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Potential Inhibition of *Melaleuca leucadendron* L. Compounds Against the NSP5 SARS CoV-2 Protein

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Abstract

COVID-19 is an infectious disease caused by Severe Acute Respiratory Syndrome (SARS-CoV-2), causing a global health emergency as a pandemic disease. The lack of certain drug molecules or treatment strategies to fight this disease makes it worse. Therefore, effective drug molecules are needed to fight COVID-19. Non Structural Protein (NSP5) or called Main Protease (Mpro) of SARS CoV 2, a key component of this viral replication, is considered a key target for anti-COVID-19 drug development. The purpose of this study is to determine whether the compounds in the *Melaleuca leucadendron* L. plant such as 1,8-cineole, terpene, guaiol, linalol, α-selinenol, ß-eudesmol and γ-eudesmol are predicted to have antiviral activity for COVID-19. Interaction of compounds with NSP5 with PDB code 6WNP analyzed using molecular docking with Molegro Virtual Docker. Based on binding affinity, the highest potential as an anti-viral is Terpineol with binding energy (-119.743 kcal/mol). The results of the interaction showed that terpinol has similarities in all three amino acid residues namely Cys 145, Gly 143, and Glu 166 with remdesivir and native ligand. *Melaleuca leucadendron* L. may represent a potential herbal treatment to act as: COVID-19 NSP5, however these findings must be validated *in vitro* and *in vivo*.

Keywords: *COVID-19, In Silico, NSP5/ 6WNP, Melaleuca leucadendron L.*

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is caused by the Severe Acute Respiratory Syndrome (SARS-CoV-2) virus which is classified as a family of coronaviruses. SARS-CoV-2 is a positive, capsulated and non-segmented single-strain RNA virus (Zu, *et al*, 2020). Symptoms that are often caused by this virus are fever, fatigue, and dry cough. In severe cases, you will experience Acute Respiratory Distress Syndrome (ARDS), sepsis, multi-organ failure, and result in death due to excessive cytokine production in the body (cytokine storm) (Mehta, *et al*., 2020).

COVID-19 is an infectious disease that is the main cause of morbidity and mortality around the world today, including Indonesia. According to the Indonesian Ministry of Health (2020), Indonesia

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has reported the first case of COVID-19 on March 2, 2020, which is suspected that the first transmission came from foreigners visiting Indonesia. Mortality caused by this virus reaches 4-5% with the most deaths occurring in the age group over 65 years. Patients infected with COVID-19 were obtained in the age group of 37-78 years with an average in the group of 56 years (Liu, *et al*., 2020).

SARS-CoV-2 is composed of Non Structural Protein (NSP) encoded by two large polyproteins, pp1a and pp1ab. These polyprotein are cleaved and transformed in NSP2 by two proteases, one of which is non-structural protein 5 (NSP5) encoded by Open Reading Frames (ORF) 1a /b (Gil and Ginex, 2020). During the replication process, the viral RNA genome is bound to a nucleocapsid and packaged into a ribonucleoprotein (RNP) complex that is important for maintaining RNA conformation for replication and genome saline (Khan, *et al*., 2020). The NSP5 protein is also a 28 kDa protein that plays a central role in viral replication in the cytoplasm of the host cell and suppresses the anti-virus of the host cell (Stobart, *et al*, 2013).

Considering the important activity in viral replication, inhibition of NSP5 protein activity is a potential target for antiviral activity. Compounds that can inhibit the replication process of this virus have the opportunity to be developed as antivirals. However, there is currently no specific therapy for COVID-19 available and it is still limited to preventive and supportive therapy to prevent further complications (Ikawati, *et al*., 2020). Currently researchers are trying to find a therapy that is inexpensive and has little side effects. This has led many researchers to increase the use of herbal ingredients as alternative medicines that have an effect that works specifically on SARS-CoV-2 (Ouassou, 2020). One of the plants that can be used is *Melaleuca leucadendron* L.

Melaleuca leucadendron L. is an aromatic plant whose species grow the most in Indonesia including the island of Java. Based on Patramurti, *et al* (2020), the distillation method of fresh *Melaleuca leucadendron* L. leaves produced 64%

essential oil containing 1,8-cineol, terpineol, guaiol, linalol, β-selinenol, α-eudesmol and γ-eudesmol. This is what makes researchers use this compound. This plant can be used as an antioxidant, antifungal, antibacterial, antiviral, anti-inflammatory, airway treatment, anticancer, analgesic, antispasmodic, sedative and hypertensive medicine (Sudradjat, 2020). Based on previous research, the plant has antiviral activity against the herpes simplex-1 virus (HSV-1) which infects African green monkey kidney cells (Vero cells) by 92% (Patramurti, *et al*, 2020).

Considering its availability, affordability and pharmacological effects, the utilization of the medicinal plant *Melaleuca leucadendron* L. can be considered as a potential therapeutic choice against SAR-CoV-2 by going through *in silico* studies with molecular docking techniques (Ruswanto, 2019). This study may show the affinity of binding compounds to receptors in the SARS-CoV-2 virus (Santos, *et al*., 2019). The advantages of this method include reducing excessive use of tools and materials, faster time, and can save experimental costs (Dona, *et al*., 2019). Then in this study will compare with remdesivir because the drug works in inhibiting viral replication through RNA dependent - RNA polymerase (Warren, *et al*, 2020).

METHODS

This study uses an Asus laptop type M451U with Intel® Core™ i5, Processor 1.9 GHz used for molecular docking using NSP5 receptors with a PDB code of 6WNP. The test compounds used are compounds from the *Melaleuca leucadendron* L. plant as well as the comparison drug remdesivir. Molecular docking is used to predict ligand complexes with receptors that produce score docking.

Ligand and Protein Preparation

The ligands used in this study were active compounds downloaded as SMILE files from PubChem (http://pubchem.ncbi.nlm.nih.gov/). The NSP 5 protein is derived from the RSCB website

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Table 1. RMSD values of native ligand at 6WNP receptors.

Native ligand	Cavity	RMSD Value			Average±SD
U5G_401(A)	Cavity 1	1.9016	1.9417	1.9235	1.922267±0.2008
	Cavity 4	7.7977	7.80467	6.10623	7.2362±0.9785

(https://www.rcsb.org/search). The ligand minimization process is carried out using Avogadro software which allows the ligand to be more flexible, then the file structure data format (SMILE) is converted into a protein data bank (mole) format. Using the Molegro Virtual Docker 6.0 software, protein stabilization is carried out to adjust to the body's physiology by removing water and hydrogen atoms. The native ligand in this study is U5G_401A which comes from PDB 6WNP. According to Stobart, *et al* (2013), 6WNP a broad-spectrum dipeptidyl Mpro inhibitor, efficiently blocking the proliferation of SARS-CoV and has a crystallographic ligand at the active site, namely the non-covalent inhibitor so that the binding target on the receptor is easier to do.

Receptor Validation

Receptor validation is carried out by eliminating water molecules and ligand references and adding hydrogen atoms using the Molegro Virtual Docker 6.0 software from CLC bio company, Denmark. Validation performed 3 times and selected with Root Mean Square Deviation (RMSD) value with a value of <2 Å (Table 1).

Prediction of Biological Activity

The ligand compounds 1,8-cineol, terpineol, guaiol, linalol, β-selinenol, α-eudesmol and γ-eudesmol in *Melaleuca leucadendron* L. were evaluated pharmacokinetically as drug candidates using the SwissADME web server (http://swissadme.ch), followed by drug similarity analysis using the Lipinski Rule of Five. Furthermore, predictions of ADMET agents were filtered using pkCSM and Protox which included LD_{50}, skin class, Ames toxicity, hepatotoxicity, and BBB obtained from the website.

Molecular Docking

Molecular docking is used to determine the value of the binding energy formed when a ligand interacts with its receptors. Specific docking refers to the ratio of the binding energy of active ingredient compounds and control ligands that bind to the same binding place in this study. This study used Molegro Virtual Docker 6.0 to simulate molecular docking. Receptor and ligand files are examined using the mole file format.

Table 2. Pharmacokinetic test of *Melaleuca leucadendron* L. compound.

Active Ingredients	GIA	BBB	P-gp Substrat
1,8 Cineole	High	Yes	No
α-eudesmol	High	Yes	No
β-selinol	High	Yes	No
γ-eudesmol	High	Yes	No
Guaiol	High	Yes	No
Linalol	High	Yes	No
Terpinol	High	Yes	No

Table 3. Lipinski rule of five test results.

Active Ingredients	Molecular Weight (g/mol)	Hydrogen Bond Donor	Acceptor Bond Donor	Log*P*	Rotatable Bonds	Lipinski Rule Violation
1,8 Cineole	154.25	0	1	2.67	0	0
α-eudesmol	222.37	1	1	3.51	1	0
ß-selinol	222.37	1	1	3.60	1	0
γ-eudesmol	222.37	1	1	3.60	1	0
Guaiol	222.37	1	1	3.42	1	0
Linalol	154.25	1	1	2.66	4	0
Terpinol	190.28	1	1	1.28	1	0

Analysis of Protein-ligand Interactions

In Molegro Virtual Docker 6.0 software, docking results are visualized at the molecular level. Based on the interaction and type of bond formed by the Active Ingredient Compound when it binds to the target protein, a study of the protein-ligand bond is carried out. Ligand-protein interactions were studied using ChemDraw Ultra. The program will provide a representative 2D schematic representation of the complex bonds between the ligands and protein.

RESULTS

Validation Resceptor

The validation stage is carried out to test the correctness by ensuring that the receptors and native ligand compounds meet the criteria so

that they can avoid errors in the receptors. This validation process is seen from the value of RMSD, which is a value to obtain a similarity in results between the native ligand and the location of similar compounds with a value of <2 Å. Based on Table 1 it is found that the RMSD in cavity 1 has the smallest RMSD so that the pose of the ligand is better because it is closer to the conformation of the native ligand.

Prediction of The Biological Activity of Compounds

The pharmacokinetic test in this study was carried out by uploading SMILES from the Active Ingredients of Herbal Compounds on the SwissADME online website (http://swissadme. ch/). Based on Table 2, it was found that the compound *Melaleuca leucadendron* L. can

Table 4. Toxicity test results.

Active Ingredients	Toxicity				
	Toxicity Class	LD$_{50}$ (mg/kg)	Hepatotoxic	Skin Sensitivity	AMES Mutagenic Test
1,8 Cineole	5	2480	NO	YES	NO
α-eudesmol	5	4300	NO	YES	NO
β-selinol	5	4300	NO	YES	NO
γ-eudesmol	5	4300	NO	YES	NO
Guaiol	5	4300	NO	YES	NO
Linalol	5	4300	NO	YES	NO
Terpinol	5	4300	NO	YES	NO
Remdesivir	4	1190	YES	NO	NO

Table 5. Binding affinity result.

Active Ingredients	Binding Affinity (Kcal/mol) NSP 5 (6WNP)
1,8 Cineole	-53.7714
α-eudesmol	-59.1145
β-selinol	-66.6822
γ-eudesmol	-62.9568
Guaiol -	72.9118
Linalol -	59.3954
Terpinol	-119.743
Native ligand (U5G_401(A)	-70.2751
Remdesivir	-114.8175

penetrate the blood-brain barrier (BBB), has good gastrointestinal absorption (GIA), and has the potential to modify concentrations in the brain even at clinically approved doses (P-gp).

Lipinski rule of five is used to determine the degree of similarity of compounds that have a certain biological activity that can further determine the feasibility of compounds as poten-

tial new drugs. Based on Table 3, the compounds 1,8-cineole, terpineol, linalol, guaiol, α-eudesmol, β-selinenol and γ-eudesmol have complied with Lipinski rule of five,

Based on Table 3, the compounds 1,8-cineole, terpineol, linalol, guaiol, α-eudesmol, β-selinenol and γ-eudesmol have complied with Lipinski rule of five so that it can be predicted that the tested compounds can be well absorbed, have good permeability, and has good oral bioavailability.

Based on Table 4, the compounds 1,8-cineole, terpineol, linalol, guaiol, α eudesmol, β-selinenol and γ-eudesmol belong to class 5 toxicity ($2000 < LD_{50} \leq 5000$), no toxic to the liver, but has a sensitivity to the skin.

Molecular Docking

In particular, the Molegro Virtual Docker software was used to perform molecular docking tests in this investigation. This test was carried out to determine the molecular interaction of the Active Ingredients of Herbal Compounds in *Melaleuca leucadendron* L.
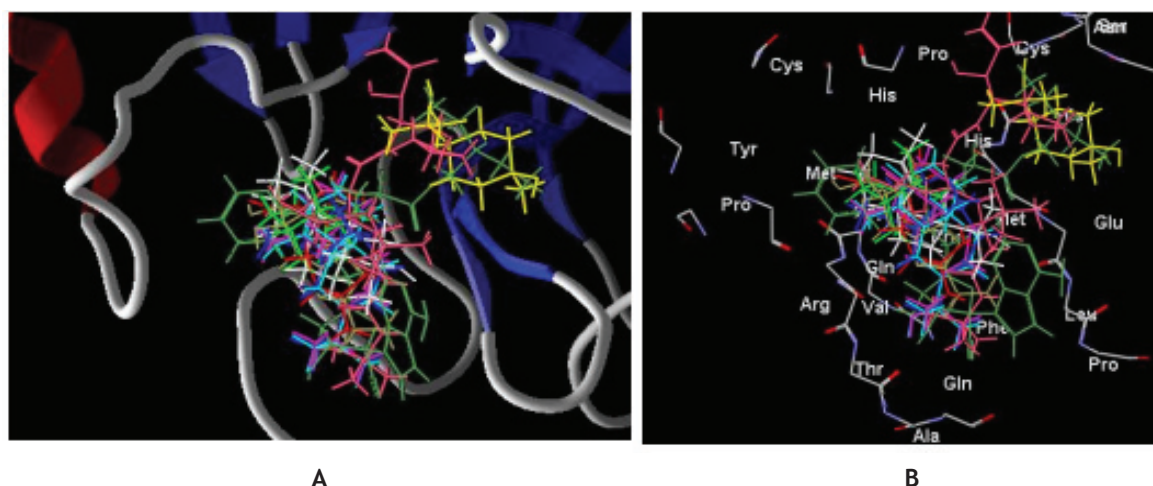

A   B

Figure 1. Molecular docking results between wireframe display test compound and 6WNP backbone display receptor. (A) display of the test compound 1,8 cineol (light green), alpha eudesmol (light blue), beta selineol (purple), gamma eudesmol (white), guaiol (dark blue), linalol (red), terpinol (yellow), remdesivir (faded green), and native ligands (pink). (B) Amino acid residues are displayed in stick mode and the pose ligand with the wireframe model using colour by chain.

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Table 6. Active site, dimension, and docking center grid.

Compound	Hidrogen Interaction			Steric Interaction		
	Amino Acid	Distance (Å)	Ligand Group	Amino Acid	Distance (Å)	Ligand Group
1,8 Cineole	-	-	-	Asp 187	3.02	C Number 9
	-	-	-	Met 49	2.67	C Number 8
Alpha-euddesmol	Arg 188	2.6	O Number 3	Met 165	2.84	C Number 2
	Gln 192	3.12	O Number 3	-	-	-
	Thr 190	3.12	O Number 3	-	-	-
Beta-selineol	Thr 190	3.08	O Number 0	Met 165	2.74	C Number 3
	-	-	-	Gln 192	-	O Number 0
	-	-	-	Arg 188	-	O Number 0
Gamma eudesmol	Glu 166	3.10	O Number 3	Met 49	2.83	C Number 11
Guaiol	Thr 190	3.13	O Number 3	Met 165	2.84	C Number 1
	-	-	-	Gln 189	3.17	C Number 8
	-	-	-	Glu 166	3.16	C Number 11
	-	-	-	Gln 192	-	O Number 3
	-	-	-	Arg 188	-	O Number 3
Linalol	His 41	3.26	O Number 10	-	-	-
	His 164	3.23	O Number 10	-	-	-
Terpinol	Cys 145	3.16	O Number 16	His 172	2.99	C Number 28
	Gly 143	3.33	O Number 16	His 163	2.76	C Number 28
	Glu 166	2.84	O Number 26	Glu 166	3.07	C Number 1
	Phe 140	2.78	O Number 26	Leu 141	3.07	C Number 5
Remdesivir	Glu 166	2.73	O Number 8	His 163	2.90	C Number 31
	Arg 188	2.16	O Number 3	Cys 145	3.14	C Number 30
	Thr 190	3.15	O Number 2	Met 49	3.12	C Number 40
	-	-	-	Tyr 54	2.81	C Number 39
	-	-	-	His 41	3.00	C Number 37
	-	-	-	Arg 188	2.84	C Number 40
	-	-	-	Met 165	3.04	N Number 11
	-	-	-	Pro 168	3.14	C Number 22
	-	-	-	His 164	-	N Number 11
	-	-	-	Gln 192	-	O Number 3
Ligan Native (U5G_401(A)	His 164	3.10	N Number 41	Thr 190	3.13	C Number 3
	Glu 166	3.12	O Number 33	Ser 144	-	-
	Gly 143	2.78	O Number 61	Gly 143	2.78	O Number 61
	His 41	2.60	O Number 58	Cys 145	3.10	N Number 41
	Cys 145	2.90	O Number 61	-	-	-

Based on Table 5, terpineol has the lowest rerank score with an average of -119.743, then compared with the rerank score on remdesivir (-114.8175 kcal/mol) and the rerank score on native ligand (-70.2751 kcal/mol).

Analysis of Protein-ligand Interactions

Amino acid residues can be observed from the analysis of the interaction between the ligand and the target protein. Amino acid residues, distances, and ligand groups in hydrogen interactions and steric interactions can be seen in
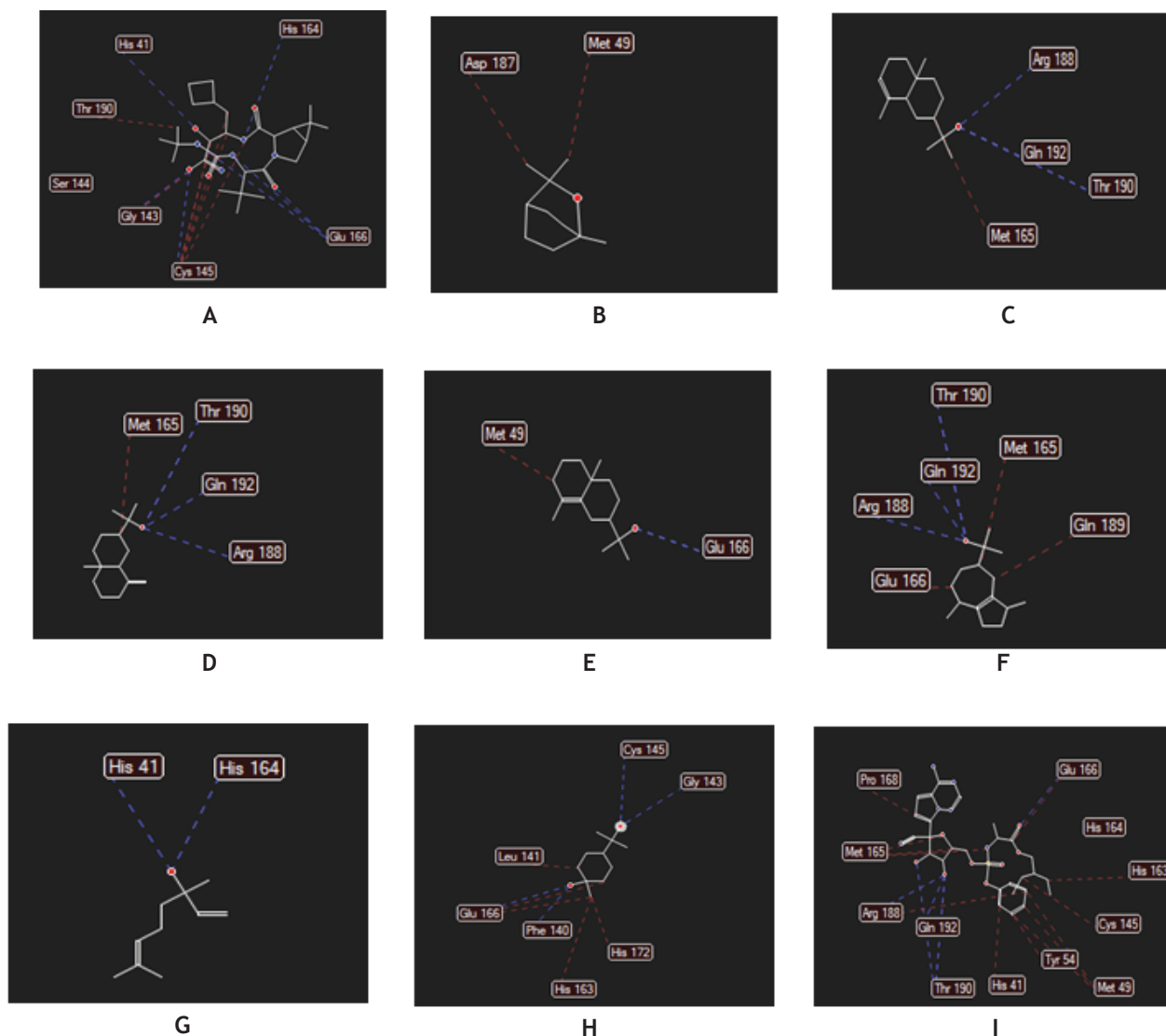
Figure 2. The result of the interaction of amino acid residues in 2 dimensions. (A) Display of native ligands U5G_401; (B) 1,8 cineol; (C) alpha eudesmol; (D) beta selineol; (E) gamma eudesmol; (F) guaiol; (G) linalol; (H) terpinol; and (I) remdesivir.

Table 6. The yellow boxes indicate amino acids similar to the NSP5 receptor native ligands.

Based on Table 6, it was found that 1.8 cineole, α-eudesmol, β-Selineol, Guaiol had no resemblance to native ligands. The γ-eudesmol compound has similarities to the Glu 166 amino acid residue, while the Linalol compound has similarities to His 164 amino acid residue, terpineol has similarities to all three amino acid residues, namely Cys 145, Gly 143, and Glu 166. Then there are no compounds. binds the same amino acids as the native ligand in steric interactions.

DISCUSSION

This research was conducted using the in silico processing method on the compound *Melaleuca leucadendron* L., where previously it had

been studied that the leaf extract of this plant has antiviral activity (Wang, *et al*., 2015). The selection of NSP5 receptors can efficiently block the proliferation of SARS-CoV, thus becoming an effective means for the treatment of COVID-19 in humans (Stobart, *et al*., 2013). At the NSP5 receptor, there is crystallographic ligand at the active site, namely non-covalent inhibitor X77 (N- (4-tert-butylphenyl) -N - [(1R) -2- (cyclohexalamino) -2-oxo-1- (pyridine-3-yl) ethyl] -1Himidazole-4-carboxamide) so that the target of tethering at the receptor is easier to do (Stobart, *et al*., 2013).

The pharmacokinetic predictions based on Table 2, it was found that the compound *Melaleuca leucadendron* L. can penetrate the blood-brain barrier (BBB) can increase the pharmacological activity of drugs in the human brain. should be considered to help reduce side effects and toxicity or to increase the efficacy of drugs whose pharmacological activity is present in the brain (Danta, *et al*, 2020). Then in the test compound from this plant has high gastrointestinal absorption (GIA), this shows that this compound is easily absorbed by the intestine so as to maximize efficiency and oral bioavailability. Thus P-gp substrates demonstrated the potential to modify concentrations in the brain even at clinically approved doses (Wang, *et al*, 2017).

The prediction of physicochemical properties was carried out Lipinski rule of five in evaluating the bioavailability of a compound. Based on Table 3, the compounds with the smallest molecular weight values are 1.8 cineole and linalol. The results showed that the molecular weight of a compound depends on the number of constituent atoms. The more constituent atoms, the greater the molecular weight, and vice versa (David, 2002).

In addition, it also looks at the log *p* value, hydrogen bonding, topological surface area, and torque. This shows that the compounds 1,8-cineole, terpineol, linalol, guaiol, α-eudesmol, β-selinenol and γ-eudesmol are predicted to have good absorption, good permeability, and good oral

bioavailability. This is because these compounds have good lipophilicity thereby increasing the selectivity of drug binding to target enzymes, the ability of ligands to bind to target enzymes or proteins, and have high absorption in the gastrointestinal tract and can penetrate the brain barrier so that it is predictable to penetrate the brain barrier. so that it can increase the pharmacological activity of drugs in the brain (Pires, *et al*., 2015).

Then in the prediction of toxicity (Table 4), compounds 1,8-cineole, terpineol, linalol, guaiol, α-eudesmol, β-selinenol and γ-eudesmol belong to class 5 toxicity ($2000 < LD_{50} \leq 5000$), so it is included in the toxicity category which is low with no symbol but needs to include a safety warning on the label (Makiyah and Tresnayanti, 2017). Meanwhile, remdesivir (the comparator drug) is categorized as class 4 toxicity because it has an LD_{50} value of 1190 mg/kg so it is dangerous if swallowed. Then the test compounds were predicted to cause no damaging effects on the liver, whereby drug-induced liver toxicity was one of the main reasons for drug failure and also led to the discontinuation of approved drugs from the market. Because adverse liver effects are unpredictable on patient health, the assessment of the risk of drug-induced liver injury is an important concern for the development of safe drugs. Then the test compound is not mutagenic, so it does not have an effect that causes cancer. However, in this study, all the test compounds caused sensitivity in the skin, so these compounds were not suitable for use as topical drugs (Jaganathan, 2021).

This validation process is seen from the value of RMSD, which is a value to obtain a similarity in results between the native ligand and the location of similar compounds with a value of <2 Å. The smaller RMSD value in the validation process indicates the position of the molecular docking test ligand close to the ligand from the crystallography results (Kontoyianni, 2004). Based on data from Table 1, it is known that the 6WNP receptor with native ligand U5G_401(A) has two

cavities that interact with the original ligand. However, in this study, cavity 1 was selected and used in this study because it has RSMD <2.

The next process *in silico* studies is molecular docking to see the ability of interactions carried out by visualization using computational methods to see clusters in compounds that have the potential to have activity as antivirals. The results from Table 5 Molecular docking, based on the results of the rerank score as the most important parameter to see the energy affinity in each compound obtained Terpineol in *Melaleuca leucadendron* L., has the lowest rerank score with an average of -119.743 kcal/mol (Figure 1), while to see the prediction of better bond stability, compared to comparison drugs, namely remdesivir with the average rerank score of -114.8175 kcal/mol and native ligand has a rerank score of -99.5461 kcal/mol with *Melaleuca leucadendron* L. The results of the interpretation of the rerank score value show that the higher the negative value of energy affinity, the stability of the bond between the ligand and the receptor becomes higher and the less energy needed to achieve stability (Syahputra, *et al*,2014). Terpineol has antimicrobial and antiviral properties due to the properties of alcohol in its structure (Patramurti, *et al*, 2020).

The result of the interaction of amino acid compounds is the result of seeing a binding between compounds and receptors, it can be seen in the pocket binding affinity of the active stus on the NSP5 receptor. Based on Figure 1, the blue color line is shown as a hydrogen bond, the red color line as a steric bond, and the green color line as an electrostatic bond (Table 6). In the results of the interaction of the test compound with the NSP5 receptor, namely 1,8 cineol, α-eudesmol, β-selinenol and Guaiol has no similarity with native ligands. The γ-eudesmol compound has similarities in the amino acid residue Glu 166, while the Linalol compound has similarities in the amino acid residue His 164, terpinol has similarities in the three amino acid residues, namely Cys 145, Gly 143, and Glu 166.

The results of the comparison drug remdesivir have only one similarity in the amino acid residue Glu 166. The similarity of amino acid residues has an important role where the potential of terpinol compounds has pharmacological activity similar to native ligand and remdesivir comparison drugs. This is in accordance with research from Konwar and Sarma (2021), namely inhibition of charged residues which include Cys145, glu 166 and gly 143. Therefore, blocking one of these residues can inhibit NSP 5 enzymatic activity.

Amino acid His (Histidine) is an amino acid that has a stabilization function at the active protease site with inhibition of activity on the protease by blocking transcription and also the viral replication process (Srivastrava, *et al.*, 2020). Gly (Glycine) is an amino acid that has a function in strengthening the body's connective body, so that viral invasion can be prevented, another function as an antiviral is to be responsible for the biochemical protein of SARS CoV-2 to inhibit the protease process (Melendez-Hevia, *et al*, 2021). Glu (Glutamate) is an amino acid that plays a role in the formation of stable compound complexes, and forms hydrogen bonds at the protease active site in the process of replication and gene expression of the SARS CoV-2 virus (Lokhande, *et al*, 2020).

Steric bonds have an influence with the occurrence of hydrogen bonds, steric bonds are referred to as van der walls bonds, these bonds provide an opportunity for a bond to become more stable. Steric bonds have two adjacent atoms with weak and non-specific tensile forces (Muchtaridi, *et al*, 2018). In the steric bond of native ligands has four bonds, namely Thr 190, Ser 144, Gly 143, and Cys 145, some compounds that have the same bond as native ligands are α-eudesmol and Guaiol. As for the comparison drug remdesivir, it also has similarities in one native ligand, namely Thr 190). This research is still limited to hypotheses as a first step in drug discovery. Further computational research is necessary to strengthen the theory before conducting experimental studies (*in vitro* and *in vivo*).

This has been proven in the research of Makson, *et al.* (2012), terpineol shows an inhibitory profile in neutrophil cell migration with a statistically significant decrease in cell numbers by inhibiting the synthesis of molecules involved in the inflammatory process, by suppressing NFKB signaling leading to a decrease in IL-6 production in lung epithelial cells, where in the event of excessive release of IL-6 into the vascular system contributes to cytokine storms (Magro, 2020). In addition, antiviral activity on terpineol may inactivate the herpes virus and possibly damage the virion sheath (Astani, *et al*, 2010).

Based on the results of this study, the terpineol compounds in *Melaluca leucadendron* L. can be used as a basis for developing effective oral drugs for COVID-19 in the future. Thus, terpineol can be an attractive candidate for the development of new drugs as COVID-19 antivirals, therefore it is hoped that future researchers can conduct *in vitro* and *in vivo* studies.

CONCLUSION

The value of the binding affinity for terpineol compounds is lower compared to remdesivir for the NSP5 receptor, but in the *in silico* amino acid analysis test, the compounds γ-eudesmol, linalool, and terpineol can be used as antivirals in COVID-19 because they have the same amino acids (Cys 145, Gly 143, and Glu 166) with remdesivir and native ligands.

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