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INTRODUCTION Coronavirus disease 2019 (COVID-19) is a disease caused by infection with the SARS-CoV-2 virus, which in January 2020 began to spread from Wuhan around the world (Hui et al., 2020). Globally, on August 30th 2020, there have been 24,854,140 confirmed cases of COVID-19, including 838,924 deaths (World Health Organization, 2020). One of the targets that have become a focus of research in the world for COVID-19 therapy was SARS-CoV-2 main protease (MPro) (Dai et al., 2020; Jin et al., 2020; Wu et al., 2020; Zhu et al., 2011).

The main protease is a key enzyme in the viral replication cycle, which proteolytically cleaves overlapping polyproteins pp1a and pp1ab into functional proteins, an essential step during viral replication (Du et al., 2004). Inhibition of these target proteins can result in disruption of the SARS-CoV-2 replication cycle (Mahmud et al., 2020; Pratama et al., 2020). The SARS-CoV-2 MPro in COVID-19 is not the same as the main protease in humans, so it becomes a promising therapeutic target (Ullrich & Nitsche, 2020).

Many compounds derived from medicinal plants have not been discovered and have great potential as therapeutic candidates (Mushtaq et al., 2018; Pan et al., 2013). In the discovery of COVID-19 therapy candidates, many natural products were used; some of them examined compounds from herbs against the SARS-CoV-2 using in silico method (Aanouz et al., 2020; Enmozhi et al., 2020; Joshi et al., 2020; Prasanth et al., 2020; Sukardiman et al., 2020). However, the discovery of compounds from medicinal plants with potential activity as SARS-CoV-2 MPro inhibitors is still being carried out today.

Etlingera elatior (known as Wualae in Tolakinese) is a medicinal plant from Indonesia which are found mainly on the island of Sulawesi, particularly Southeast Sulawesi (Fristiohady et al., 2020; Fristiohady et al., 2019). Etlingera elatior contains various types of compounds, including flavonoids and steroids with various pharmacological activities, one of them as antimicrobial (Sahidin et al., 2019; Wahyuni et al., 2018). However, there has been no specific development of its antiviral activity until now, especially to the SARS virus family. Flavonoid and steroid group compounds as found in E.

elatior have been widely researched on their activity to the SARS-CoV-2 and have shown promising results as a drug candidate for COVID-19 (Islam et al., 2020; Suwannarach et al., 2020). Therefore, this study aims to identify compounds from the flavonoid and steroid group contained in E. elatior, which have potential as SARS-CoV-2 MPro inhibitors. MATERIALS AND METHODS Ligand preparation The ligands used in this study were compounds contained in E. elatior. A total of seven compounds contained in E. elatior were selected in this study based on the KNApSAcK database (http://www.knapsackfamily.com/KNApSAcK/) (Afendi et al., 2012). The compound identity, as well as their two-dimensional structure, can be seen in Table I. The

three-dimensional ligand conformation was obtained from the KNApSAcK 3D database (http://knapsack3d.sakura.ne.jp/) (Nakamura et al.,

2013). The compounds saved in .mol format, then converted into .pdb format using the OpenBabel 2.4.1 GUI software. Table I. Identity of the compounds contained in E. elatior based on the KNApSAcK database No _C_ID KNApSAcK _Compounds _2D structure _ _1 _C00000947 _Catechin _/ _ _2 _C00002724 _Chlorogenic acid _/ _ _3 _C00005141 _Kaempferol 3-glucuronide _/ _ _4 _C00005373 _Isoquercetin _/ _ _5 _C00029821 _Sitostenone _/ _ _6 _C00030200 _Ergosterol peroxide _/ _ _7 _C00037023 _Demethoxy curcumin _/ _ _ Receptor preparation The three-dimensional structure of the SARS-CoV-2 MPro was obtained from the Protein Data Bank (PDB) website http://www.rcsb.org/pdb/.

The receptor with the PDB ID 6LU7 and resolution 2.16 Å was chosen. Furthermore, the unique ligands and water molecules were removed from the receptor. Then, the receptor was added with polar hydrogen and given a charge (Kollman charge). All preparation procedures were performed using AutoDock 4 software (Morris et al., 2009). Validation method The native ligand from the 6LU7 receptor (N-[(5-methylisoxazol-3-yl)carbonyl]alanyl-l-valyl-N~1~-((1R,2Z)-4-(benzyloxy)-4-oxo-1-{[(3R)-2-oxopyrrolidin-3-yl]methyl}but-2-enyl)-l-leucinamide; an inhibitor N3) (Jin et al.,

2020) was separated from the protein, then re-docked using AutoDock 4 software into the previous active site. The native ligand conformation from the docking procedure was taken and overlayed with the native ligand conformation before docking. Furthermore, validation is done by looking at root-mean-square deviation (RMSD) parameters, calculated using PyMOL software. An RMSD value of fewer than 2.0 Å indicates that the method is valid and can be used for the docking process (Bell & Zhang, 2019). Molecular docking simulation The simulation was carried out using previously valid parameters. The three-dimensional structure of the compounds in E.

elatior was docked to the SARS-CoV-2 MPro receptor's active site, which is then analyzed for its binding energy and amino acid interactions. The active site coordinates were x=-9.732, y=11.403, and z=68.925, with the dimensions of the grid box, were 64, 60, and 60 Å, respectively. The docking process in AutoDock 4 has been performed with 100 number of GA runs for each ligand. Prediction of Activity Spectra for Substances The in silico Prediction of Activity Spectra for Substances (PASS) were carried out to get biological activity spectra of compounds accessed through PASS web server (http://www.way2drug.com/PASSOnline/predict.php) (Marwaha et al., 2007). This server estimates the predicted activity spectrum of a compound as probable activity (Pa) and probable inactivity (Pi).

Prediction of this spectrum by PASS is based on structure-activity relationship analysis of the training set containing more than 205,000 compounds exhibiting more than 3,750 kinds of biological activities. For probabilities range, the Pa and Pi values vary from 0.000 to 1.000. The PASS prediction results were interpreted and used flexibly: Only activities with Pa > Pi are considered as possible for a particular compound. If Pa >0.7, the chance to find activity is experimentally high. If Pa is >0.5 but less than <0.7, the chance to find activity is experimentally low, but the compound is probably different from known pharmaceutical agents. If Pa <0.5, the chance to find activity is experimentally is low, but the chance to find structurally NCE's is high.

RESULTS AND DISCUSSION Validation method Validation was carried out to see the strength of affinity prediction through re-docking the native ligand into its binding site. The validation results can be seen in Figure 1. It showed that the RMSD value of the native ligand was 1.3 Å, with the binding energy obtained was -7.30 kcal/mol. This shows that the molecular docking method used is valid because of the RMSD value below 2.0 Å. / Figure 1. Validation of the SARS-CoV-2 MPro receptor PDB ID 6LU7, the native ligand position before docked (red) and after docked (blue) overlayed with RMSD 1.3 Å Molecular docking simulation The bioactive compounds in E.

elatior after docked showed varied binding energies as shown in Table II. In general, E. elatior compounds from the database were dominated by polyphenols such as flavonoids and phenylpropanoid, then the steroid compounds. The flavonoid compounds such as quercetin, curcumin, etc., have been previously studied in silico against the SARS-CoV-2 MPro receptor, as Cherrak et al. (2020) reported. Meanwhile, the type of steroid has been previously studied by Ghosh et al. (2020). As shown by the docking results in Table II, the steroid group showed better inhibitory activity than the flavonoid groups to SARS-CoV-2 MPro receptor.

The docking results show that the steroids' binding energy, namely ergosterol peroxide and sitostenone, was -10.4 and -9.17 kcal/mol, respectively. Compared to the flavonoid group, the lowest binding energy was shown by catechins (-8.64 kcal/mol), while the binding energy of the other compounds was in the range of -6.53 to -7.9 kcal/mol. Table II. The binding energy of the compounds in E. elatior to the SARS-CoV-2 MPro receptor Compounds _Compound group _Binding energy (kcal/mol) _Ki (nM) _ _Catechins _Flavonoid _-8.64 _467,520 _ _Chlorogenic acid _Phenyl-propanoid _-6.53 _16,380 _ _Kaempferol 3-glucuronide _Flavonoid _-7.08 _6,450 _ _Isoquercetin _Flavonoid _-7.09 _6,310 _ _Sitostenone _Steroid _-9.17 _188.59 _ _Ergosterol peroxide _Steroid _-10.4 _23.62 _ _Demethoxycurcumin _Polifenol _-7.9

_1,630 _ _ Molecular interactions The top two compounds that ranked by their binding energy, ergosterol peroxide and sitostenone, were analyzed for their amino acid interactions with the SARS-CoV-2 MPro receptor and compared with the interactions of the native co-crystal ligand (N3 inhibitor). The interactions' tabulation data can be seen in Table III, while the two-dimensional interaction can be seen in Figure 2. The native ligand forms hydrogen bonds with amino acids Gly-143; Cys-145; Glu-166; Gln-189; and Thr-190.

The native ligand also forms several types of hydrophobic interactions with residues His-41; Met-49; Met-165; Leu-167; Pro-168; and Ala-191, while the rest were Van der Waals interactions with ten residues. The steroid sitostenone forms a hydrogen bond with the amino acids Gln-192. Ergosterol peroxide forms hydrogen bonds with Thr-26 and Gly-143. Sitostenone forms hydrophobic interactions with six amino acid residues Leu-27; His-41; Met-49; Cys-145; His-163; and Met-165, as well as Van der Waals interactions with 13 other amino acid residues.

Ergosterol peroxide compounds form hydrophobic interactions with five amino acid residues, specifically His-41; Met-49; Cys-145; Met-165; and Arg-188, and form Van der Waals interactions with ten other amino acid residues. Overall, the interaction on sitostenone is more similar to the interaction of native ligands with a similarity level of 82.6% compared to ergosterol peroxide with 56.52%. The interaction pattern shows that the hydrophobic group on the ligands influences the SARS-CoV-2 MPro receptor's affinity. This is what causes the steroid class compounds to give good affinity for this molecular docking simulation.

This is also related to the native ligand structure, an inhibitor of SARS-CoV-2 MPro, which is composed of several non-polar peptide groups. In terms of three-dimensional interactions (Figure 3), ergosterol peroxide does not occupy the protein's surface as large as the native ligand. However, the functional groups on its compounds bind to a larger hydrophobic region in the protein surface (brown area), and one oxygen group can interact in the polar region (blue area).

Simultaneously, sitostenone compounds form a similar orientation to the native ligand in occupying the surface of the receptor's binding pocket. Table III. Amino acid interactions of native and test ligands Interaction residues _ _N3 inhibitor (native ligand) _Sitostenone _Ergosterol peroxide _ _Thr-24 _- _- _ _Thr-25 _- _Thr-25 _ _Thr-26 _Thr-26 _Thr-26 _ _- _Leu-27 _Leu-27 _ _His-41 _His-41 _His-41 _ _Met-49 _Met-49 _Met-49 _ _- _- _Pro-52 _ _- _- _Tyr-54 _ _Phe-140 _- _- _ _Leu-141 _Leu-141 _- _ _Asn-142 _Asn-142 _Asn-142 _ _Gly-143 _Gly-143 _Gly-143 _ _Ser-144 _Ser-144 _- _ _Cys-145 _Cys-145 _Cys-145 _ _His-163 _His-163 _- _ _His-164 _His-164 _His-164 _ _Met-165 _Met-165

_Met-165 _ _Glu-166 _Glu-166 _Glu-166 _ _Leu-167 _Leu-167 _- _ _Pro-168 _Pro-168 _- _ _Asp-187 _- _Asp-187 _ _Arg-188 _Arg-188 _Arg-188 _ _Gln-189 _Gln-189 _Gln-189 _ _Thr-190 _Thr-190 _- _ _Ala-191 _Ala-191 _- _ _Gln-192 _Gln-192 _- _ _The similarity of interaction with native ligand (%) _82.6 _56.52 _ _ / A / B / C Figure 2. Two-dimensional interactions of native ligand (A), sitostenone (B), and ergosterol peroxide (C) to SARS-CoV-2 MPro receptor / A / B / C Figure 3.

Three-dimensional interactions of native ligand (A), sitostenone (B), and ergosterol peroxide (C) to SARS-CoV-2 MPro receptor Prediction of Activity Spectra for Substances The PASS prediction was carried out on native ligand, ergosterol peroxide, and sitostenone compounds to see and compare their probability level as COVID-19 therapy (Table IV). The native ligand was predicted to have activity in severe acute respiratory syndrome treatment, 3C-like protease (Human coronavirus) inhibitor, protease inhibitor, and antiviral, with Pa value of 0.357; 0.358; 0.321; and 0.312, respectively.

However, ergosterol peroxide and sitostenone were only predicted to have antiviral activity with a Pa value of 0.418 and 0.495, respectively. Table IV. In Silico PASS Prediction results Ligands _Activities prediction _Pa _Pi _ _Native _Severe acute respiratory syndrome treatment _0.357 _0.005 _ _ _3C-like protease (Human coronavirus) inhibitor _0.358 _0.006 _ _ _Protease inhibitor _0.321 _0.008 _ _ _Antiviral _0.312 _0.033 _ _Sitostenone _Antiviral _0.495 _0.026 _ _Ergosterol peroxide _Antiviral _0.418 _0.073 _ _ CONCLUSION Compounds in E.

elatior (ergosterol peroxide and sitostenone) showed potential as inhibitor candidates for the SARS-CoV-2 MPro receptor. Although the PASS server's in silico prediction does not show specific activity against the receptor like native ligand, the bioactive compounds were predicted to have potential as antiviral. Moreover, from the molecular docking simulation, ergosterol peroxide and sitostenone showed better affinity against SARS-CoV-2 MPro compared to flavonoid groups and the native ligand.

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