54 mg/kg, 1,628.571 mg/kg, and 1,616.77 mg/kg, respectively, while the control compound had LD_{50} value of 595.50 mg/kg. All tested compounds were classified as class-4 toxicity ($300 < LD_{50} \leq 2000$). Perisbivalvin, apioside,

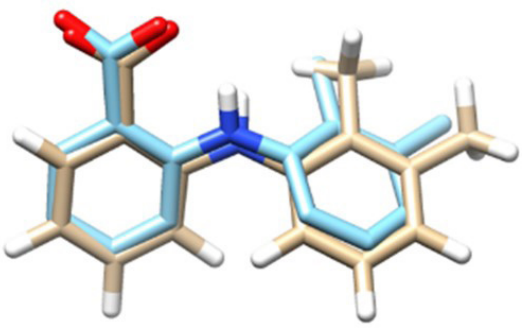

Figure 2. Crystal Structure of 5IKR Original Ligand (brown) with Redocked Ligand (blue) with RMSD value of 0.49 Å

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

Compound Name	Toxicity Parameters LD50 (mg/kg)	Class
Mefenamic acid	595.50	4
Perisbivalvin	715.543	4
Apioside	1,628.571	4
Pelargonidine 3-sambubioside	1,616.776	4

and pelargonidin 3-sambubioside had better LD_{50} values than mefenamic acid. According to the toxicity class tabulation conducted by Kesuma et al. (2018), class-4 toxicity was relatively low. The perisbivalvin, apioside, and pelargonidin 3-sambubioside were predicted to be safer than the mefenamic acid.[24]

The structure-activity relationship with docking only focused on the compatibility of the bond between the drugs and the receptor, and thus it is necessary to observe the lipophilic nature of the drug compounds. Apioside had a molecular weight of 564.496 Da, and pelargonidine 3-sambubioside had a molecular weight of 565.504 Da. Molecular weights over 500 Da cannot diffuse across the cell membrane.[18,25] Perisbivalvin had a molecular weight of 272.26 Da, and mefenamic acid had a molecular weight of 335.87 Da. Perisbivalvin potentially has good penetration power compared to the others.

5. Conclusion

This study concluded that perisbivalvin was predicted as new candidate as anti-inflammatory agent which has an affinity againts PTGS2 protein with binding energy of -7.63 kcal/mol. Perisbivalvin has a lower toxicity than the control compound. The molecular weight of perisbivalvin is 272.26 considered having a potential activity to penetrate cell membranes; perisbivalvin, therefore, is predicted to be a candidate of a new compound that has an anti-inflammatory activity. The experimental *in vitro* and *in vivo* studies should be conducted in the future to support these *in silico* studies.

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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	1.89	272.26	1	6
Apioside	-1.48	564.49	8	14
Pelargonidine 3-sambubioside	-0.86	565.50	9	13

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]

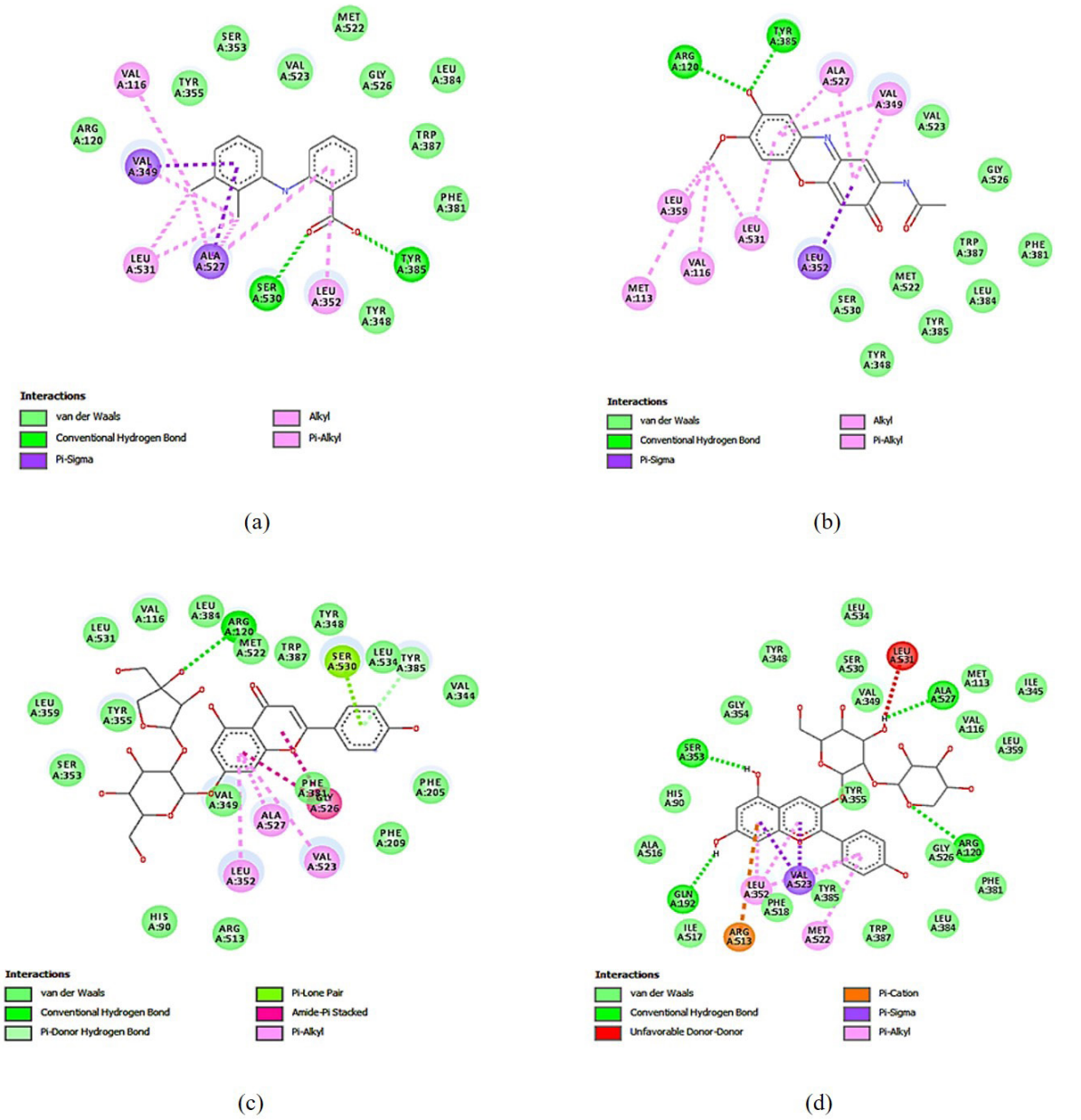

Figure 3. Visualization of (a) Control Compound Interaction with PTGS2, (b) Perisbivalvin with PTGS2, (c) Apioside with PTGS2, and (d) Pelargonidin 3-sambubioside with PTGS

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