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Inhibition of Spike Protein of SARS-CoV2 from (Merremia mammosa (Lour) Hall. F.) Bioactive Compounds: Molecular Docking and ADMET Study

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ABSTRACT

Spike protein is a receptor protein that has e role in the entry step of SARS-CoV2. This protein will bind to the ACE2 receptor in the human body and activate TMPRSS2. Inhibition of this protein will prevent the binding of the virus to host cells to spread the infection. This study aims to identify the activity of bioactive compounds of Merremia mammosa (Lour) tuber obtained from LC-MS/MS QTOF analysis of a previous study against the Spike protein of SARS-CoV2 using molecular docking and ADMET analysis. Molecular docking was conducted using SARS-CoV2 spike protein (PDB id. 6M0J) using Maestro Schrodinger software. Results showed that from 206 compounds there are 8 compounds of Merremia mammosa (Lour) that have lower predictive binding energies than standard drugs arbidol, hydroxychloroquine, and chloroquine. Result: 206 compounds of Merremia mammosa (Lour) tuber were successfully docked, there were 8 compounds that have docking scores more negative than standard drugs. It indicates that 8 compounds are more active than the positive controls. ADMET study revealed all of those potential ligands had the possibility to be developed as drugs. Conclusion: Molecular docking simulations were successfully utilized to identify the potential compounds from Merremia mammosa (Lour) tuber with the activity as an inhibitor for spike protein of SARS-CoV2. Further in vitro assay and purification are needed for future research.

Keywords: *Merremia mammosa (Lour), SARS-CoV2, Molecular docking, ADMET*

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INTRODUCTION

The SARS-CoV-2 virus is responsible for the worldwide outbreak of COVID-19. Currently, there is no specific drug designed to target this virus. Therefore, scientists have been exploring the potential use of existing drugs, such as hydroxychloroquine and remdesivir, in repurposing them to combat the virus. However, the side effects associated with these drugs have led researchers to look for newer, more effective drugs that are selective in preventing the virus from replicating (de Almeida et al., 2020; Farooq & Ngaini, 2021; Zheng, 2020).

In Indonesia, one of the plants that are traditionally used to combat respiratory tract-related diseases is Merremia mammosa (Lour). Its tuber also can be used as an alternative medicine for DM and diabetic wounds. The main compound of Merremia mammosa (Lour) or bidara upas is resin glycoside (Kitagawa et al., 1996). It also contains 4 important compounds, namely: flavonoids (as anti-inflammatory and antidiabetic), alkaloids (as antibacterial), polyphenols (as antioxidants) and tannins (as antibacterial). Flavonoid compounds in bidara upas are active as anti-inflammatory and anti-diabetic. It can inspire macrophages to produce growth factors and cytokines such as EGF, TGF-β, IL-1, IL-4, IL8 in the inflammatory and proliferative phases of the wound healing process. The growth factor produced will then induce fibroblasts and will synthesize collagen and keratinocytes, both of which will show activity in wound healing. Antidiabetic flavonoids have the ability to inhibit the enzymes glucosidase and alpha amylase, which are involved in the breakdown of carbohydrates into monosaccharides. This makes them a potential treatment option for diabetes. With this inhibition, there is no glucose absorbed and there is a decrease in blood glucose levels (Cyntia & Widodo, 2012; Hidayat, 2013; Jadhav & Puchchakayala, 2012). Bidara upas also reported to have good activity against H1N1 influenza virus and Mycobacterium tuberculosis infection (Agil et al., 2021; Purwitasari et al., 2020). The objective of this research was to investigate the interaction between the spike protein of SARS-CoV2 and Merremia mammosa (Lour) through the process of docking. Previously, our investigation using LC-MS/MS QTOF equipment, discovered a total of 206 compounds in four different fractions (96% ethanol extract, butanol, ethyl acetate, and n-hexane) obtained from Merremia mammosa (Lour) (Purwitasari & Agil, 2022).

MATERIAL AND METHODS

Hardware and software

The computational analysis in this study was performed using Maestro Schrödinger 2021-2 software, which is based in New York, NY, USA, and run on a Dell Workstation with Linux Ubuntu 20.04.3 LTS operating system. The workstation had an octa-core Intel® Xeon(R) W-2223 CPU @ 3.60GHz, 16 GB of RAM, and a NVIDIA Quadro P2200 GPU.

Preparation of ligands and receptor

The 2D structures of compounds obtained from LC-MS/MS profiling as well as standard drugs arbidol, hydroxychloroquine and chloroquine were generated using Chemdraw, then optimized and converted into 3D by LigPrep module in Schrodinger 2021-2 as well as protonated with Epik at pH 7.4 and OPLS4 forcefield in order to restore improper or missing bonds, assign protonation, possible ionization, and tautomeric states (Choudhary et al., 2020; Ikram et al., 2015; Schrödinger Release 2022-1, 2022b, 2022c; Zubair et al., 2021). Regarding the spike protein SARS-CoV-2 receptors (PDB id. 6M0J), the Protein Preparation Wizard module in Maestro Schrödinger 2021-2 was used to remove the residual solvent, optimize hydrogen bonding, protonate the molecule using ProtAssign and PROPKA, and add partial charge with the OPLS4 forcefield (Madhavi Sastry et al., 2013; Olsson et al., 2011; Schrödinger Release 2022-1, 2022d).

Molecular Docking

Glide was employed in the molecular docking procedure using both rigid receptor and flexible ligand settings with extra precision (XP) mode. Additionally, to forecast the most effective

compounds that can inhibit SARS-CoV-2 receptors by binding tightly, we adopted the molecular mechanics-generalized Born surface area (MM-GBSA) approach to score the docked pose (Friesner et al., 2006; Genheden & Ryde, 2015; Schrödinger Release 2022-1, 2022b, 2022c, 2022a).

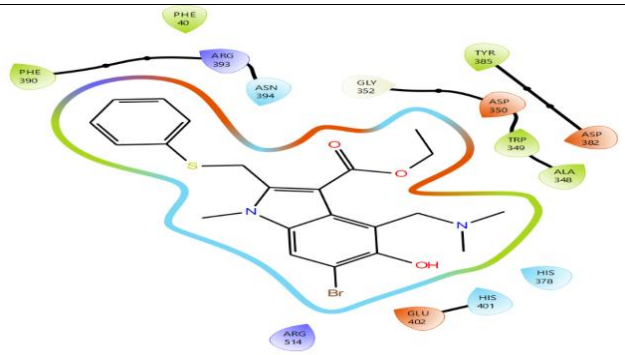
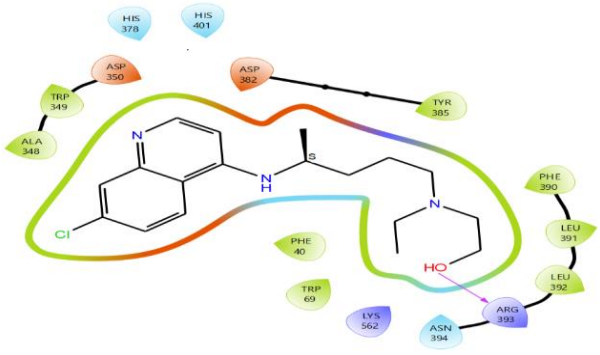
ADMET Analysis

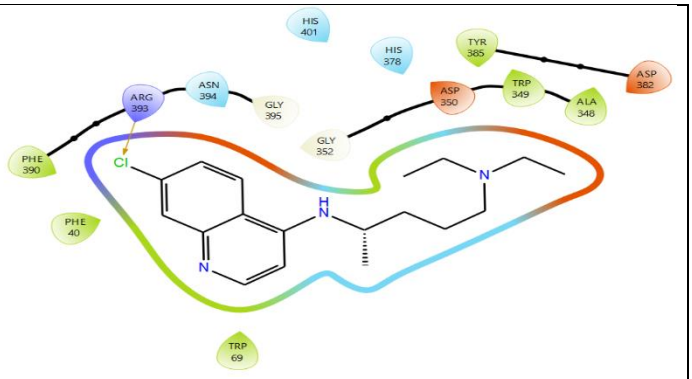
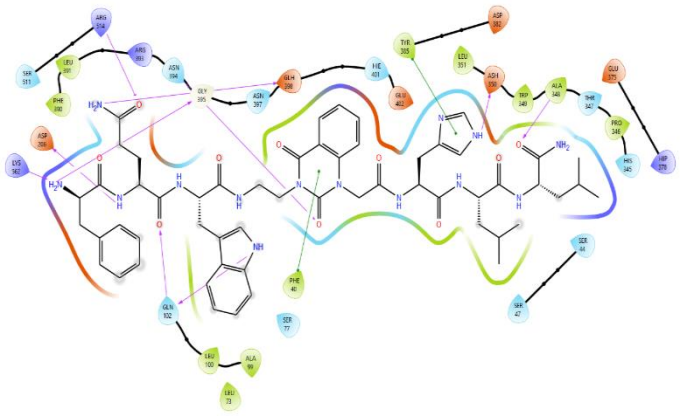
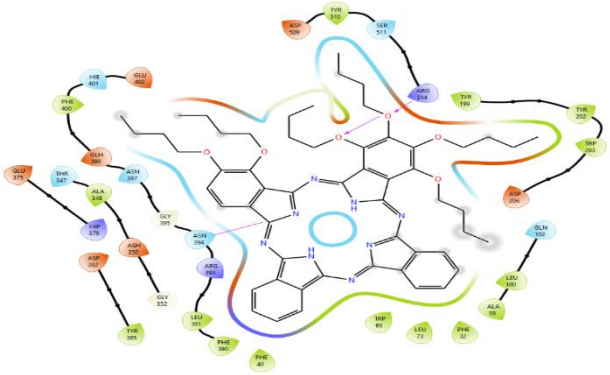
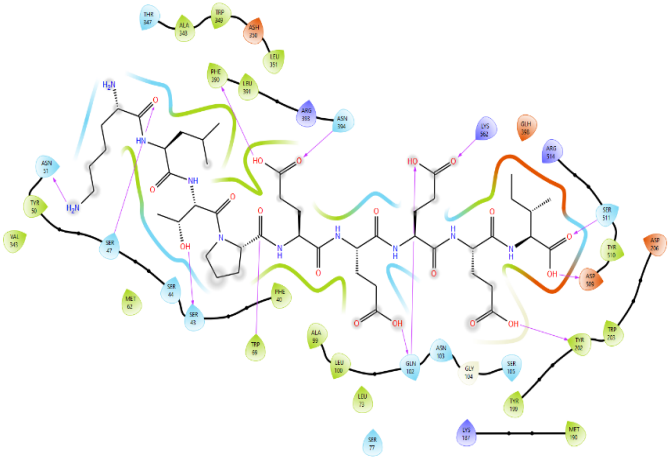
When searching for drugs from medicinal plants, it's important to ensure that the potential compounds comply with Lipinski's Rule of Five. To assess the pharmacokinetics of a drug candidate, which includes its absorption, distribution, metabolism, and excretion in the human body, ADMET prediction is used. SwissADME and Protox were used in this study to analyze the ADMET prediction.

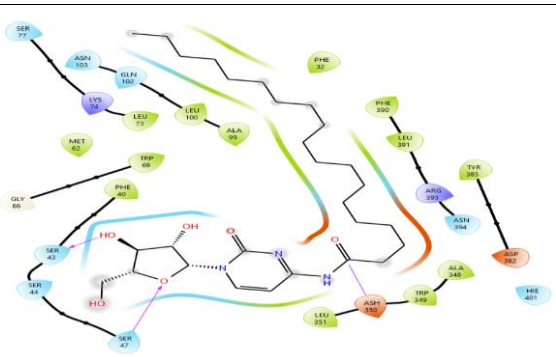
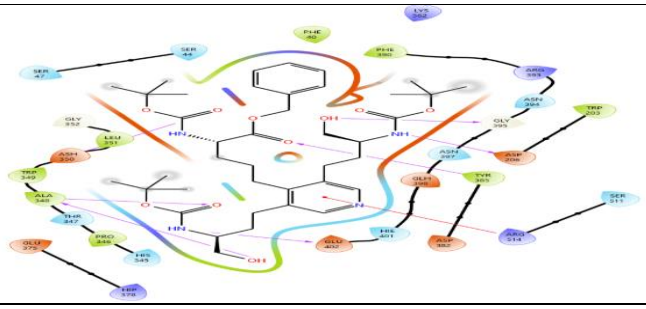
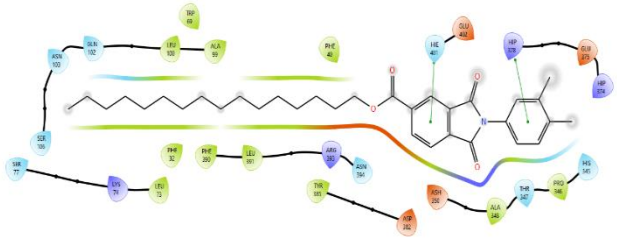
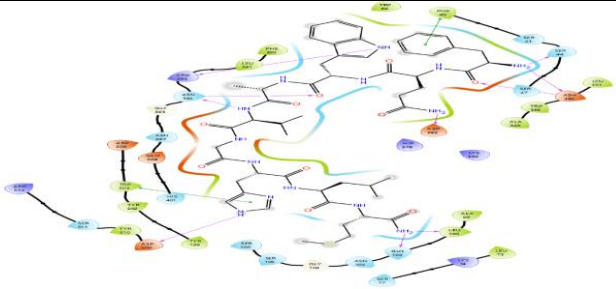
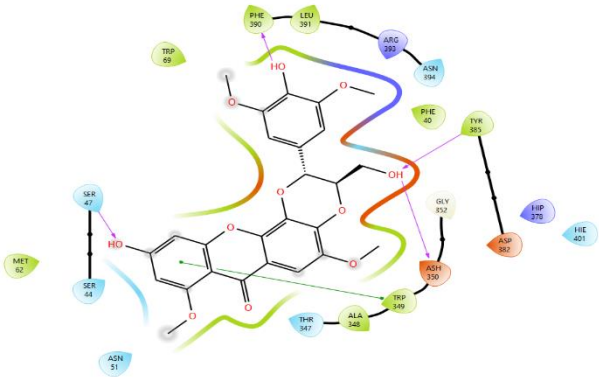
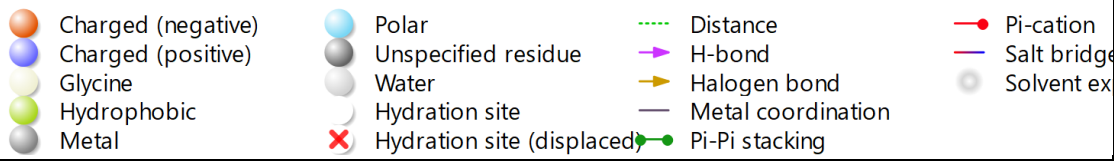
RESULT

To identify potential compounds that can inhibit the spike protein of SARS-CoV-2, a total of 206 Merremia mammosa (Lour) compounds obtained from a previous study were subjected to molecular docking simulations. The optimized structures of these compounds were docked to the viral spike protein binding site, resulting in successful docking of all 206 compounds with the binding site of the spike protein of SARS-CoV-2 (PDB.id: 6M0J Out of the 206 compounds, 8 were found to have MMGBS values ranging from -75.9322 to -60.2985, which is much lower than the MMGBS values of standard drugs such as arbidol (-14.9259), hydrochloroquine (-59.996), and Chloroquine (-44.3516) as shown in Table 1. This suggests that the compounds are more active than the positive controls. The more negative the value of this energy, the lower the free energy and the stronger the binding. Therefore, further purification and NMR analysis of these predicted compounds are recommended to elucidate their molecular structure and confirm their activity against SARS-CoV-2.

TABLE 3-1.: "Docking Pose of Protein Spike of SARS CoV 2 with ligands of Merremia mammosa and standard drugs"

Compound	MMGBSA (kcal/mol)	
Arbidol	-14.9259	
Hydroxychloroquine	-59.996	

Chloroquine	-44.3516	
D-Phenylalanyl-L-glutaminyl-N-{2-[1-(2-{[(2S)-1-{[(2S)-1-{[(2S)-1-amino-4-methyl-1-oxo-2-pentanyl]amino}-4-methyl-1-oxo-2-pentanyl]amino}-3-(1H-imidazol-5-yl)-1-oxo-2-propanyl]amino}-2-oxoethyl)-2,4-d ioxo-1,4-dihydro-3(2H)-chinazolinyl]ethyl}-L-tryptophanamid	-75.4322	
Hexa(butoxy)phthalocyanine	-71.9822	
L-Lysyl-L-leucyl-L-threonyl-L-prolyl-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl-L-isoleucine	-68.9332	

1-(β-D-Arabinofuranosyl)-4-(nonadecanoylamino)-2(1H)-pyrimidinone	-67.0339	
Benzyl 5-{3,5-bis[(3S)-4-hydroxy-3-({[(2-methyl-2-propanyl)oxy]carbonyl}amino)butyl]-4-pyridinyl}-N-{[(2-methyl-2-propanyl)oxy]carbonyl}-L-norvalinate	-63.9406	
Hexadecyl 2-(3,4-dimethylphenyl)-1,3-dioxo-5-isoindolinecarboxylate	-61.8083	
D-Phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-L-histidyl-L-leucyl-L-methioninamide	-60.6731	
Gemixanthone A	-60.2985	
		

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ADMET analysis was done towards 8 compounds of Merremia mammosa. Result showed that from 8 compounds there is no compound that meet the requirement to Lipinski Rule's of 5 due to big molecular weight. Moreover, toxicity of all potential ligands were investigated.

TABLE 3-2.: "Pharmacokinetics and druglikeness properties of potential ligands"

No	Compounds	Molecule Weight (<500) g/mol	Log P (<5)	H-bond Donor (<5)	H-acceptor (<10)
1	1-(β-D-Arabinofuranosyl)-4-(nonadecanoylamino)-2(1H)-pyrimidinone	523,71	1,79	4	7
2	Benzyl 5-{3,5-bis[(3S)-4-hydroxy-3-({[(2-methyl-2-propanyl)oxy]carbonyl}amino)butyl]-4-pyridinyl}-N-{[(2-methyl-2-propanyl)oxy]carbonyl}-L-norvalinate	758,94	1,98	5	11
3	D-Phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-L-histidyl-L-leucyl-L-methioninamide	1087,3	-3,71	13	12
4	Gemixanthone A	512,46	-0,29	3	11
5	Hexa(butoxy)phthalocyanine	947,17	-0,29	2	12
6	Hexadecyl 2-(3,4-dimethylphenyl)-1,3-dioxo-5-isoindolinecarboxylate	519,71	6	0	4
7	L-Lysyl-L-leucyl-L-threonyl-L-prolyl-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl-L-isoleucine	1087,18	-4,9	15	21
8	D-Phenylalanyl-L-glutaminyl-N-{2-[1-(2-{[(2S)-1-{[(2S)-1-{[(2S)-1-amino-4-methyl-1-oxo-2-pentanyl]amino}-4-methyl-1-oxo-2-pentanyl]amino}-3-(1H-imidazol-5-yl)-1-oxo-2-propanyl]amino}-2-oxoethyl)-2,4-d ioxo-1,4-dihydro-3(2H)-chinazolinyl]ethyl}-L-tryptophanamid	1087,23	-2,25	10	12

The toxicity class of each ligand was determined using the ProTox-II webserver, and the results showed that all of the ligands had different toxicity classes. Compounds number 3 and 8 belong to the higher toxicity class with an LD50 of 2400 mg/kg, while compound number 6 belongs to the lowest toxicity class with an LD50 of 61 mg/kg. It can be concluded that the administration of compounds number 3 and 8 is estimated to be safer than compound number 6. However, all of these potential ligands have the possibility to be developed as drug compounds, as shown in Table 3.

TABLE 3-3.: "Toxicity class of potential ligands"

NO	Molecule	Predicted LD50 (mg/kg)	Predicted Toxicity Class	Cytotoxicity
1	1-(β-D-Arabinofuranosyl)-4-(nonadecanoylamino)-2(1H)-pyrimidinone	1000	4	Inactive
2	Benzyl 5-{3,5-bis[(3S)-4-hydroxy-3-({[(2-methyl-2-propanyl)oxy]carbonyl}amino)butyl]-4-pyridinyl}-N-{[(2-methyl-2-propanyl)oxy]carbonyl}-L-norvalinate	430	4	Inactive
3	D-Phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-L-histidyl-L-leucyl-L-methioninamide	2400	5	Inactive
4	Gemixanthone A	550	4	Inactive
5	Hexa(butoxy)phthalocyanine	2000	4	Inactive
6	Hexadecyl 2-(3,4-dimethylphenyl)-1,3-dioxo-5-isoindolinecarboxylate	61	2	Inactive
7	L-Lysyl-L-leucyl-L-threonyl-L-prolyl-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl-L-isoleucine	2000	4	Inactive
8	D-Phenylalanyl-L-glutaminyl-N-{2-[1-(2-{[(2S)-1-{[(2S)-1-{[(2S)-1-amino-4-methyl-1-oxo-2-pentanyl]amino}-4-methyl-1-oxo-2-pentanyl]amino}-3-(1H-imidazol-5-yl)-1-oxo-2-propanyl]amino}-2-oxoethyl)-2,4-dioxo-1,4-dihydro-3(2H)-chinazolinyl]ethyl}-L-tryptophanamid	2400	5	Inactive

DISCUSSION

Upas bidara is able to cure throat and respiratory organ infections. For generations, boiled tubers of upas bidara have been used to treat tuberculosis. Apart from that, bidara upas is a plant that is known for its pharmacological effects that can prevent the multiplication of the HIV virus, H1N1 influenza virus and Mycobacterium tuberculosis infection (Agil et al., 2021; Farizal, 2012; Julianto et al., 2015; Purwitasari et al., 2020; Sutrisno, 2014).

In this result, as many as 8 compounds were predicted to have inhibition activity towards spike protein of SARS-CoV2 in silico (PDB id: 6M0J). One flavonoid compound was reported, which was gemixanthone A, showed a good inhibitory against spike protein of SARS-CoV2 with MMGBSA value -60.2985. It has Hydrogen Bond with SER 47, ASH 350, TYR 385 and PHE 390.

The inhibition of the early step of SARS-CoV-2 infection can be achieved by using these potential compounds. However, the inhibitory potency of other isolates and the extract must be further tested through in vitro, in vivo, and clinical studies to support their application as a medicine for COVID-19 disease (Moradkhani et al., 2021; Olubiy et al., 2020; Rutwick Surya & Praveen, 2021).

CONCLUSION

The study successfully utilized molecular docking to identify potential compounds from the Merremia mammosa (Lour) plant that have the ability to inhibit the spike protein of SARS-CoV-2. However, further research is required, such as purification and NMR characterization, to fully investigate their potential as a treatment for SARS-CoV-2.

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Authors' contribution

All of the authors of this manuscript were involved in the research and the writing process. SS is the main researcher who has ideas, design concepts, writing, correspondence, and revision of articles. NP, EQ, MA, SM and JJ were data collectors and drafted manuscripts and revised articles. NP and S analyses data and revised articles.

Conflict of interests

The authors confirm that the content of this article has no conflict of interest

REFERENCE

1. Agil, M., Studiawan, H., & Purwitasari, N. (2021). Efficacy of Merremia mammosa Hall Terpenoid Fraction againts Mycobacterium tuberculosis. Research Journal of Pharmacy and Technology, 14(12). https://doi.org/10.52711/0974-360X.2021.01143
2. Choudhary, M. I., Shaikh, M., Atia-Tul-Wahab, & Atta-Ur-Rahman. (2020). In silico identification of potential inhibitors of key SARS-CoV-2 3CL hydrolase (Mpro) via molecular docking, MMGBSA predictive binding energy calculations, and molecular dynamics simulation. PLoS ONE, 15(7 July). https://doi.org/10.1371/journal.pone.0235030
3. Cyntia, V., & Widodo, A. (2012). Pengaruh Pemberian Ekstrak Daun Kumis Kucing (Orthosiphon aristatus) Terhadap Penurunan Kadar Glukosa Darah Tikus Wistar Yang Diinduksi Aloksan. Jurnal Kedokteran Diponegoro, 1(1), 112493.
4. de Almeida, S. M. V., Santos Soares, J. C., dos Santos, K. L., Alves, J. E. F., Ribeiro, A. G., Jacob, Í. T. T., da Silva Ferreira, C. J., dos Santos, J. C., de Oliveira, J. F., de Carvalho Junior, L. B., & de Lima, M. do C. A. (2020). COVID-19 therapy: What weapons do we bring into battle? Bioorganic and Medicinal Chemistry, 28(23). https://doi.org/10.1016/j.bmc.2020.115757
5. Farizal, J. (2012). Pengaruh Pemberian Ekstrak Etanol Umbi Bidara Upas (Merremia mammosa) Terhadap Proliferasi Limfosit dan Produksi Roi Makrofag Studi Eksperimental Infeksi Salmonella Typhimurium pada Mencit Balb/C. Diponegoro University.
6. Farooq, S., & Ngaini, Z. (2021). Natural and Synthetic Drugs as Potential Treatment for Coronavirus Disease 2019 (COVID-2019). In Chemistry Africa (Vol. 4, Issue 1). https://doi.org/10.1007/s42250-020-00203-x
7. Friesner, R. A., Murphy, R. B., Repasky, M. P., Frye, L. L., Greenwood, J. R., Halgren, T. A., Sanschagrin, P. C., & Mainz, D. T. (2006). Extra precision glide: Docking and scoring incorporating a model of hydrophobic enclosure for protein-ligand complexes. Journal of Medicinal Chemistry, 49(21). https://doi.org/10.1021/jm051256o
8. Genheden, S., & Ryde, U. (2015). The MM/PBSA and MM/GBSA methods to estimate ligand-binding affinities. In Expert Opinion on Drug Discovery (Vol. 10, Issue 5). https://doi.org/10.1517/17460441.2015.1032936
9. Hidayat, T. S. N. (2013). Peran Topikal Ekstrak Gel Aloe Vera pada Penyembuhan Luka Bakar derajat Dua Dalam. Universitas Airlangga.
10. Ikram, N. K. K., Durrant, J. D., Muchtaridi, M., Zalaludin, A. S., Purwitasari, N., Mohamed, N., Rahim, A. S. A., Lam, C. K., Normi, Y. M., Rahman, N. A., Amaro, R. E., & Wahab, H. A. (2015). A virtual screening approach for identifying plants with anti H5N1 neuraminidase activity. Journal of Chemical Information and Modeling, 55(2). https://doi.org/10.1021/ci500405g
11. Jadhav, R., & Puchchakayala, G. (2012). Hypoglycemic and antidiabetic activity of flavonoids: Boswellic acid, Ellagic acid, Quercetin, Rutin on streptozotocin-nicotinamide induced type 2 diabetic rats. International Journal of Pharmacy and Pharmaceutical Sciences, 4(2).
12. Julianto, I. G. P., Elfiah, U., & Sofiana, K. D. (2015). Pengaruh Pemberian Ekstrak Umbi Bidara Upas (Merremia mammosa (Lour)) terhadap Proses Penyembuhan Luka dan Kadar Gula Darah pada Tikus Wistar Jantan Hiperglikemi. Artikel Ilmiah Hasil Penelitian Mahasiswa, 1(1), 1.
13. Kitagawa, I., Baek, N. I., Yokokawa, Y., Yoshikawa, M., Ohashi, K., & Shibuya, H. (1996). Indonesian medicinal plants. XVI. Chemical structures of four new resin-glycosides, merremosides f, g, h1, and h2, from the tuber of Merremia mammosa (Convolvulaceae). Chemical and Pharmaceutical Bulletin, 44(9). https://doi.org/10.1248/cpb.44.1693
14. Madhavi Sastry, G., Adzhigirey, M., Day, T., Annabhimoju, R., & Sherman, W. (2013). Protein and ligand preparation: Parameters, protocols, and influence on virtual screening enrichments. Journal of Computer-Aided Molecular Design,

27(3). https://doi.org/10.1007/s10822-013-9644-8
15. Moradkhani, S., Farmani, A., Saidijam, M., & Taherkhani, A. (2021). COVID-19: docking-based virtual screening and molecular dynamics study to identify potential SARS-CoV-2 spike protein inhibitors from plant-based phenolic compounds. Acta Virologica, 65(3). https://doi.org/10.4149/av_2021_308
16. Olsson, M. H. M., Søndergaard, C. R., Rostkowski, M., & Jensen, J. H. (2011). PROPKA3: Consistent Treatment of Internal and Surface Residues in Empirical p<italic>K</italic>a Predictions BT - Journal of Chemical Theory and Computation. Journal of Chemical Theory and Computation, 7(2). https://doi.org/https://doi.org/10.1021/ct100578z
17. Olubiy, O. O., Olagunju, M., Keutmann, M., Loschwitz, J., & Strodel, B. (2020). High throughput virtual screening to discover inhibitors of the main protease of the coronavirus SARS-CoV-2. Molecules, 25(14). https://doi.org/10.3390/molecules25143193
18. Purwitasari, N., & Agil, M. (2022). Metabolite Profiling of Extract and Fractions of Bidara Upas (Merremia Mammosa (Lour.) Hallier F.) Tuber Using UPLC-QToF-MS/MS. Biomedical and Pharmacology Journal, 15(4). https://biomedpharmajournal.org/vol15no4/metabolite-profiling-of-extract-and-fractions-of-bidara-upas-merremia-mammosa-lour-hallier-f-tuber-using-uplc-qtof-msms/
19. Purwitasari, N., Agil, M., & Studiawan, H. (2020). Activity of ethyl acetate fraction of merremia mammosa hall as anti-influenza a (H1N1). Indian Journal of Forensic Medicine and Toxicology, 14(3). https://doi.org/10.37506/ijfmt.v14i3.10734
20. Rutwick Surya, U., & Praveen, N. (2021). A molecular docking study of SARS-CoV-2 main protease against phytochemicals of Boerhavia diffusa Linn. for novel COVID-19 drug discovery. VirusDisease, 32(1). https://doi.org/10.1007/s13337-021-00683-6
21. Schrödinger Release 2022-1. (2022a). Desmond Molecular Dynamics System. LLC.
22. Schrödinger Release 2022-1. (2022b). Glide. LLC.
23. Schrödinger Release 2022-1. (2022c). Prime. LLC.
24. Schrödinger Release 2022-1. (2022d). Protein Preparation Wizard; Epik. LLC.
25. Sutrisno, D. E. (2014). Effect of Suspension of Bidara Upas (Merremia tuberosa (L) Rendle.) Powder on Blood Glucose Levels of Alloxan-Induced Wistar Male White Rats [Thesis]. : STIFAR. Sekolah Tinggi Ilmu Farmasi Semarang.
26. Zheng, J. (2020). SARS-coV-2: An emerging coronavirus that causes a global threat. International Journal of Biological Sciences, 16(10). https://doi.org/10.7150/ijbs.45053
27. Zubair, M. S., Maulana, S., Widodo, A., Pitopang, R., Arba, M., & Hariono, M. (2021). Gc-ms, lc-ms/ms, docking and molecular dynamics approaches to identify potential sars-cov-2 3-chymotrypsin-like protease inhibitors from zingiber officinale roscoe. Molecules, 26(17). https://doi.org/10.3390/molecules26175230