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Potency Of Andrographolide, L-Mimosine And Asiaticoside Compound As Antiviral For Covid-19 Based On In Silico Method

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ABSTRACT

Introduction - COVID-19 is an infectious disease that is a global challenge, making it necessary for innovation and the development of antiviral agents in prevention and treatment efforts. Indonesia is known as a country rich in potential plants as medicine, a potential antiviral plant among them *Andrographis paniculata* , *Mimosa pudica* and *Centella asiatica*. The compound that have antiviral activity in each of these plants are andrographolide (*Andrographis paniculata*), L-mimosine (*Mimosa pudica*) and asiaticoside (*Centella asiatica*). The purpose of this study is to identify the potential of the andrographolide, l-mimosine and asiaticoside to inhibit SARS COV-2 protein and to predict the molecular drug profile which refers to lipinski's rule of 5.

Purpose - The purpose of this study was to determine the potential of *Andrographis paniculata* , *Mimosa pudica* and *Centella asiatica* compounds in inhibiting the SARS CoV-2 protein and to determine the prediction of drug profiles such as molecules referring to Lipinski's rule of 5.

Methodology - The methods used in this research by molecular docking and lipinski's Ro5 using PKCSM. The control compounds used are favipiravir and remdesivir.

Results - The results of the affinity of target protein bonds using molecular docking obtained the best results in NSP3 proteins with An Asiaticoside docking score of -10.1 kcal / mol stronger than favipiravir -5.3 kcal/mol and remdesivir -8.6 kcal/mol. As for the compounds L-mimosine -6.1 kcal / mol and Andrographolide -7.7 kcal / mol. The compounds of andrographolide and L-mimosine showed good results and met the 5 aspects of Lipinski's Ro5, but asiaticoside compounds did not good enough. .

Conclusion - The Research has concluded that the compound of the *Andrographis paniculata* , *Mimosa pudica* and *Centella asiatica* have a good potential in inhibiting SARS cov2 protein that is stronger than favipiravir and almost the same with remdesivir activity.

Keywords - Andrographolide, L-mimosine, Asiaticoside, SARS CoV-2, In Silico.

INTRODUCTION

COVID-19 caused by the agent SARS-CoV-2 has infected more than 100 million people worldwide. In Indonesia in particular, according to data published by JHU CSSE until May 9, 2022, COVID-19 cases have infected more than 6 million people with a total death toll of 156,000. Symptoms of this disease mainly include fever, cough, sore throat, runny nose and difficulty breathing (Chen, 2020). More than a year has passed, but the COVID-19 pandemic has not been effectively controlled. This is because there is no specific and effective antiviral to prevent SARS-CoV-2 infection. The presence of viral mutations also exacerbates the virus control process. These mutations produce new variants with different phenotypes, transmission patterns, and virulence (Susilo, 2021). Minor changes in viral proteins caused by mutations have the potential to limit the efficacy of vaccination as an antiviral (W, 2021). So, it is necessary to conduct further studies and developments regarding research on COVID-19 antiviral drugs to find innovations in COVID-19 antiviral drugs in solving COVID-19 problems.

Indonesia has about 30,000 types of medicinal plants. This has caused Indonesia to get the nickname live laboratory. With this wealth, Indonesia has the potential to develop herbal medicinal products whose quality is equivalent to modern medicine. One of the herbal treatments that can be developed during the current pandemic is antiviral. Identification of antiviral compounds from herbs is a relevant approach for the early prevention of SARS-CoV-2 infection. Some herbal plants that have the potential as antivirals are *Andrographis paniculata, Mimosa pudica* and *Centella asiatica.*

The three herbal plants have been proven by previous studies related to their activity as antiviral. *Andrographis paniculata* has been shown to have anti-inflammatory, anticancer, antiobesity and antidiabetic properties (Dai, 2019). In addition, the Andrographolide compound contained in the *Andrographis paniculata* has antiviral properties in many types of viral infections (Gupta, 2017). In addition, extract of *Mimosa pudica* also has antiviral activity which has been proven in a study by Malayan et al in 2013 against the mumps virus. *Centella asiatica* also has antiviral activity against several viral strains such as the HIV virus Human

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Immunodeficiency Virus, hepatitis B virus, and herpes simplex virus (HSV) (Thanigaivel, 2014).

One method that can be used to track the antiviral activity of the three plants is the in silico method. The in silico test is an experiment or test carried out using computer simulations. The in silico test has been used as a method to initiate innovation of new drug compounds and improve efficiency optimally. The purpose of the in silico test is to predict, hypothesize, provide new innovations, or new advances in treatment and therapy (Hardjono, 2013). The advantage of using the in silico method is that it can reduce the use of excessive tools, materials, and experimental animals and save costs (Dona, 2019).

In testing using the in silico test, the method that can be used is the molecular docking method. Docking is an attempt to align the ligand as a mini molecule to the receptor which is a protein molecule by paying attention to the nature of both (Jessen, 2007). The result of this method is a bond energy that will be a reference to determine the feasibility of a compound as a candidate for a new drug compound. Based on this background, this study was conducted to determine the antiviral activity of COVID-19 on *Andrographis paniculata, Mimosa pudica,* and *Centella asiatica* compounds which can be a reference for further research in the discovery of new drugs.

METHOD

This study uses an experimental method by conducting an in silico test. Data obtained from results docking consisting of a docking score and the value of Root Mean Square Distances (RMSD) as well as data on the drug-like molecule profile values referring to Lipinski's rule of 5.

Protein preparation and test ligands were carried out using DS Visualizer. Proteins that have been downloaded through the PDB website are prepared by opening them then water molecules, ligands and others are removed until the remaining protein as a receptor, then stored in PDB format. Ligand preparation is done by removing protein residues until the original ligand remains. Then the file is saved in PDB format. The preparation of the test ligand was carried out by changing the structure of the test compound that had been downloaded via PubChem into 3D using Marvin Sketch and then the file was saved in PDB format

Before doing the docking process, the PDB format needs to be converted to PDBQT first. The conversion is done using Autodock Tools. The PDB protein was opened, then hydrogen was added polarly and then stored in PDBQT format. The original ligand or the test ligand was added with hydrogen and then clicked merge non polar, then saved in PDBQT format. After that, the gridbox menu is used to adjust the area of protein and ligand docking. If the ligands and proteins are ready, the docking process can be carried out using Autodock Vina. Prior to the docking process between the protein and the test ligand, a validation docking was carried out between the protein and the original ligand.

All files needed in the docking process must be in the same folder. Then create a new text document with the file name conf.txt. The text document contains information on the filename of the protein (receptor), the ligand and the corresponding x, y and z values in the grid box. Furthermore, the text document is stored in the same folder. The docking process is done by writing cmd in the address of the folder, after that, write the vina code in the format vina.exe –config conf.txt –log log.txt and then enter. Next, the docking results will appear in the form of RMSD values, conformations and docking scores. Then, data analysis was performed by selecting the RMSD value <2Å with the lowest docking score. Furthermore, the docking results are stored to continue the visualization process. Visualization of docking results is done using DS Visualizer. Opened the PDBQT protein format file and the best docking score conformation, then linked the 2 files. Then the results of the visualization resulted in interactions between proteins and ligands in the form of protein bonds with ligands and bonds with several amino acids. After that, the results are ready for analysis.

Lipinski's rule of 5 test was carried out to predict the bioavailability of compounds. After the structure of the compound is downloaded via PubChem, the cannonical SMILES is entered on the pkCSM website http://biosig.unimelb.edu.au/pkcsm/prediction. Then run predictions to generate predictive data in the form of molecular properties of Ro5. The data were analyzed by referring to Lipinski's rule of 5. If more than 2 aspects of Lipinski's rule of 5 are violated, the compound is predicted to have problems with bioavailability.

RESULT AND DISCUSSION

The in silico test carried out by computational techniques using the molecular docking method serves to predict the binding affinity between a compound ligand and a target protein molecule which is useful in perform rational drug design. Meanwhile, Lipinski's Ro5 prediction using pkCSM functions to predict the bioavailability of a compound. This study aims to determine the antiviral potential of andrographolide, L-mimosine and Asiaticoside with target proteins 3Cl-pro, Nsp3 and PD-ACE2 in SARS-CoV-2, and then the results were compared with favipiravir and remdesivir. Comparative compounds of favipiravir and remdesivir were used because both compounds act on viral RNA polymerase (Main Protease) which is also known as 3-chymotrypsin-like protease (3CLpro) which can provide good activity in inhibiting the replication and transcription of the COVID-19 virus. The sequence of the 2019-nCoV M-Pro protein is similar to that of the SARS-CoV and MERS-CoV proteins, which are mainly involved in the replication cycle. In addition, Shah et al's study in 2020 showed that the protease inhibitors favipiravir and Remdesivir which act on viral RNA polymerase can provide activity both in binding to receptors in silico and potential as COVID-19 inhibitors. So, favipiravir and remdesivir were chosen as comparison compounds in this study.

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In the molecular docking test method, the results obtained are in the form of RMSD values and docking scores. RMSD (Root Mean Square Deviation) is a validation parameter of the molecular docking method. The docking method is said to be valid if it has an RMSD value of 2Å (Ruswanto, 2015). The RMSD value is used to see the similarity between the docking ligands and the crystallographic ligands. The smaller the RMSD value indicates that the predicted ligand position is getting better because it is getting closer to the original conformation (Dany. P., 2013). While the docking score is the energy required for the test compound to bind to the target protein. If the resulting docking score is getting smaller, then the energy required for the test compound to bind to the target protein is also small and vice versa, so that the resulting bond is stronger. The molecular docking results data of this research can be seen in Table 1.

Protein	Test Compound	Target Protein	RMSD value (<2.00 Å)	Docking Score (kcal/mol)	Conformation
SARS CoV-2	Andrographolide	3Cl-Pro	1,819	-6,3	5
		Nsp3	0.000	-7,7	1
		PD-ACE2	1,760	-6,2	6
	Asiaticoside	3Cl-Pro	0.000	-9,8	1
		Nsp3	0.000	-10,1	1
		PD-ACE2	1.505	-8,4	9
	L-Mimosine	3Cl-Pro	1,279	-4,8	7
		Nsp3	0.000	-6,1	1
		PD-ACE2	1,454	-4,1	3
	Favipiravir	3Cl-Pro	1,807	-4,6	3
		Nsp3	0.000	-5,3	1
		PD-ACE2	1.972	-3,8	7
	Remdesivir	3Cl-Pro	1.753	-7,4	3
		Nsp3	1.934	-8,6	3
		PD-ACE2	1.250	-6,4	3

Table 1. Molecular docking results for andrographolide, asiaticoside, L-mimosine test compounds and comparison compounds favipiravir and remdesivir

Based on the results in the table stating the value of the binding affinity of the target protein using molecular docking, the best results were obtained for NSP3 protein with Asiaticoside docking score of -10.1 kcal/mol, followed by Andrographolide docking score of -7.7 kcal/mol and the last compound L-mimosine -6.1 kcal/ moles. The results of the comparison between favipiravir and remdesivir with Nsp3 were -5.3 kcal/mol and -8.6 kcal/mol, respectively. So it can be concluded that the affinity value of asiaticoside compounds with Nsp3 protein is stronger than favipiravir and remdesivir. The lower the binding affinity value, the better stability of the interaction between the ligand and the receptor.

In the molecular docking test, visualization results in the form of 2D and 3D were obtained. Each test compound was visualized against 3 receptors, namely 3Cl-Pro, NSP3, and PD-ACE2 proteins. The 3Cl-Pro protein is a protein that plays an important role in the design of the COVID-19 antiviral. Various studies in silico protein 3Cl-Pro is effective for inhibiting the main protein of SARS-CoV-2. So that the inhibition of the main protease will cause disruption of the replication and transcription of non-structural viral proteins which will cause the virus to die. The NSP3 protein is the largest protein encoded by the coronavirus (CoV) genome. Nsp3 is an important component of the replication/transcription complex. The Nsp3 protein plays a role in promoting cytokine expression and polyprotein cleavage (Astuti, 2020). While the PD-ACE2 protein is a receptor protein where both SARSCoV and SARS-CoV-2 are bound. SARS-CoV downregulates the ACE2 protein by binding to the S protein, causing lung injury. ACE2 will provide antiatrophic, antifibrotic, anti-inflammatory, antioxidant and vasodilating effects, thus providing protection to tissues (Yu, 2016).

The results of molecular docking visualization of andrographolide compounds to 3Cl-Pro protein in 2D and 3D forms in Figure 1 resulted in several types of bond interactions in the form of conventional hydrogen and carbon hydrogen bonds. Conventional hydrogen bonds are formed from andrographolide compounds with 3CLpro on the amino acid residues HIS164 and GLN192. The carbon hydrogen bonds form the amino acid residue PRO168. The results of molecular docking androgapholide visualization of NSP3 protein in 2D and 3D (Figure 2) showed conventional hydrogen bonds to amino acid residues ASP22, ILE131, GLY130, AND ALA129. The carbon hydrogen bonds form the amino acid residue PHE156. The Pi-Donor interaction hydrogen bond formed amino acid residue PHE156, and alkyl bond formed amino acid residue VAL49. The results of molecular docking androgapholide visualization of PD-ACE2 protein in 2D and 3D forms (Figure 3) show conventional hydrogen bonds in amino acid residues ASN546 and SER420, and HIS 535. Hydrogen bonding is one of the factors that affect protein stability. Hydrogen bonds play an important role in molecular conformation, aggregation and functionalization of various chemical systems. So that the more hydrogen bonds formed, the stronger and more stable the bond between the ligand and the protein will be (Glowacki ED, 2013).

Figure 4 is the result of molecular docking asiaticoside visualization of 3Cl-pro protein in 2D and 3D forms. In the results of 2D and 3D visualization of asiaticoside compounds, conventional hydrogen bonds are formed on amino acid residues LYS137, THR135, THR199, ASN133,

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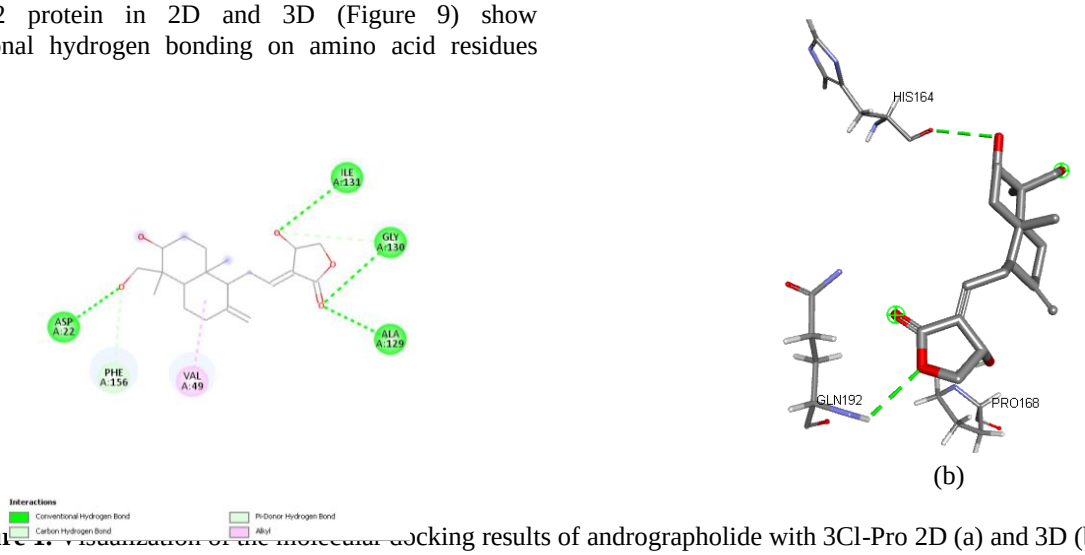
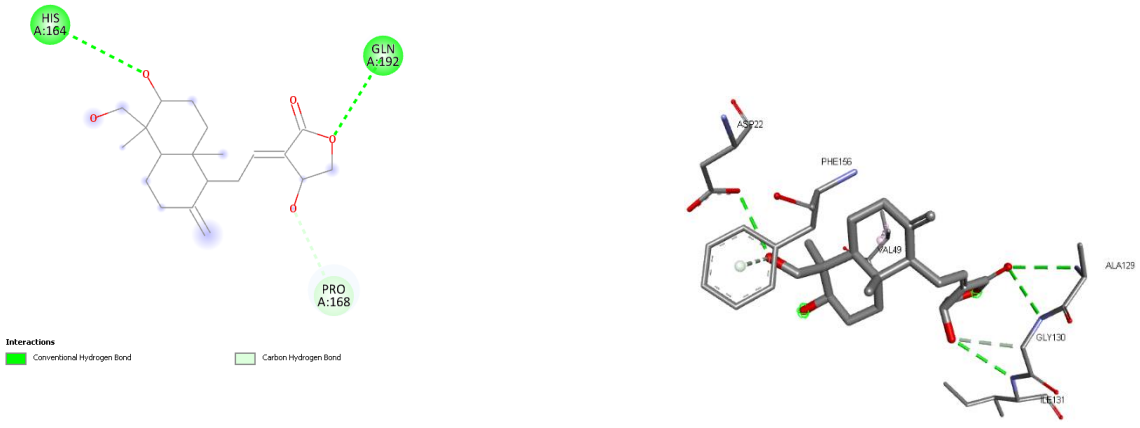
ASP197, and THR196. In the carbon-hydrogen interaction, the amino acid GLY195 is formed. The results of visualization of molecular docking asiaticoside against NSP3 protein in 2D and 3D forms in Figure 5. show that asiaticoside compounds form attractive charges on amino acid residues ARG131, and LYS137. Conventional hydrogen bonds on amino acids residues THR199, ASN238, ASP197, THR135, ASN133 , THR169, and ALA194. And there is a carbon hydrogen bond on the amino acid ALA193. In Figure 6. the results of molecular docking asiaticoside visualization of PD-ACE2 protein in 2D and 3D form show conventional hydrogen bonds in amino acid residues ASN546, SER420, and GLU430. And there is a carbon hydrogen bond on the amino acids LYS313 and PHE314.

Visualization results of L-mimosine molecular docking of 3Cl-Pro protein in 2D and 3D (Figure 7). Produces a conventional hydrogen bond to form the amino acid residue SER144. The results of molecular visualization of L-mimosine docking to NSP3 protein in 2D and 3D (Figure 8) showed conventional hydrogen bonding in amino acid residues ASN40, ALA129, GLY130, and SER128. The results of molecular visualization of L-mimosine docking on PD-ACE2 protein in 2D and 3D (Figure 9) show conventional hydrogen bonding on amino acid residues SER547, ALA533, LYS416, and HIS535. Unfavorable negative-negative bonds are formed on the amino acid residue GLU549. Overall test compounds Andrographolide, asiaticoside and L-mimosine have good hydrogen bonding and have a strong bonding affinity as indicated by the low docking score. The best binding interaction between the compound and the 3 SARS CoV-2 proteins was obtained by the asiaticoside compound with a docking score of -9.8 (Asiaticoside – 3Cl-Pro), -10.1 (Asiaticoside – NSp3) and -8.4 (Asiaticoside – PD-ACE2). These results indicate that asiaticoside is predicted to have a stronger binding affinity with 3 SARS CoV-2 proteins compared to other test compounds including favipiravir and remdesivir compounds. The test compound andrographolide and L-mimosine were predicted to have a stronger binding affinity for the 3 SARS CoV-2 proteins compared to the comparison compound favipiravir and were close to the potency of remdesivir.



(b)

Figure 1. Visualization of the molecular docking results of andrographolide with 3Cl-Pro 2D (a) and 3D (b) proteins



(a) (b)

Figure 2. Visualization of the results of molecular docking of andrographolide with Nsp3 2D (a) and 3D (b) proteins

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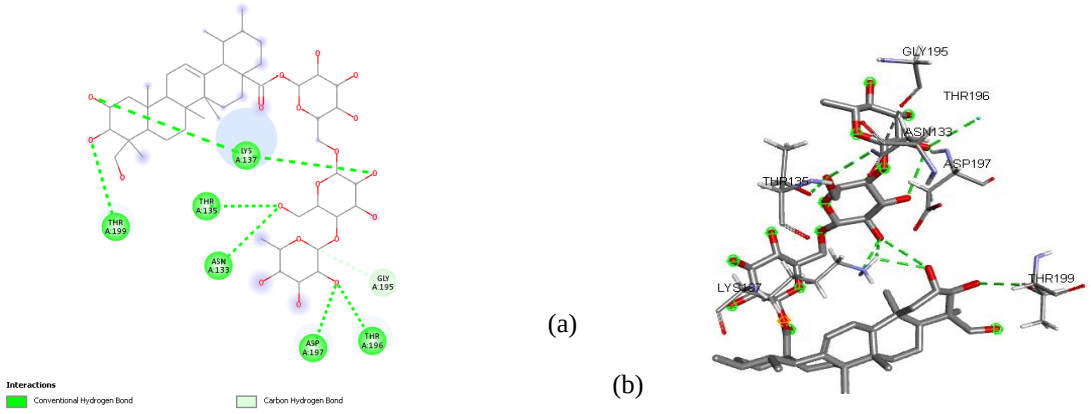
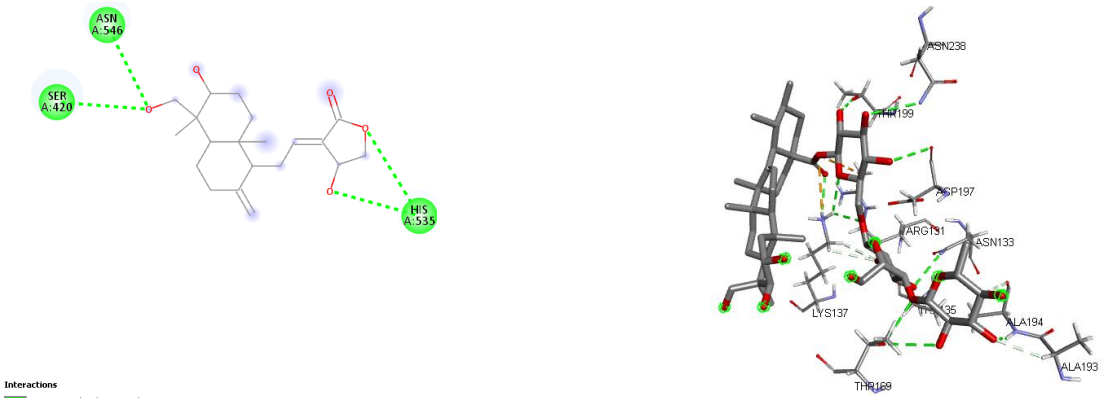


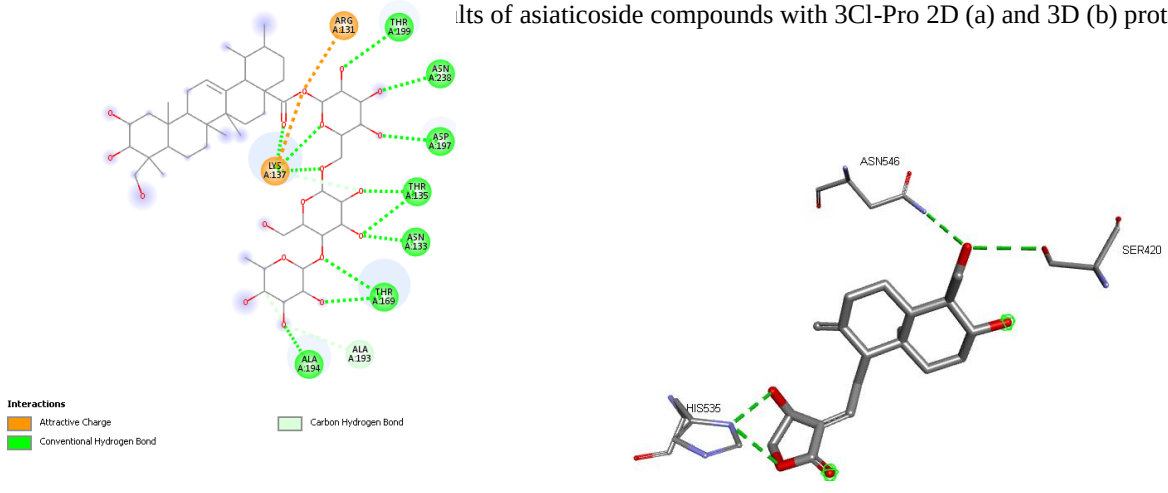
(a) (b)

Figure 3. Visualization of the molecular docking results of andrographolide with PD-ACE2 2D (a) and 3D (b) proteins



(a) (b)

Figure lts of asiaticoside compounds with 3Cl-Pro 2D (a) and 3D (b) proteins



(a) (b)

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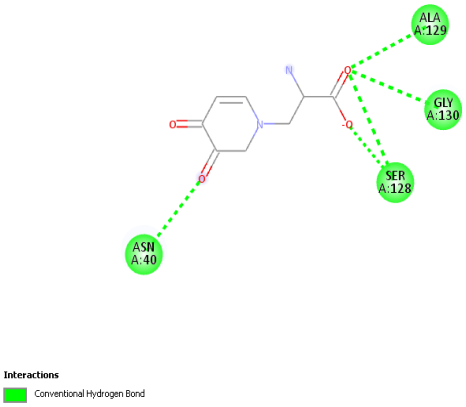
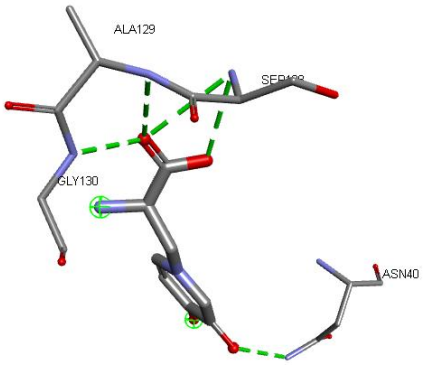
Figure 5. Visualization of molecular docking results of asiaticoside compounds with 2D (a) and 3D (b) Nsp3 proteins



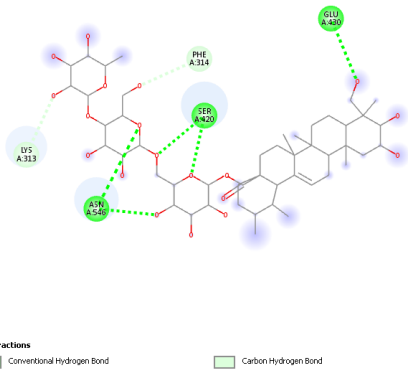
(a)



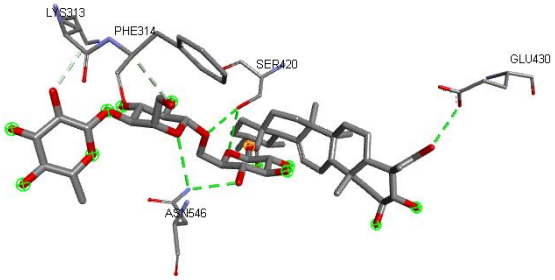
(b)

Figure 6. Visualization of molecular docking of asiaticoside compounds with PD-2D (a) and 3D (b) proteins

results ACE2

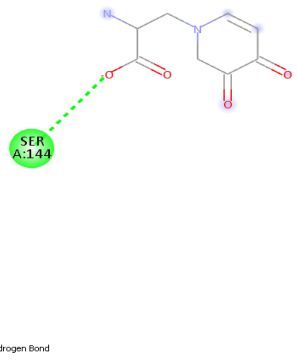


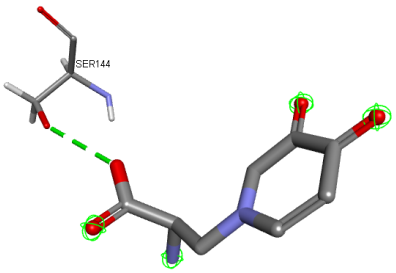
(a)



(b)

Figure 7. Visualization of molecular docking results of L-mimosine with 3Cl-Pro 2D (a) and 3D (b) proteins





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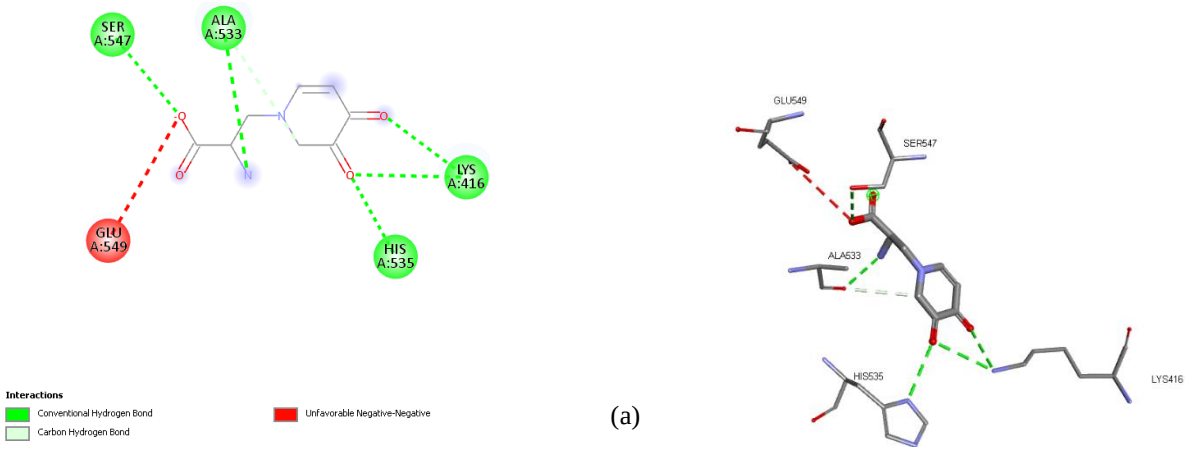
(a) (b)

Figure 8. Visualization of molecular docking results of L-mimosine with Nsp3 2D (a) and 3D (b) proteins



(a)

(b)

Figure 9. Visualization of molecular docking results of L-mimosine with PD-ACE2 2D (a) and 3D (b) proteins

The results of molecular docking visualization of the comparison compound favipiravir against 3Cl-Pro protein in 2D and 3D (Figure 10). The bond formed is carbon hydrogen on the amino acid residue GLN189. Halogen bond on amino acid residue ARG188. The T-Shaped Pi-Pi bond forms the amino acid residue HIS 41 and a pi-alkyl bond in the amino acid residue MET165. The results of the molecular docking visualization of the comparison compound of favipiravir against the NSP3 protein in 2D and 3D forms (Figure 11). The bonds formed are conventional hydrogen on the amino acid residues of PHE132 and ILE131. p-alkyl bonds in amino acid residues ALA38 and ALA50. The results of molecular docking visualization of the comparison compound favipiravir against PD-ACE2 protein in 2D and 3D (Figure 12). The bonds formed are conventional hydrogen on amino acid residues SER420 and LYS313. As well as carbon hydrogen bonds on amino acid residues PHE314.

Figure 13 shows the results of the molecular docking visualization of remdesivir's comparator against 3Cl-Pro protein in 2D and 3D forms. The bonds formed are attractive and pi-anions on amino acid residues ASP289, LYS137, ARG131, ASP197. Conventional hydrogen bonding to the amino acid residue THR199. Halogen bond on amino acid residue ARG188. As well as alkyl and Pi-alkyl bonds formed amino acid residues LEU286. Figure 14 shows the results of molecular docking visualization of remdesivir comparator against NSP3 protein in 2D and 3D forms. The bonds formed are conventional hydrogen on the amino acid residues PHE156, LEU126, VAL49, ILE131. Hydrogen bonding on amino acid residues ALA38 and GYL130. As well as alkyl and Pi-alkyl bonds formed amino acid residues PHE132 and ALA50. Figure 15 shows the results of molecular docking visualization of remdesivir comparator against PD-ACE2 protein in 2D and 3D forms. The bonds formed are attractive charge and Pi-cation on the amino acid residue LYS416. Conventional hydrogen bonding on amino acid residues HIS535, GLU536, LYS534. As well as the Pi-sigma bond, the amino acid residue LYS541 is formed.

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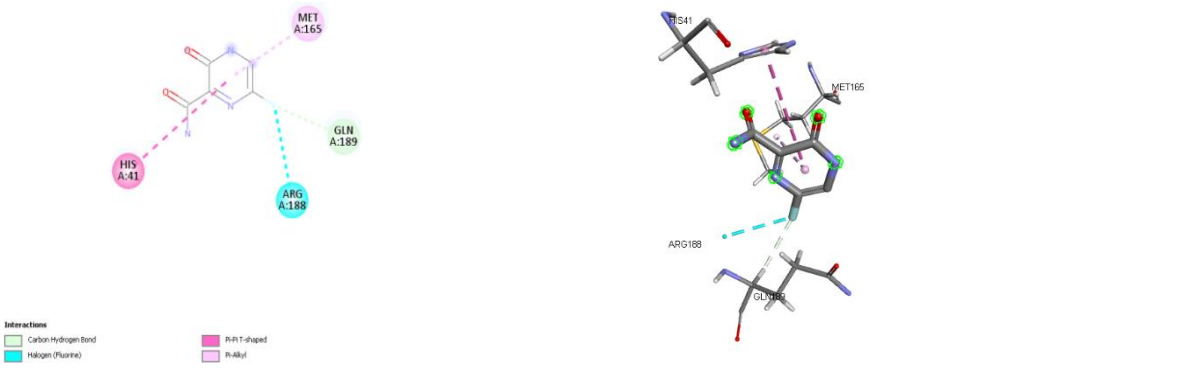
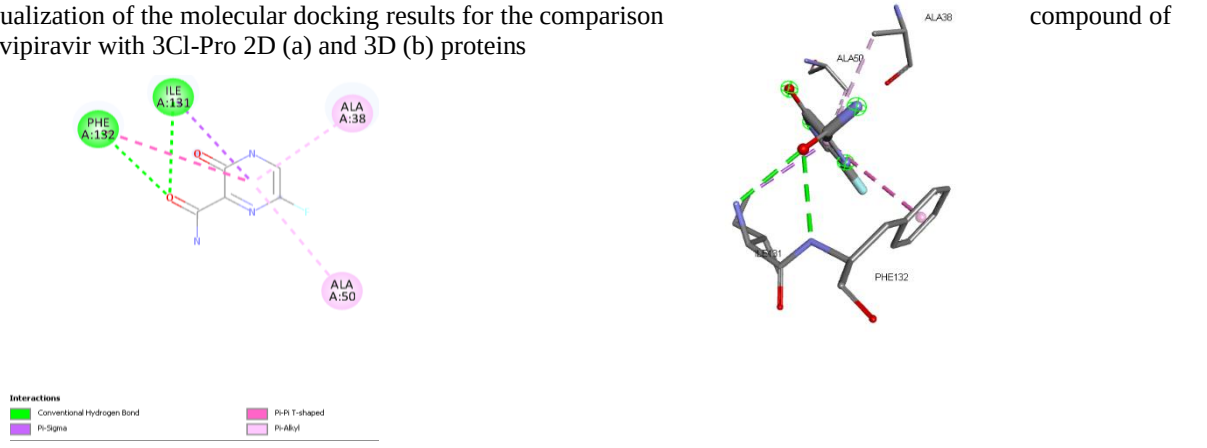


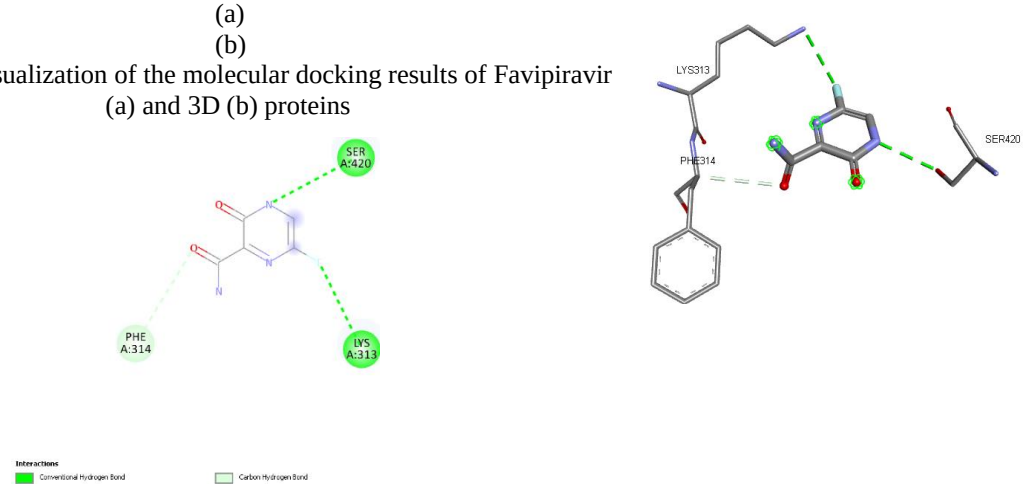
(a) (b)

Figure 10. Visualization of the molecular docking results for the comparison compound of favipiravir with 3Cl-Pro 2D (a) and 3D (b) proteins



(a)
(b)

Figure 11. Visualization of the molecular docking results of Favipiravir with Nsp3 2D (a) and 3D (b) proteins



(a) (b)

Figure 12. Visualization of the molecular docking results of Favipiravir with PD-ACE2 2D (a) and 3D (b) proteins

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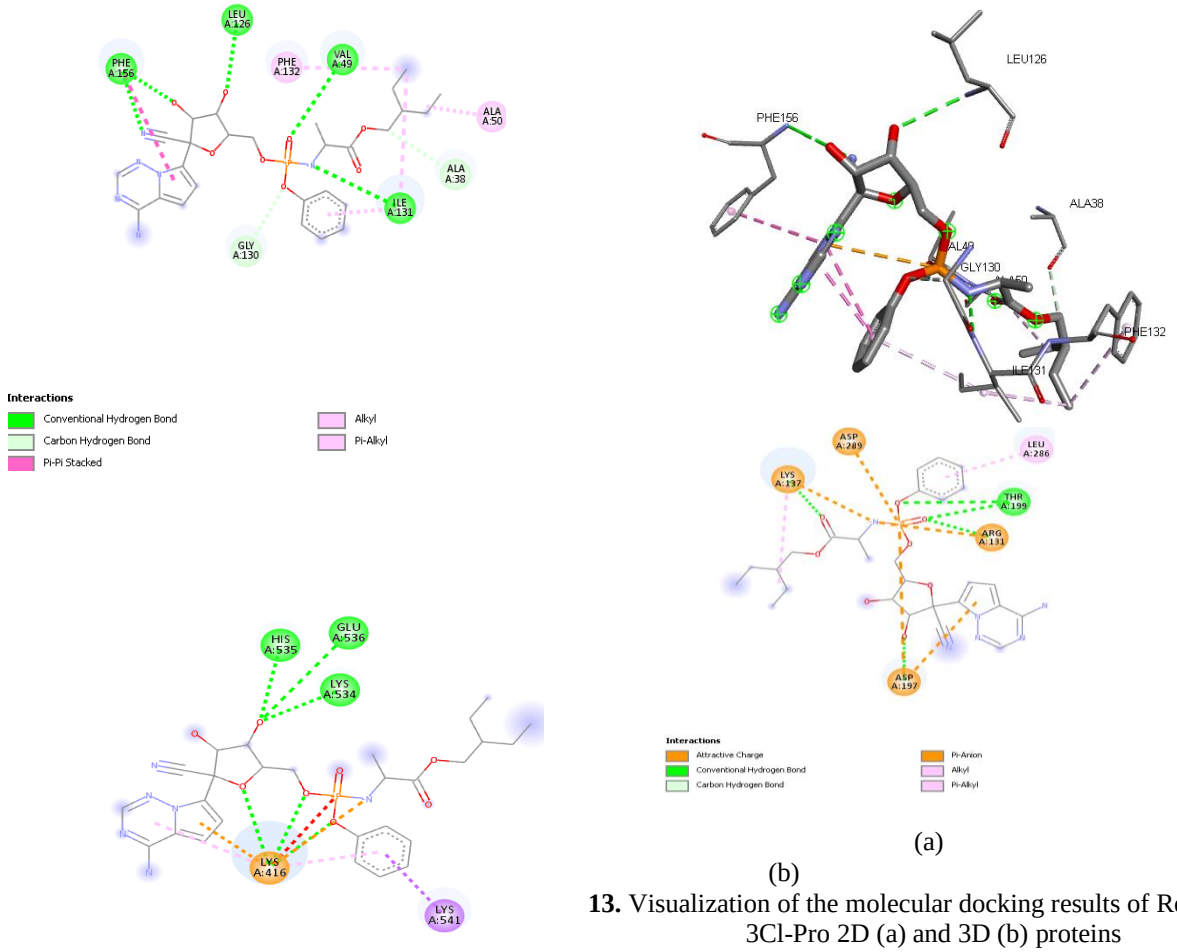
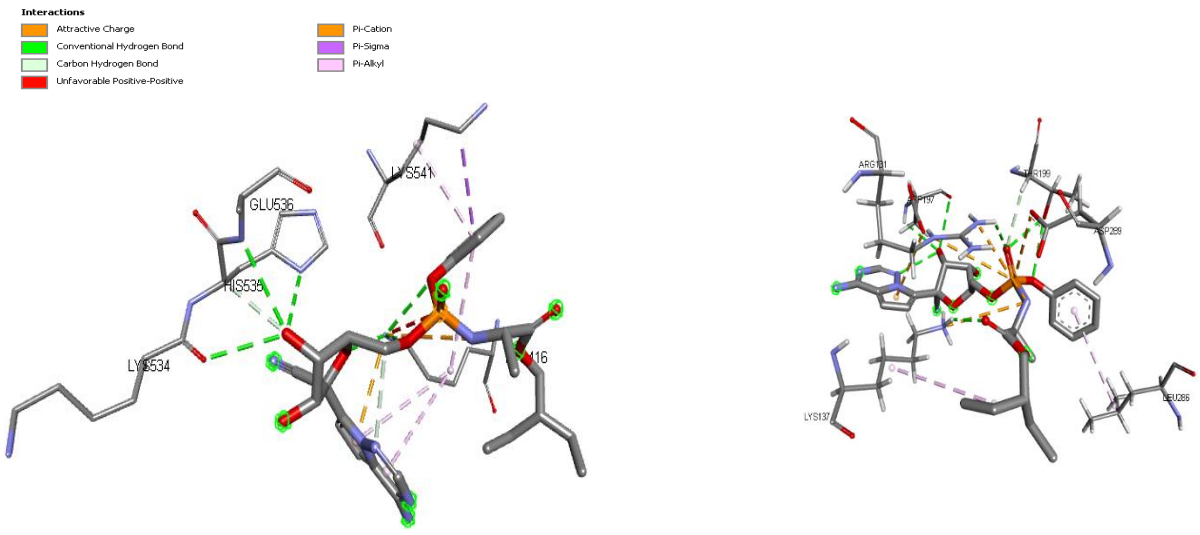


(a) (b)

Figure 13. Visualization of the molecular docking results of Remdesivir with 3Cl-Pro 2D (a) and 3D (b) proteins



(a) (b)

Figure 14. Visualization of the molecular docking results of Remdesivir with Nsp3 2D (a) and 3D (b) proteins

(a) (b)

Figure 15. Visualization of the molecular docking results of Remdesivir compound with PD-ACE2 protein 2D (a) and 3D (b)

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Analysis of the similarity of the molecule to the drug (drug likeness) was carried out based on Lipinski's rule of five (Ro5) which states that a compound has properties similar to drugs. The aim is to determine the bioavailability or pharmacological activity that can be active if given orally to humans from the compound to be used as a ligand. The aspects that will be assessed in Lipinski's (Ro5) rules for drug-like molecules are logP 5 (P= Partition coefficient in the octanol/water system which will determine its lipophilicity), molecular weight (BM) 500 g/mol, the number of hydrogen bond acceptors is 10, and the number of hydrogen bond donors is 5 (Lipinski, 2004). The results of Lipinski's (Ro5) test in this study can be seen in table 2 below:

Table 2. The results of data test lipinski's Ro5

No	Compounds	Lipinski's Ro5 aspects				
		Molecular Weight	LogP	Donor	Acceptor	Rotatable Bonds
1.	Asiaticoside	959.133	-1.0328	12	19	9
2.	L-Mimosine	198.178	-1.0342	3	5	3
3.	Andrographolide	350.455	1.9626	3	5	3

Based on the results of the Lipinski's Ro5 data table from the aspect of molecular weight that meets the requirements of 500 g/mol, namely Androgafolid of 350,455 g/mol and L-Mimosine 198,178 g/mol, while the asiaticoside compound does not meet the requirements of 959,133 g/mol. According to Lipinski et al (1997) stated that the compound will be difficult to absorb and the permeability is low if the molecular weight is > 500 g/mol. While the Log P aspect of all compounds met the requirements of 5, namely Asiaticoside -1.0328, L-mimosine -1.0342, and Androgafolid 1.9626. For hydrogen bond acceptors that meet the requirements of 10, namely L-Mimosine and Androgafolid which are 5 each, while Asiaticoside does not meet the requirements, namely 19. As well as the aspect of the number of hydrogen donors that meet the requirements, only L-mimosine and Androgafolid are 3 each while Asiaticoside does not meet the requirements, namely 12. Based on these results, it can be concluded that the best results were obtained by L-mimosine and Andrographolide compounds because all aspects met the requirements while Asiaticoside compounds violate more than 2 aspects of Lipinki's Ro5. This means that if more than two aspects are violated, then the test compound may have problems with its bioavailability.

CONCLUSION AND RECOMMENDATION

The asiaticoside compound from the *Centella asiatica* had the best docking score on 3 SARS CoV-2 proteins compared to all test compounds including the comparison compounds favipiravir and remdesivir. So it is suspected to have good antiviral activity against COVID-19. However, asiaticoside compounds have Lipinski's Ro5 properties that do not fulfill all aspects, so it is suspected that they have problems with their bioavailability. Because of this, it is necessary to pay attention to the design of the formulation of asiaticoside compounds. The overall results of andrographolide and L-mimosine complied with all aspects of Lipinski's Ro5 and had a better docking score than the comparison compound favipiravir and almost the same with remdesivir activity. So it can be concluded that these three compounds have the potential to be further developed regarding their activity as an antiviral for COVID-19. The results of this study are expected to be an additional reference for readers, besides that it can be developed for further research using other methods such as molecular dynamics and in vitro or in vivo testing. So it is hoped that it will be able to provide a solution for the treatment of COVID-19, especially in Indonesia.

REFERENCES

Astuti, I. &. (2020). Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. Diabetes and Metabolic Syndrome: Clinical Research and Reviews. 14(4):407-412.

Chen, N. Z. (2020). Epidimiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*, 395(10223):507-513.doi:https://doi.org/;10.1016/S0140-6736(20)30211-7.

Dai, Y. C. (2019). Overview of pharmacological activities od Andrographis paniculata and its major compound andrographolide. *Crit Rev Food Sci Nutr*, 59(sup1:S17-S29.

Dany. P., L. J. (2013). Stellar Superfluids. *Inspire*, INT-PUB-009.

Docherty AB, H. E. (2020). Features of 2013 UK Patients in Hospital with COVID-19 Using the ISARIC WHO Clinical Characterisation Protocol: Prospective Observational Cohort Study. *BMJ*, 2(369):1-2.

Dona, R. F. (2019). Studi In Silico, Sintesis, dan Uji Sitotoksik Senyawa P-Metoksi Kalkon terhadap Sel Kanker Payudara MCF-7. *J Sains Farm Klin*, 6(3):243.

Glowacki ED, V. M. (2013). Hydrogen-bonds in molecular solids-from biological systems to organic electronics. *J Mater Chem*, 1:3742-3753.

Gupta, S. M. (2017). Broad-spectrum antiviral properties of andrograpolide. *Arch Virol*, 162(3):611-623.

Hardjono, S. (2013). Sintesis dan Uji Aktivitas Antikanker Senyawa 1-(2-Klorobenzoiloksi)urea dan 1-(4-klorobenzoiloksi)urea. *Berk Ilm Kim Farm*, 2(1):1.

Jessen, F. (2007). *Introduction to Computational Chemistry 2nd Ed.*

Malayan, J. S. (2013). Anti-mumps virus activity by extracts

ISSN 2961-7758

of Mimosa pudica, a unique Indian medicinal plant. *Indian J Virol*, 24(2):166-173.doi:https://doi.org/10.1007/s13337-013-0143-2.

Ruswanto. (2015). Molecular docking empat turunan isonicotino hydrazide pada mycobacterium tuberculosis enoyl-acyl carrier protein reductase (InhA). Vol13,No.

Shah, B. M. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive stud. *Lancet*, 395(102223):5017-513.doi:https://doi.org/10.1016/S0140-6736(20)30211-7.

Susilo, A. O. (2021). TINJAUAN PUSTAKA Review of Current Literatures. *J Penyakit Dalam Indonesia*, 9(1).

Thanigaivel, S. D. (2014). Comparative evaluation of the anti-Hepatitis B virus activity of Centella asiatica and Camellia sinensis (green tea). *BMC Infect Dis*, 14(S3).doi:https://doi.org/10.1186/1471-2334-14-s3-p21.

Yu, e. a. (2016). Angiotensin-(1-5), an active mediator of renin-angiotensin system, stimulates ANP secretion via Mas receptor. *Peptides*, 09.009.

Astuti, I. &. (2020). Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. Diabetes and Metabolic Syndrome: Clinical Research and Reviews. 14(4):407-412.

Chen, N. Z. (2020). Epidimiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*, 395(10223):507-513.doi:https://doi.org/;10.1016/S0140-6736(20)30211-7.

Dai, Y. C. (2019). Overview of pharmacological activities od Andrographis paniculata and its major compound andrographolide. *Crit Rev Food Sci Nutr*, 59(sup1:S17-S29.

Dany. P., L. J. (2013). Stellar Superfluids. *Inspire*, INT-PUB-009.

Docherty AB, H. E. (2020). Features of 2013 UK Patients in Hospital with COVID-19 Using the ISARIC WHO Clinical Characterisation Protocol: Prospective Observational Cohort Study. *BMJ*, 2(369):1-2.

Dona, R. F. (2019). Studi In Silico, Sintesis, dan Uji Sitotoksik Senyawa P-Metoksi Kalkon terhadap Sel Kanker Payudara MCF-7. *J Sains Farm Klin*, 6(3):243.

Glowacki ED, V. M. (2013). Hydrogen-bonds in molecular solids-from biological systems to organic electronics. *J Mater Chem*, 1:3742-3753.

Gupta, S. M. (2017). Broad-spectrum antiviral properties of andrograpolide. *Arch Virol*, 162(3):611-623.

Hardjono, S. (2013). Sintesis dan Uji Aktivitas Antikanker Senyawa 1-(2-Klorobenzoiloksi)urea dan 1-(4-klorobenzoiloksi)urea. *Berk Ilm Kim Farm*, 2(1):1.

Jessen, F. (2007). *Introduction to Computational Chemistry 2nd Ed.*

Malayan, J. S. (2013). Anti-mumps virus activity by extracts

of Mimosa pudica, a unique Indian medicinal plant. *Indian J Virol*, 24(2):166-173.doi:https://doi.org/10.1007/s13337-013-0143-2.

Ruswanto. (2015). Molecular docking empat turunan isonicotino hydrazide pada mycobacterium tuberculosis enoyl-acyl carrier protein reductase (InhA). Vol13,No.

Shah, B. M. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive stud. *Lancet*, 395(102223):5017-513.doi:https://doi.org/10.1016/S0140-6736(20)30211-7.

Susilo, A. O. (2021). TINJAUAN PUSTAKA Review of Current Literatures. *J Penyakit Dalam Indonesia*, 9(1).

Thanigaivel, S. D. (2014). Comparative evaluation of the anti-Hepatitis B virus activity of Centella asiatica and Camellia sinensis (green tea). *BMC Infect Dis*, 14(S3).doi:https://doi.org/10.1186/1471-2334-14-s3-p21.

Yu, e. a. (2016). Angiotensin-(1-5), an active mediator of renin-angiotensin system, stimulates ANP secretion via Mas receptor. *Peptides*, 09.009.

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