Original Research Article

Docking Simulation Analysis of Natural Ingredients As Anti Virus SARS-Cov-2 on Helicase Inhibitors

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ABSTRACT

Aims: To find active compounds from natural ingredients that have the potential to be antivirals of SARS-CoV-2.
Study design: Simulation research
Place and Duration of Study: Physics Laboratory, Department of Physics Education, Universitas Kristen Indonesia, between December 2021 and August 2022.
Methodology: The method used is a computational simulation commonly known as docking simulation or molecular docking. There are several steps taken, namely ligand and receptor preparation, docking simulation and analysis of simulation results.
Results: The results obtained were from 22 ligand compounds of natural material selected as helicase receptor inhibitors, 14 ligand compounds were found that met the requirements according to Lipinski's five rules, namely Emodin, Luteolin, Curcumin, Kaemferol, Quercetin, Myricetin, Scutellarein, 10-Gingerol, Shogaol, Mangostin, Piseatanol, Diallyl disulfide, Cyperotundone and Eugenol. Of the 14 ligand compounds simulated with helicase receptors, it turned out that 14 stable ligand compounds were used as helicase receptor inhibitors. However, among the 14 ligands, myricetin is the most stable ligand with the smallest Gibbs free energy value, which is -8.7 kcal/mol.
Conclusion: An active ingredient compound has been found that has the potential as an antivirus sars-COV-2 in the Helicase receptor, Myricetin from clove plants (S*yzygium aromaticum*). These results can be used as a basis for drug development for the development of SARS-COV-2 antivirus in the future.

Keywords: [SARS-CoV-2, docking, ligand, gibbs free energy, drug]

1. INTRODUCTION

SARS-CoV-2 is a virus that has an envelope. So this virus belongs to the Coronaviridae family. The sheath structure of the SARS-CoV-2 virus is very important in its survival [1]. The life cycle of the SARS-CoV-2 virus begins with the spike protein (S protein) binding to the Angiotensin Converting Enzyme 2 (ACE2) receptor on the host cell, in this case human cells. After that, the virus will enter the host cell facilitated by the transmembrane protein TMPRSS2 to release its genetic material [2]. Then when the virus has been attached to the surface of the host cell, then the virus will enter the host cell. After that, the virus will secrete its genetic material. In the host cell of the virus will multiply genetic material which will then

form a new virion. One of the proteins involved in this step is a helicase inhibitor [3]. Furthermore, if the shape of the virus is perfect, it will be released out of the cell through the process of ecocytosis.

SARS-CoV-2 infection in humans, as well as the replication cycle of this virus in human cells, is highly dependent on various proteases. Therefore, understanding the relevant protease functions is critical to identify and develop antiviral drugs that can effectively prevent or treat COVID-19. The diverse proteases involved in SARS-CoV-2 infection not only present significant challenges but also provide abundant potential opportunities to target proteases as an antiviral strategy. By inhibiting the presence of protease proteins that play a role in the viral replication cycle in the host cell, the SARS-CoV-2 virus will die and will not be able to infect its host again.

The SARS-CoV-2 virus that infects humans will cause diseases such as bronchitis, gastroenteritis, hepatitis, systemic diseases, and can cause death. Based on the genomic analysis of the COVID-19 virus, it was found that the SARS-CoV-2 virus was very similar to the SARS-CoV virus and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [4]. Various ways are being done to overcome the COVID-19 pandemic. One of them is by utilizing antivirals sourced from natural ingredients. There are many chemicals that have active compounds that could be considered as sources of development of sars-CoV-2 antiviral drugs.

In several countries, one of which is China, has proposed the use of traditional herbal medicine recipes to treat patients who are positive for SARS-CoV-2. Some studies have also shown that a number of herbal remedies have activity as potential antivirals. However, there are not many studies reported on the activity of herbal medicines as antivirals. So that in this study, the activity of active compounds from natural ingredients that have potential as antiviral will be analyzed. The active compound used in the study is an active compound from the results of previous studies that have been reported can inhibit the SARS-COV and MERS-COV viruses. This is because genetically SARS-CoV-2 is almost the same as SARS-CoV and MERS-CoV. So it is hoped that the active compound will also be able to inhibit the SARS-CoV-2 virus.

The traditional synthesis of new compounds using conventional methods is time consuming and expensive. On the other hand, in silico screening provides a new alternative. In silico screening is much more effective than in vitro or in vivo screening. In silico screening in relation to disease was carried out to find potential inhibitors [5]. The advantage of in silico screening is its ability to distinguish active and inactive compounds so that this can save time and other resources [6]. In silico screening involves a large amount of molecular data, and ranks them from best to worst, some of which cannot even bind to the receptor and so cannot be included in further experiments [7].

In silico screening techniques can be classified based on special modeling of molecular recognition and the types of algorithms used in database searches. If the three-dimensional structure of the target is known (or at least the active side of the target is known), then structure-based in silico screening can be carried out. This method is based on the principle of complementarity, that is, the receptors of biologically active compounds complement the compounds themselves like a padlock and lock model. Conversely, if ligands are known in structure and activity, then ligand-based in silico screening can be carried out with the principle of similarity, where similar compounds are assumed to have similar effects [8].

Structure-based in silico screening is a useful means of identifying the guide compound once the three-dimensional structure of the target has been determined [9]. This is useful for

narrowing chemical libraries that need to be investigated so that the focus of the researchers can be directed to the compounds results of the silico screening. Therefore, there is no doubt that this method will be very useful in the new drug discovery process in the future. Some of the programs used for in silico screening include DOCK, FlexX, GOLD, ICM, GLIDE, SLIDE, LigandFit, FRED, and Surflex [10].

In practice, in silico screening involves molecular docking methods, so this method was also developed. The target to be achieved from the screening of in silico is the determination of ligands that have the best prospects to be used as new drugs so that the highlighted thing is the affinity of ligand bonds with receptors. So the purpose of this study is to conduct a simulated analysis of docking active compounds from natural ingredients that have the potential to be anti-virus SARS-Cov-2 in Helicase Inhibitors.

2. MATERIAL AND METHODS

2.1 Hardware, Software and Materials

The hardware used in the study was a desktop computer with the Lenovo Ideapad Flex 5 14ARE05 Laptop brand equipped with an AMD Ryzen 5 4500U Processor with Radeon Graphics 2.38 GHz, 8.00 GB RAM (7.37 GB usable), System type 64-bit operating system, x64-based processor. This research is a computational research that uses software for simulation. The software used for simulation is Autodock vina 1.1.2. For material preparation and analysis of simulation results, VMD (Visual Molecular Dynamics Program) software version 1.9.1, Autodock tools, and Pymol are used. For minimization using Avogadro 1.91 software.

This study used material in the form of data downloaded from the Protein Data Bank website. This data is experimental data from X-Ray Diffraction which contains coordinate data of the three-dimensional structure of the SARS-CoV-2 receptor. The SARS-CoV-2 receptor data used is Helicase [3]. In this study, Ligands were used in the form of active compounds from natural ingredients that have the ability to inhibit the bonds between receptors that support the survival of the SARS-CoV-2 virus. The ligand was downloaded from the PubChem website which contains the three-dimensional structure of the active compound of natural ingredients.

Table 1. Ligand Compounds from the Indonesian Medicinal Plant Database derived from natural ingredients that have activity against SARS-CoV-2

No.	Compound	Source	Reference
1	Emodin	Rhinoceros ketepeng ***(****Cassia alata****)***	[11]
2	Luteolin	Celery ***(****Apium graveolens****)***	[12]
3	Theaflavin 3,3-digallate	Black tea ***(****Camellia sinensis****)***	[13]
4	Curcumin	Turmeric ***(****Curcuma sp.****)***	[14]
5	Kaemferol	Guava ***(****Psidium guajava****)***	[14]
6	Quercetin	Orange ***(****Citrus aurantium****)***	[15]
7	Myricetin	Clove ***(****Syzygium aromaticum****)***	[16]
8	Scutellarein	Sapu manis ***(****Scoparia dulcis****)***	[16]
9	10-Gingerol	Ginger ***(****Zingiber officinalis****)***	[17]
10	Shogaol	Ginger ***(****Zingiber officinalis****)***	[17]
11	Mangostin	Mangosteen ***(****Garcinia mangostana****)***	[18]
12	Piseatanol	Wine ***(****Vitis vinifera****)***	[18]
13	Diallyl disulfide	Garlic ***(****Allium cepa****)***	[18]

14	Andrographiside	Sambiloto ***(****Andrographis paniculata****)***	[18]
15	Biorobin	Banyan ***(****Ficus benjamina****)***	[18]
16	Neohesperidin	Orange ***(****Citrus aurantium****)***	[18]
17	(-)-Epigallocatechin Gallate	Black tea ***(****Camelia sinensis****)***	[18]
18	Cyperotundone	Teki grass ***(****Cyperus rotundus****)***	[18]
19	Theaflavin-3-O-Gallate	Black tea ***(***Camelia sinensis***)***	[18]
20	Phyllanemblinins B	Malacca fruit ***(****Phyllanthus emblica****)***	[18]
21	Quercitrin	Meniran (*Phyllantus niruri* L.)	[19]
22	Eugenol	Salam (*Syzygium polyanthum*)	[20]

2.2 Procedure

2.2.1 Availability of Receptors and Ligands

The receptors and ligands used were first downloaded on the website. For receptor compounds used Helicase can be downloaded from the Protein Data Bank (PDB) [21]. The same was also done on the ligand compounds used in the study. There are 22 natural ligand compounds available for download from the PubChem Database [22].

2.2.2 Receptor and Ligand Preparation

After obtaining the receptors that will be used in the study, the SARS-CoV-2 virus receptors are first prepared with the desired conditions. At this stage the receptor to be used is cleaned of O_2 content or solvents that are usually bound in the receptor crystal structure. Then the file will be minimized and the format will be changed to .pdbqt. This preparation process is carried out using Pymol software.

The same applies to the ligands to be used.The 22 ligand compounds from natural ingredients were first cleaned and prepared according to the required conditions. Generally, the downloaded ligands have a .sdf data format, even though what is needed is a ligand in the same .pdb data format as the receptor data format. So that the ligand data format is converted using Pymol software into .pdb. Furthermore, the ligands will be minimized until the best and most stable energy and pose are found. The file format that the Autodock Vina docking simulation software can recognize is in the .pdbqt extension. So that the receptor and ligand files which originally had a .pdb extension were changed to .pdbqt. Then so that the simulation conditions match the conditions in the real environment, the receptor and ligand are placed in a box surrounded by water. The parameters to determine the size of the grid (grid box) are adjusted to the size of the receptor or commonly known as blind docking. This is done in order to optimize the simulation time to be carried out. The following are grid box determination parameters for receptors and ligands.

out = out.pdbqt
center_x = -15.535
center_y = 22.715
center_z = -48.965
size_x = 80
size_y = 106
size_z = 120

2.2.3 Docking Simulation

The software used in the docking simulation process is Autodock Vina. Some of the files needed as input in the docking simulation process are receptor files and ligand files that have been prepared in advance. Furthermore, it takes another file, namely the config file. which includes a pre-defined grid box size. Autodock vina software is run in the Command Prompt window using certain commands. The length of time required in the docking simulation process depends on the parameters that have been determined in the config file. After completing the docking simulation, the results of the docking mode (binding mode) between the receptor and the ligand may be obtained with the amount of energy released (affinity value). The docking simulation process will be repeated 5 times so that the trend and consistency of the results can be seen. After completion, the results that are the output of the Autodock Vina software will then be analyzed.

2.3.4 Simulation Data Analysis

The results of the docking simulation are then analyzed using Pymol and VMD software. Several parameters that can be analyzed using both software are energy (Affinity Value) and the resulting ligand-receptor binding mode.

3. RESULTS AND DISCUSSION

3.1 Identify Receptors And Ligands

The docking simulation process begins with preparing the receptor to be used. At the stage of preparing the receptor, the macromolecular structure used was downloaded from the Protein Data Bank (PDB) with the website address [23]. In this study, the SARS-CoV-2 receptor used was Helicase. The PDB code for the receptor is 6ZSL.

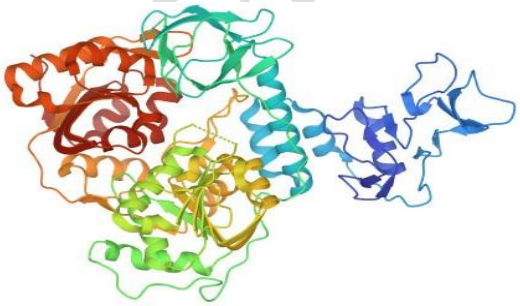


Fig. 1 Helicase Receptor Structure with PDB code 6ZSL

In determining the receptor used, there are 2 receptor selection requirements, namely resolution ≤ 2 and the Ramachandran plot ≥ 90% of amino acid residues are in the most favored regions. The Helicase Receptor with PDB code 6ZSL has a resolution of 1.94 and in the Ramachandran plot 90% of the amino acid residues are in the most favored regions, thus qualifying to be selected as SARS-CoV-2 receptors. The helicase receptor with the PDB code 6ZSL has 2 chains, namely A and B with a Sequence Length of 603. However, it turns out that the helicase receptor coded for PDB 6ZSL is an incomplete PDB file because there are 27 missing atoms (Tabel 2). To fix this atomic loss (missing atom) then repairs are carried out using Pymol software. The purpose of this fix is to restore the receptor file to be intact so that it is valid when simulated.

Table 2. Missing Atom the SARS-COV-2 receptor

No.	Receptor	PDB code	Missing Atom
1.	Helikase	6ZSL	LYS B 28 : CG CD CE NZ

	LYS B 94 : CG CD CE NZ ASP B 101 : CG OD1 OD2 ASN B 102 : CG OD1 ND2 ARG B 161 : CG CD NE CZ NH1 NH2 ARG B 178 : CG CD NE CZ NH1 NH2 ARG B 186 : CG CD NE CZ NH1 NH2 LYS B 189 : CG CD CE NZ ARG B 212 : CG CD NE CZ NH1 NH2 THR B 214 : OG1 CG2 LYS B 218 : CG CD CE NZ ARG B 392 : CG CD NE CZ NH1 NH2 LYS B 524 : CG CD CE NZ GLU B 591 : CG CD OE1 OE2 LYS A 28 : CG CD CE NZ MET A 68 : CG SD CE LYS A 73 : CG CD CE NZ LYS A 94 : CG CD CE NZ ARG A 155 : CG CD NE CZ NH1 NH2 ARG A 178 : CG CD NE CZ NH1 NH2 LYS A 202 : CG CD CE NZ ARG A 212 : CG CD NE CZ NH1 NH2 LYS A 218 : CG CD CE NZ LEU A 219 : CG CD1 CD2 THR A 228 : OG1 CG2 ARG A 248 : CG CD NE CZ NH1 NH2 LYS A 347 : CG CD CE NZ

3.2 Ligand Identification

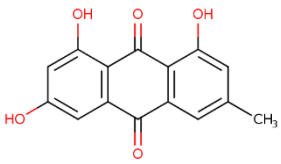
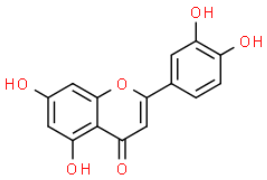
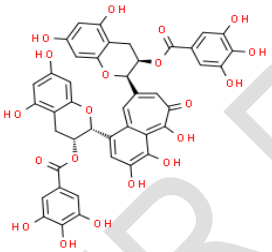
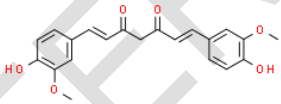
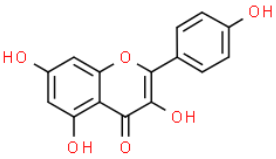
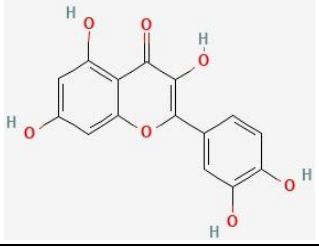
The 3D structure ofthe ligand life to be used in the simulation is first downloaded from the PubChem Database [22]. There are 22 ligand compounds from natural ingredients. Of the 22 ligand compounds that have been downloaded, they will be tested using Lipinski's Rule of Five. The physicochemical characteristics possessed by drugs are required to comply with "The Rule of Five". A compound can be considered bioavailable or usable if:

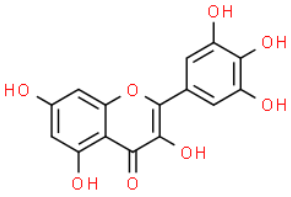
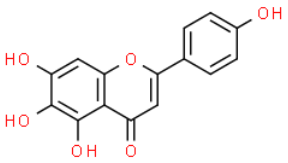
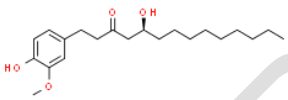
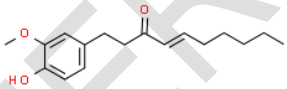
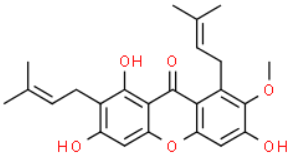
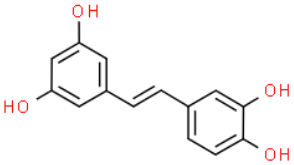
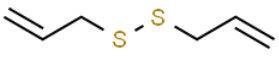
1. Molecular weight less than 500 g/mol (<500 g/mol),
2. Hydrogen Bond Donor Count less than 5 (<5)
3. Hydrogen Bond Acceptor Count less than 10 (<10)
4. Have log $P_{o/w}$ (MLOGP) lipophility of less than 4.15 (<4.15) [24]

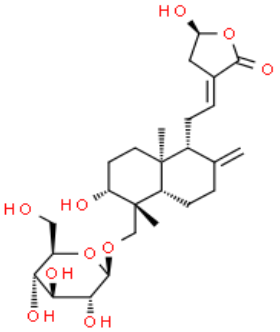
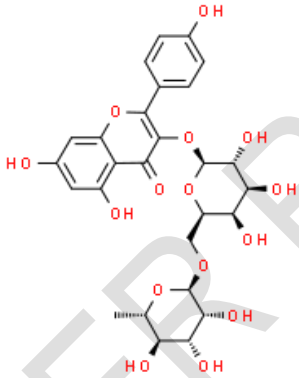
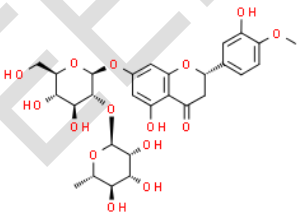
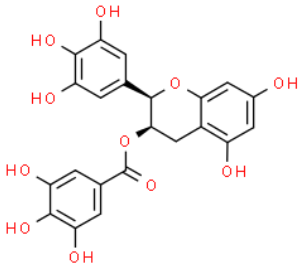
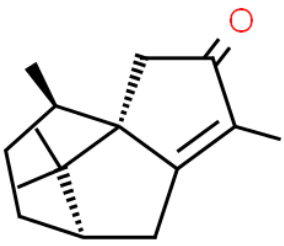
For compounds that can be used as ligands are those that meet the 3-4 conditions of Lipinski's Rule of Five. The ligand test with Lipinski's Rule of Five was carried out using one of the online-based computer program applications that can be accessed by the public, namely Swiss ADME. Swiss ADME can be used by accessing the website [25]. From table 3, it can be observed that of the 22 ligands analyzed, it turns out that there are 14 ligands that fulfill Lipinski's five laws and 8 that do not, so that only 14 ligands will proceed to the docking simulation stage, namely Emodin, Luteolin, Curcumin, Kaemferol, Quersetin, Myricetin, Scutellarein, 10-Gingerol, Shogaol, Mangostin, Piseatanol, Diallyl disulfide, Cyperotundone and Eugenol.

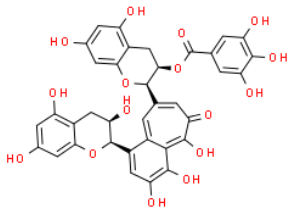
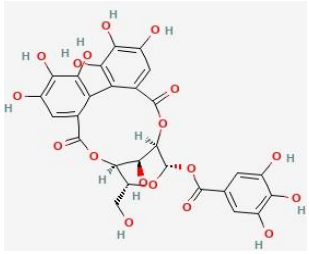
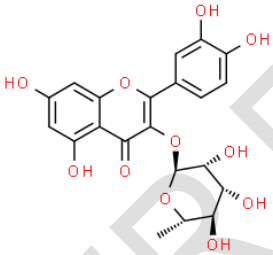
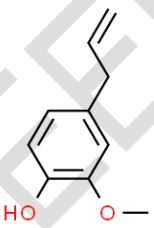
Table 3. Ligand compounds derived from natural materials that have activity against SARS-CoV-2

No.	Compound (PubChem CID)	Molecular Formula	Structure	Lipinski's Rule of Five (RO5)

1.	Emodin (3220)	$C_{15}H_{10}O_5$		Molecular Weight : 270.24 g/mol Hydrogen Bond Donor Count : 3 Hydrogen Bond Acceptor Count :5 Log $P_{o/w}$ (MLOGP): 0.36 Meets RO5 criteria : **YES**
2.	Luteolin (5280445)	$C_{15}H_{10}O_6$		Molecular Weight : 286.24 g/mol Hydrogen Bond Donor Count : 4 Hydrogen Bond Acceptor Count :6 Log $P_{o/w}$ (MLOGP): -0.03 Meets RO5 criteria : **YES**
3.	Theaflavin 3,3-digallate (136277567)	$C_{43}H_{32}O_{20}$		Molecular Weight : 868.7 g/mol Hydrogen Bond Donor Count : 13 Hydrogen Bond Acceptor Count :20 Log $P_{o/w}$ (MLOGP): -1.44 Meets RO5 criteria : **NO**
4.	Curcumin (969516)	$C_{21}H_{20}O_6$		Molecular Weight : 368.4 g/mol Hydrogen Bond Donor Count : 2 Hydrogen Bond Acceptor Count :6 Log $P_{o/w}$ (MLOGP): 1.47 Meets RO5 criteria : **YES**
5.	Kaemferol (5280863)	$C_{15}H_{10}O_6$		Molecular Weight : 286.24 g/mol Hydrogen Bond Donor Count : 4 Hydrogen Bond Acceptor Count :6 Log $P_{o/w}$ (MLOGP): -0.03 Meets RO5 criteria : **YES**
6.	Quercetin (5280343)	$C_{15}H_{10}O_7$		Molecular Weight : 302.23 g/mol Hydrogen Bond Donor Count : 5 Hydrogen Bond Acceptor Count :7 Log $P_{o/w}$ (MLOGP): -0.56 Meets RO5 criteria : **YES**

7.	Myricetin (5281672)	$C_{15}H_{10}O_8$		Molecular Weight : 318.23 g/mol Hydrogen Bond Donor Count : 6 Hydrogen Bond Acceptor Count :8 Log $P_{o/w}$ (MLOGP): -1.08 Meets RO5 criteria : **YES**
8.	Scutellarein (5281697)	$C_{15}H_{10}O_6$		Molecular Weight : 286.24 g/mol Hydrogen Bond Donor Count : 4 Hydrogen Bond Acceptor Count :6 Log $P_{o/w}$ (MLOGP): -0.03 Meets RO5 criteria : **YES**
9.	10-Gingerol (168115)	$C_{21}H_{34}O_4$		Molecular Weight : 350.5 g/mol Hydrogen Bond Donor Count : 2 Hydrogen Bond Acceptor Count : 4 Log $P_{o/w}$ (MLOGP): 3.06 Meets RO5 criteria : **YES**
10.	Shogaol (5281794)	$C_{17}H_{24}O_3$		Molecular Weight : 276.4 g/mol Hydrogen Bond Donor Count : 1 Hydrogen Bond Acceptor Count : 3 Log $P_{o/w}$ (MLOGP): 2.90 Meets RO5 criteria : **YES**
11.	Mangostin (5281650)	$C_{24}H_{26}O_6$		Molecular Weight : 410.46 g/mol Hydrogen Bond Donor Count : 3 Hydrogen Bond Acceptor Count : 6 Log $P_{o/w}$ (MLOGP): 2.19 Meets RO5 criteria : **YES**
12.	Piseatanol (667639)	$C_{14}H_{12}O_4$		Molecular Weight : 244.24 g/mol Hydrogen Bond Donor Count : 4 Hydrogen Bond Acceptor Count : 4 Log $P_{o/w}$ (MLOGP): 1.67 Meets RO5 criteria : **YES**
13.	Diallyl disulfide (16590)	$C_6H_{10}S_2$		Molecular Weight : 146.3 g/mol Hydrogen Bond Donor Count : 0 Hydrogen Bond Acceptor

				Count : 2 Log $P_{o/w}$ (MLOGP): 2.53 Meets RO5 criteria : **YES**
14.	Andrographiside (44593583)	$C_{26}H_{40}O_{10}$		Molecular Weight : 512.6 g/mol Hydrogen Bond Donor Count : 6 Hydrogen Bond Acceptor Count : 10 Log $P_{o/w}$ (MLOGP): -0.29 Meets RO5 criteria : **NO**
15.	Biorobin (15944778)	$C_{27}H_{30}O_{15}$		Molecular Weight : 594.5 g/mol Hydrogen Bond Donor Count : 9 Hydrogen Bond Acceptor Count : 15 Log $P_{o/w}$ (MLOGP): -3.43 Meets RO5 criteria : **NO**
16.	Neohesperidin (442439)	$C_{28}H_{34}O_{15}$		Molecular Weight : 610.6 g/mol Hydrogen Bond Donor Count : 8 Hydrogen Bond Acceptor Count : 15 Log $P_{o/w}$ (MLOGP): -3.04 Meets RO5 criteria : **NO**
17.	(-)-Epigallocatechin Gallate (65064)	$C_{22}H_{18}O_{11}$		Molecular Weight : 458.4 g/mol Hydrogen Bond Donor Count : 8 Hydrogen Bond Acceptor Count : 11 Log $P_{o/w}$ (MLOGP): -0.44 Meets RO5 criteria : **NO**
18.	Cyperotundone (12308615)	$C_{15}H_{22}O$		Molecular Weight : 218.33 g/mol Hydrogen Bond Donor Count : 0 Hydrogen Bond Acceptor Count : 1 Log $P_{o/w}$ (MLOGP): 3.56 Meets RO5 criteria : **YES**

19.	Theaflavin-3-O-Gallate (135458101)	$C_{36}H_{28}O_{16}$		Molecular Weight : 716.6 g/mol Hydrogen Bond Donor Count : 11 Hydrogen Bond Acceptor Count : 16 Log $P_{o/w}$ (MLOGP): -1.11 Meets RO5 criteria : **NO**
20.	Phyllanemblinins B (10941235)	$C_{27}H_{22}O_{18}$		Molecular Weight : 634.5g/mol Hydrogen Bond Donor Count : 11 Hydrogen Bond Acceptor Count : 18 Log $P_{o/w}$ (MLOGP): -2.42 Meets RO5 criteria : **NO**
21.	Quercitrin (5280459)	$C_{21}H_{20}O_{11}$		Molecular Weight : 448.4 g/mol Hydrogen Bond Donor Count : 7 Hydrogen Bond Acceptor Count : 11 Log $P_{o/w}$ (MLOGP): -1.84 Meets RO5 criteria : **NO**
22.	Eugenol (3314)	$C_{10}H_{12}O_2$		Molecular Weight : 164.20 g/mol Hydrogen Bond Donor Count : 1 Hydrogen Bond Acceptor Count : 2 Log $P_{o/w}$ (MLOGP): 2.01 Meets RO5 criteria : **YES**

3.3 Docking Result Analysis

Gibbs free energy (ΔG binding) is a parameter of conformational stability between the ligand and the receptor. Thermodynamically, metabolic reactions in the body are exergonic and endergonic. Exergonic reactions are reactions that produce Gibbs free energy, which is the energy used to do work at a constant temperature and pressure. Exergonic reactions cause the free energy of the reactant molecules to decrease, because the free energy is released during the reaction. Therefore, the free energy of the products is lower than that of the reactants. The lower the free energy of a molecule, the more stable the molecule is and the reaction proceeds spontaneously. This is called thermodynamic equilibrium, the more negative the free energy, the more spontaneous the reaction or will quickly form a stable conformation [26].

Based on the Gibbs energy generated in the docking simulation performed on *the Helicase* receptor and 14 ligands, the results were obtained as shown in table 4.

Table 4. Gibbs free energy (ΔG binding) Helicase Receptors and Ligands

No.	Ligands	PubChem ID	Gibbs free energy (ΔG*binding)*
1	Emodin	3220	**-7.9**

2	Luteolin	5280445	**-8.0**
3	Curcumin	969516	**-6.5**
4	Kaemferol	5280863	**-7.7**
5	Quersetin	5280343	**-8.5**
6	Myricetin	5281672	**-8.7**
7	Scutellarein	5281697	**-7.6**
8	10-Gingerol	168115	**-6.4**
9	Shogaol	5281794	**-5.8**
10	Mangostin	5281650	**-8.0**
11	Piseatanol	667639	**-6.8**
12	Diallyl disulfide	16590	**-3.3**
13	Cyperotundone	12308615	**-7.3**
14	Eugenol	3314	**-5.4**

From table 4, it can be observed that the smallest gibbs energy value was obtained by the Mirisetin ligand with a Gibbs energy value of -8.7 kcal/mol. This means that the bond formed between the Helicase receptor and the myrisetin ligand is the most stable among the others. The pose of the ligand formed is shown in Figure 2.

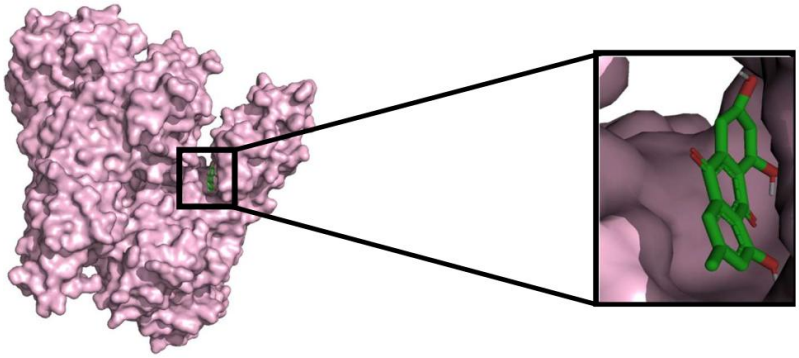


Fig. 2 Helicase Receptor Pose and Mirisetin Ligand (Green: Carbon, Red: Hydrogen, White: Oxygen)

Based on the results that have been described, of the 22 active compounds from natural ingredients, namely: Rhinoceros ketepeng (Cassia alata), Celery (Apium graveolens), Black tea (Camellia sinensis), Turmeric (Curcuma sp.), Guava (Psidium guajava), Orange (Citrus aurantium), Cloves (Syzygium aromaticum), Sapu manis (Scoparia dulcis), Ginger (Zingiber officinalis), Mangosteen (Garcinia mangostana), Grapes (Vitis vinifera), Garlic (Allium cepa), Sambiloto, (Andrographis paniculata), Banyan (Ficus benjamina), Orange (Citrus aurantium), Black tea (Camellia sinensis), Grass teki (Cyperus rotundus), Black tea (Camelia sinensis), Malacca fruit (Phyllanthus emblica), Turmeric (Curcuma longa L.), Meniran (Phyllantus niruri L.) and Salam (Syzygium polyanthum) which were analyzed using Lipinski's five law rules, only 14 active compounds passed the test and were considered to have bioavailable properties, namely compounds from natural ingredients. Rhinoceros ketepeng (Cassia alata), Celery (Apium graveolens), Turmeric (Curcuma sp.), Guava (Psidium guajava), Orange (Citrus aurantium), Clove plant (Syzygium aromaticum), Sapu manis (Scoparia dulcis), Ginger (Zingiber officinalis), Ginger (Zingiber officinalis), Mangosteen (Garcinia mangostana), Wine (Vitis vinifera), Garlic (Allium cepa), Grass (Cyperus rotundus) and Salam (Syzygium polyanthum).

Of the 14 compounds from natural ingredients that meet Lipinski's rules, then the 14 compounds from natural ingredients will be docked at the Helicase receptor. The results obtained are the 14 compounds from these natural ingredients have the potential as SARS-CoV-2 antivirals. This can be observed in table 4. It is shown that the Gibbs free energy (ΔG Binding) or bond energy resulting from the docking simulation is negative. The negative value means that the bond between the receptor and the 14 ligands forms a stable bond. The lower the free energy of a molecule, the more stable the molecule and the reaction will proceed spontaneously [26]. Although the overall binding energy value of the receptor and ligand is negative, the value of the obtained binding energy varies between each ligand and receptor.

If analysis of each receptor is carried out, then for *the helicase* protein receptor, the most stable ligand that binds to this receptor is the Myricetin ligand with a gibbs energy value of -8.7 kcal/mol. So that the Myricetin compound from the Clove plant (Syzygium aromaticum) has the inhibitory activity of *helicase* receptors from SARS-CoV. The receptor that plays an important role in viral replication is helicase. So that by inhibiting the activity of this receptor it will stop the multiplication of the virus and will stop the life cycle of the SARS-CoV virus. The other 13 ligands also have the same potential, but the binding energy is higher than that of myrisetin. So that the Myricetin ligand compound has great potential to be used as a drug candidate for the development of SARS-CoV-2 antiviral drugs in the future.

4. CONCLUSION

Active ingredient compounds that have potential as SARS-CoV-2 antivirals at helicase receptors are Emodin compounds from the rhinoceros Ketepeng plant (Cassia alata), Luteolin compounds from Celery plants (Apium graveolens), Curcumin compounds from Turmeric plants (Curcuma sp.) , Kaemferol compounds from Guava (Psidium guajava) plants, Quercetin compounds from Citrus plants (Citrus aurantium), Myrisetin compounds from Clove plants (Syzygium aromaticum), Scutellarein compounds from sapu manis plant (Scoparia dulcis), 10-Gingerol compounds and Shogaol compounds from Ginger plant (Zingiber officinalis), Mangostin compound from Mangosteen plant (Garcinia mangostana), Piseatanol compound from Grape plant (Vitis vinifera), Diallyl disulfide compound from Garlic plant (Allium cepa), Cyperotundone compound from Grass teki (Cyperus rotundus) plant and Eugenol compounds from the Salam plant (Syzygium polyanthum). This is indicated by the gibbs free energy produced from the docking simulation which has a negative value, meaning that the 14 ligands above have potential as antiviral SARS-CoV-2.

The greatest potential that allows it to be developed as an antiviral for SARS-CoV-2 that inhibits the helicase receptor is Myrisetin compounds from Clove plants (Syzygium aromaticum) which have the lowest Gibbs free energy value of -8.7 kcal/mol. This indicates that the bond formed is the most stable among the receptor binding and other ligands. These results can be used as the basis for the development of SARS-CoV-2 antiviral drugs in the future.

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