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Molecular docking activity of peristrophe bivalvis on non small cell lung cancer

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A B S T R A C T

Cancer is a genetic disease in which cells are unable to control their functions normally. As cancer develops, old cells will survive when they should die, and new cells will grow when they are not needed. These extra cells can divide endlessly and can form growths called tumors . This research was carried out to know whether peristrophine, apioside, and pelargonidin 3-Sambubioside compounds could be developed as a drug in Non-Small Cell Lung Cancer (NSCLC) with the in silico method at the ROS1 receptor with the Protein Data Bank code 3ZBF with the native ligand crizotinib. Peristrophine, apioside, and pelargonidin 3-Sambubioside compounds have an affinity for ROS1 protein with binding energies of -6.12 kcal/mol on peristrophine, -6.74 kcal/mol on apioside, and -7.54 kcal/mol of pelargonidin 3-Sambubioside. Peristrophine, apioside, and pelargonidin 3-Sambubioside have a molecular mechanism in inhibiting ROS1 in Non-Small Cell Lung Cancer (NSCLC) through the formation of hydrogen bonds in the protein ROS1. From Lipinski's analysis, the peristrophine test compound has met the requirements and seen from the LD50 value of the peristrophine test compound, apioside and pelargonidin 3-Sambubioside has the same toxicity class as the comparison compound, namely crizotinib at class 4 toxicity

INTRODUCTION

Lung cancer consists of two types, namely Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC), of all lung cancer cases that occur in Indonesia 20% of the causes are Small Cell Lung Cancer (SCLC) and 80 % occurs due to Non-Small Cell Lung Cancer (NSCLC), NSCLC is all types of lung cancer except SCLC. NSCLC can be caused by air pollution and unhealthy living habits such as tobacco smoking, lung cancer in Indonesia is caused by 63% of men in Indonesia smoking and causing 26,069 deaths in 2018 (Suraya et al 2020).

Cancer is a genetic disease in which cells are unable to control their functions normally. As cancer develops, old cells will survive when they should die, and new cells will grow when they are not needed. These extra cells can divide endlessly and can form growths called tumors (Sebastian et al 2021).

Cancer is a genetic disease in which cells are unable to control their functions normally. As cancer develops, old cells will survive when they should die, and new cells will grow when they are not needed. These extra cells can divide endlessly and can form growths called tumors (National Cancer Institute 2019).

Cell signaling can be affected by ROS1 by joining or fusion with FIG, CD47, or SDC4 so that the signaling process in cell formation will become abnormal in the presence of ROS1 fusion and the resulting cells are abnormal, signaling pathways that are affected in Non-Small Cell Lung Cancer (NSCLC) disease is Phosphatidylinostide-3-Kinase

Mammalian Target Of Rapamycin (PI3K – mTOR) where this pathway affects the growth, development, and survival of cells Husna and Kurniawan 2017, Jyeli et al 2016, Kurtis et al 2013 & Putra 2020. The RAS signaling pathway can also be influenced by ROS1, Mitogen-Activated Protein Kinase (MAPK) which affects the proliferation process and morphogenesis process (Giancotti and Ruoslahti 1999). Kurtis et al 2013). In addition, ROS1 is also known to affect the signaling pathway of transcription (JAK-STAT) where this pathway plays a role in gene transcription (Raychaudhuri and Raychaudhuri 2017). Peristrophine dan pelargonidin 3-sambubioside is an anthocyanin compound found in magenta plants (Peristrophe bivalvis (L.) Merr) (khue et al 2014 & Zafra-Stone et al. 2007).

Anthocyanins present in a variety of fruits and vegetables provide natural pigmentation and exhibit a variety of antioxidant protection and therapeutic benefits including genomic DNA integrity, strong cardioprotective properties, neuroprotection, anti-inflammatory, and anticarcinogenic properties. In addition to giving color to food, anthocyanins can prevent lipid auto oxidation and lipid peroxidation in biological systems. Apioside in magenta plant (Peristrophe bivalvis (L.) Merr) belongs to the flavonoid group that can be used as therapy in the treatment of dry cough (antitussive), anti-inflammatory in the lungs, and antioxidant. (Guan et al 2012) .

Flavonoids that function as antioxidants are found in the ethanol extract of magenta leaves. Flavonoids are a class of phenolic compounds that can be found in many plants. Flavonoids are composed of 15 carbon atoms as the basic nucleus. Flavonoids are composed of a C6 - C3 - C6 configuration, namely 2 aromatic rings connected by three carbon atoms (Parwata, Ratnayani, Listya 2015).

Treatment of Non-Small Cell Lung Cancer (NSCLC) has been successfully carried out using crizotinib with ALK, ROS1, and MET receptors targeting. The Comprehensive Cancer Network (NCCN) recommends that crizotinib be used for patients with known ROS1 fusion (Guo et al. 2019). The mechanism of action of Crizotinib is by inhibition of ALK (anaplastic lymphoma kinase). ALK can activate various signaling athways involved in cell proliferation and survival processes, including the PI3K pathway, RAS/MEK pathway, and JAK/STAT pathway. ALK inhibitors also have a similar mechanism of action by binding to ATP-binding and blocking ALK activation (Kurtis et al 2013, Pathak et al 2016 & Seebacher et al 2019).

Molecular docking is a process of interaction of two molecules in silico. In silico testing, the receptor acts as a macromolecule and the test substance acts as a ligand or macromolecule that can act as an inhibitor. So, in the docking process, there are four steps. namely as follows (Chaudhary and Mishra 2016).

The term free radical refers to any molecular species that have one or more unpaired electrons. Free radicals including reactive oxygen (ROS; eg, superoxide (O2-), hydroxyl (OH–), hydroperoxyl (HOO–), peroxyl (ROO–), and alkoxyl (RO–) nitrogen species radicals (RNS) can react with DNA, RNA, protein, and lipids, leading to cellular toxicity. In particular, ROS production can be endogenous [24]. ROS1 is known to affect signaling pathways molecular pathway Janus Kinase Signal Transducers and activators of transcription (JAK-STAT) where this pathway plays a role in transcription [Kurtis et al 2013 & Raychaudhuri, S.K. and Raychaudhuri 2017).

This research was carried out to know whether peristrophine, apioside, and pelargonidin 3-Sambubioside compounds could be developed as a drug in Non-Small Cell Lung Cancer (NSCLC) with the in silico method at the ROS1 receptor with the Protein Data Bank code 3ZBF with the native ligand crizotinib.

This research was carried out based on the results of previous studies showing that Peristrophe bivalvis (L.) Merr etanol extract has strong antioxidant activity with an IC50 value of 15.675 ppm (Adrianta 2020).

METHODS

Research Material

In this study, macromolecular data used as receptors are needed which are obtained from the Protein Data Bank (PDB) website which can be accessed via the link (https://www.rcsb.org/structure/3ZBF) using the PDB code 3ZBF, with native ligands. Crizotinib. The test compounds, namely apioside and pelargonidin 3-Sambubioside, the structure was obtained at the link (https://pubchem.ncbi.nlm.nih.gov/compound/11626560) and the peristrophin compound in two-dimensional form was drawn on the Chemdraw Ultra 12.0 application which then the two-dimensional structure- it was converted into three dimensions using the chem 3D pro 12.0.2.

Tools

A set of Asus Vivobook S14 A411UF laptops with 8GB RAM specifications and 1 TeraByte ROM and an 8th Gen Intel Core i5 processor. Molecular docking program. In this study, the Autodock tools-1.5.6 program was used. The program used to reduce the total energy of the test compound so that the test compound is more stable is the chem 3D pro 12.0.2 program. To find out the amino acid binding between the receptor and the ligand, use the protein plus website which can be accessed via the link (https://proteins.plus/).

Research Method

Optimization of the 3-Dimensional Structure of Peristrophine, Apioside and Pelargonidin 3-Sambubiosde Compounds

Optimization of the 3-dimensional structure was carried out so that the test compound was more stable by using the chem 3D pro 12.0.2 program.

ROS1 Protein Preparation

Protein preparation was carried out using the Autodock tools-1.5.6 program by separating the 3-dimensional structure of the ROS1 protein from its native ligand.

Molecular Docking Method Validation

The validation of the molecular docking method was carried out using the Autodock Tools 1.5.6 application by redocking the native ligand on the ROS1 protein that had its native ligand removed. The method validation parameter is Root Mean Square Deviation (RMSD). Acceptable RMSD is 3.0 (Rastini *et al* 2013 & Siswandono 2016).

Peristrophine, Apioside and Pelargonidin 3-Sambubioside Docking on ROS1 Protein

Peristrophine, apioside, and pelargonidin 3-Sambubioside compounds that have been optimized were

docked to the ROS1 protein with the PDB code 3ZBF which had its native ligand removed using the Autodock Tools application with the same docking procedure as during method validation. The results of the analysis showed the conformation of the compound bond in the protein with the value of the bond energy.

Binding of Amino Acids to ROS1 Receptors with Peristrophine, Apioside, and Pelargonidin 3-Sambubioside

To determine the amino acid binding between amino acids at the ROS1 receptor and peristrophine, apioside, and pelargonidin 3-sambubioside compounds, this was done by entering the docking results between the receptor and peristrophin, apioside or pelargonidin 3-sambubioside compounds in PDB format. On the Protein Plus website, you can see the types of bonds and bonds between amino acids at the ROS1 receptor and peristrophin compounds, apioside or pelargonidin 3-sambubioside.

Toxicity Prediction

To determine the Lethal Dose 50 (LD_{50}) value of the test compound and the comparison compound, a test was conducted using Predicting Small-Molecule Pharmacokinetic and Toxicity Properties using Graph-Based Signatures (pKCSM) which is accessed online through the website (*http://structure.bioc.cam.ac.uk/pkcsm*).

Lipinski Analysis

Lipinski's rule can determine the physicochemical properties of ligands to determine the hydrophobic/hydrophilic character of a compound to pass through cell membranes by passive diffusion and relate to the toxicity of a drug.

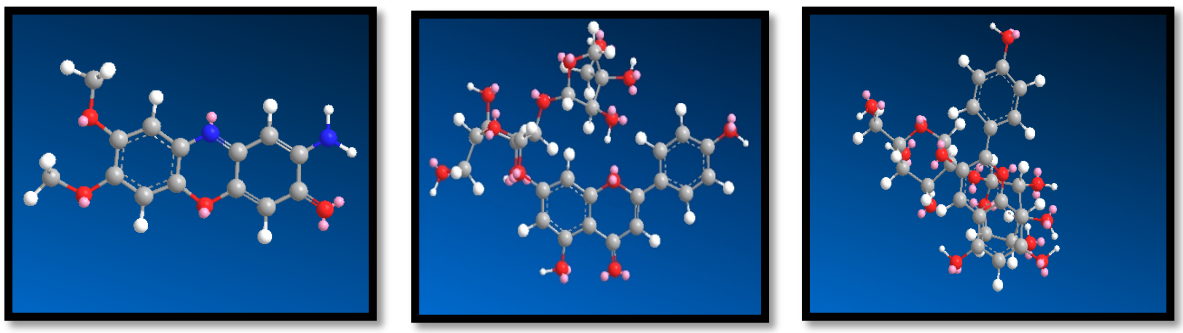
Data analysis

The results of molecular docking can be seen by looking at the bond energy and hydrogen bonds formed. Bond energy is used to indicate the strength of the bonds between compounds and proteins. The lower the bond energy value, the stronger and more stable the bonds are. The type of hydrogen bond formed is used to analyze the interaction mechanism formed. Is it the same as native ligand or comparison compound.

RESULTS AND DISCUSSION

Optimization of the 3-Dimensional Structure of Peristrophine, Apioside and Pelargonidin 3-Sambubioside Compounds

The 3-dimensional structure of the downloaded quercetin compound was optimized using the chem 3D pro 12.0.2 program with the optimization step, namely pressing the calculation option then selecting the MM2 menu and selecting the minimize energy menu and clicking run to get the structure of the compound peristrophin, apioside and Pelargonidin 3-Sambubioside which most stable. The success of compound optimization is indicated by the total energy of the optimization results being smaller than the previous energy. The test results can be seen in figure 1.

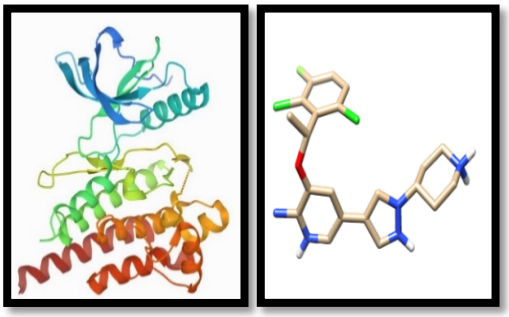


a) b) c)

Figure 1. Results of Compound 3-Dimensional Structure Optimization a). Peristrophin, b). Apioside and c). Pelargonidine 3 Sambubioside

ROS1 Protein Preparation

The ROS1 protein was prepared by separating the protein from its native ligand using the autodock tools 1.5.6 program to obtain a protein structure without native ligand in Figure 1 and a separate native ligand structure as shown in Figure 2. The separation of protein with native ligand aims to provide a pocket for the compound. assay for binding to ROS1 protein. The protein chain selected in this test is the A chain that binds to the native ligand 3-[(1R)-1-(2,6-dichloro-3-fluorophenyl) ethoxy]-5-(1-piperidine-4-yl-1H -pyrazol-4-yl) pyridine-2-amine C21 H22 Cl2 F N5 O.



a). b).

Figure 2. a). 3 Dimensional Structure of ROS1 Protein Without Ligand and b). Native Ligand Protein ROS1

Molecular Docking Method Validation

The validation of the molecular docking method was carried out using the Autodock tools 1.5.6 application by redocking the native ligand-protein ROS1, namely crizotinib with prepared ROS1 protein.

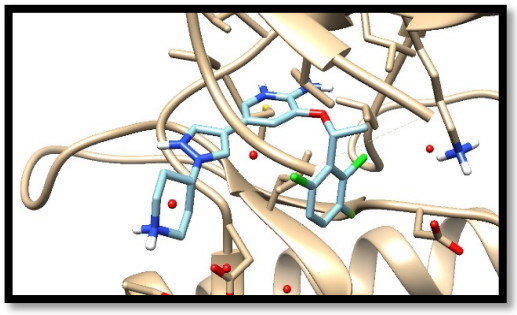


Figure 3. Visualization of the interaction of ROS1 protein with native ligands with an RMSD value of 1.34 A.

Peristrophine, Apioside and Pelargonidin 3-Sambubioside Docking on ROS1 Protein

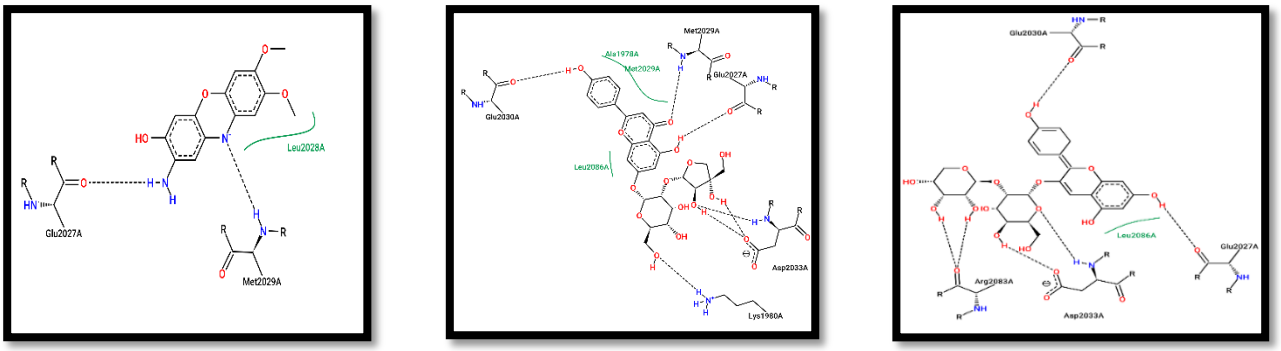
The docking of peristrophine, apioside, and pelargonidin 3-sambubioside compounds that have been optimized on the ROS1 protein was carried out using the Autodock tools 1.5.6 application with the same procedures and coordinates as in the validated method validation. The results of docking peristrophine, apioside, and pelargonidin 3-sambubioside on ROS1 protein, obtained 100 bond conformations between peristrophine, apioside, and pelargonidin 3-sambubioside with ROS1 protein, which is then selected one conformation with the lowest binding energy value that shows the most stable bond.

Binding of Amino Acids to ROS1 Receptors with Peristrophine, Apioside, and Pelargonidin 3-Sambubioside

Amino acid bonds between Peristrophine Compounds, Apioside, Pelargonidin 3-Sambubioside, and Native Ligands on the receptor can be seen by entering the docking results into the protein plus web and it can be seen which types of bonds and amino acids have bonds with the ligand. It can be seen in table 1 and figure 4.

Table 1. Results of Docking and Bonding with Amino Acids on Peristrophin Compounds, Apioside, Pelargonidin 3-Sambubioside and Native Ligands on ROS1 Protein

No	Compound	Docking Score *(kcal/mol)*	Hydrogen Bond
1	Native Ligan	-8,28	Met2029A dan Glu2027A
2	Peristrophine	-6,12	Glu2027A dan Met2029A
3	Apioside	-6,74	Asp2033A, Glu2027A, Met2029A, Glu2030A dan Lys1980A
4	Pelargonidin 3-sambubioside	-7,54	Glu2027A, Asp2033A, Arg2083A dan Glu2030A



a). b). c).

Figure 4. Interaction Visualization of Docking Results from a). Peristrophin, b). Apioside and c). Pelargonidine 3-Sambubioside on ROS1 Receptor Protein.

Toxicity Predictions

Toxicity parameters LD_{50} of Peristrophine, Apioside, Pelargonidin 3-Sambubioside, and the comparison compound crizotinib were obtained from the Predicting Small-Molecule Pharmacokinetic and Toxicity Properties program using Graph-Based Signatures (pKCSM). The results of determining the toxicity parameters of peristrophin, apioside, and pelargonidin 3-sambubioside compounds and the comparison compound crizotinib can be seen in the table 2.

Lipinski Analysis

Lipinski's rule can determine the physicochemical properties of ligands to determine the hydrophobic/hydrophilic character of a compound to pass through cell membranes by passive diffusion and relate to the toxicity of a drug. The results of Lipinski's five analyses can be seen in table 3.

Table 2. Toxicity Parameters of Peristrophine, Apioside, and Pelargonidin 3-Sambubioside Compounds and Comparative Compounds, Crizotinib

No	Compound	Toxicity Parameters LD_{50} (mg/kg)	Toxicity Class
1	Peristrophine	650,974	4
2	Apioside	1.628,571	4
3	Pelargonidin 3-sambubioside	1.616,776	4
4	Crizotinib	1.442,455	4

Description : LD_{50} (Lethal Dose 50)
Class 1 : Fatal if swallowed (LD_{50} 5)
Class 2 : Fatal if swallowed (5 < LD_{50} 50)
Class 3 : Toxic if swallowed (50 < LD_{50} 300)
Class 4 : Harmful if swallowed (300 < $LD_{50} \leq$ 2000)
Class 5 : May be harmful if swallowed (2000 < $LD_{50} \leq$ 5000)
Class 6 : Non-toxic (LD_{50} > 5000) (Putra 2020).

Table 3. Analysis of Lipinski's Five Laws for Peristrophine, Apioside, and Pelargonidin 3-Sambubioside Compounds and Comparative Compounds, Crizotinib

No	Compound	Log P	MW	Donor H Bond	H-binding acceptor
		<5	<500	<5	<10
1.	Peristrophine	1,8922	272,26	1	6
2.	Apioside	-1,4852	564,496	8	14
3.	Pelargonidin 3-sambubioside	-0,8603	565,504	9	13
4.	Crizotinib	5,0377	450,345	2	6

Descriptions :
Log P : logarithm Partition coefficient less than 5
MW : molecular weight less than 500
Donor H bonds : expressed by the number of O-H and N-H groups less than 5
H-binding acceptor : expressed by the number of O and N atoms less than 10 (Putra 2020 & Syahputra 2014).

DISCUSSION

From the results of the optimization of the three-dimensional structure, the initial total energy is reduced to obtain a more stable three-dimensional structure, Peristrophine shows the total energy before being reduced is 63.2662 kcal/mol and after being reduced to 26,3106 kcal/mol, in the apioside compound the total energy before being reduced is 501.5565 kcal. /mol and after being reduced to 65.0657 kcal/mol and the pelargonidin 3-Sambubioside compound before being reduced was 13629.7387 kcal/mol and after being reduced to 31.0462 kcal/mol after optimization using the chem3D Pro 12.0.2 application.

The method validation parameter is the RMSD value. This RMSD value is the distance between the receptor and the native ligand. The RMSD value obtained in this study was 1.34 A, which means that the molecular docking method used has been validated where the RMSD value is not more than 3A (Rastini et al 2013 & Siswandono 2016). visualization of interactions on the validation of the molecular docking method can be seen in Figure 3.

The results of docking between peristrophine, apioside, pelargonidin 3-sambubioside, and native ligand compounds with ROS1 protein showed that the binding energy was negative. In ROS1 protein, Peristrophine, apioside, and pelargonidin 3-sambubioside compounds have lower binding energies than native ligands. This shows that peristrophin, apioside, and pelargonidin 3-sambubioside compounds have binding affinities not as good as native ligands in binding to the active site of ROS1. The results of this study regarding the binding energy values of native ligands, peristrophin compounds, apioside, and pelargonidin 3-sambubioside on the target protein ROS1 and binding with amino acids can be seen in table 4.

The results of checking the bonds with amino acids show that there are hydrogen bonds in the amino acids Glu2027A, Asp2033A, Arg2083A, and Glu2030A which have similarities with native ligands wherein the native ligands there are hydrogen bonds in Met2029A and Glu2027A so that they may have activities similar to native ligands as drugs. in Non-Small Cell Lung Cancer (NSCLC) because of the similarity of bonds with the amino acid Glu2027A.

The results of the study which can be seen in Table 2 show that peristrophine, apioside, and pelargonidin 3-sambubioside compounds have an LD_{50} value, the highest is apioside 1,628,571 mg/kg, the lowest LD_{50} value is peristrophin compound with a value of 650,974 mg/kg. which shows that all the test and comparison compounds are classified as toxic class 4 which means they are dangerous if swallowed. While the comparison compound has an LD_{50} value of 1,442,455 mg/kg and is included in the class 4 toxicity which means it is dangerous if swallowed. So the test compounds apioside and pelargonidine 3-sambubioside are predicted to have safer toxicity compared to the comparison compound, namely crizotinib.

From the results that can be seen in Table 3, the molecular weight of more than 500 Da cannot diffuse through the cell membrane. The greater the log P-value, the more hydrophobic the molecule. Molecules that are too hydrophobic tend to have a high level of toxicity because they will be retained longer in the lipid bilayer and distributed more widely in the body so that the selectivity of binding to the target enzyme is reduced. A log P-value that is too negative is also not good because the molecule cannot pass through the lipid bilayer membrane. The number of

hydrogen bond donors and acceptors describes the higher the hydrogen bonding capacity, the higher the energy required for the absorption process to occur. In general, Lipinski's rule describes the solubility of certain compounds to penetrate cell membranes by passive diffusion (Syahputra 2014).

Peristrophine compounds meet Lipinski's five law requirements, Peristrophine compounds can be estimated to have good ability to penetrate biological membranes and are easy to absorb with a log P value of not more than 5 so that they easily penetrate lipid bilayer membranes and are not too hydrophobic because the molecules involved that are too hydrophobic tend to have a high level of toxicity because they will be retained longer in the lipid bilayer and distributed more widely in the body so that the selectivity of binding to the target enzyme is reduced. While the apioside compound has a mines log P value so that because the molecule cannot pass through the lipid bilayer membrane. The crizotinib compound has a log P value greater than 5 so that it easily penetrates the lipid bilayer membrane and is not too hydrophobic because molecules that are too hydrophobic tend to have a high level of toxicity because they will be retained longer in the lipid bilayer and distributed more widely in the body. so that the selectivity of binding to the target enzyme is reduced. The LD_{50} value obtained by crizotinib is better than that of peristrophine the molecular weight of crizotinib is greater than that of peristrophine so that the affinity of crizotinib compounds is lower and the LD_{50} value is better. The best LD_{50} value for apioside compounds is due to the negative log P value where the apioside compound is unable to penetrate the lipid bilayer membrane.

CONCLUSIONS AND SUGGESTIONS

Peristrophine, apioside, and pelargonidin 3-Sambubioside compounds have an affinity for ROS1 protein with binding energies of -6.12 kcal/mol on peristrophine, -6.74 kcal/mol on apioside, and -7.54 kcal/mol of pelargonidin 3-Sambubioside. peristrophine, apioside, and pelargonidin 3-Sambubioside have a molecular mechanism in inhibiting ROS1 in Non-Small Cell Lung Cancer (NSCLC) through the formation of hydrogen bonds in the protein ROS1. From Lipinski's analysis, the peristrophine test compound has met the requirements and seen from the LD50 value of the peristrophine test compound, apioside and pelargonidin 3-Sambubioside has the same toxicity class as the comparison compound, namely crizotinib at class 4 toxicity.

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