Molecular docking study of fatty acids from *Pliek U Oil* in the inhibition of SARS-CoV-2 protein and enzymes

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Abstract. This study aimed to analyze the fatty acid in *Pliek U oil* andevaluate its inhibitor potential based on the interaction to several proteins and enzymes in SARS-CoV-2 using the in silico approach. *Pliek U oil* containing capric acid, caprylic acid, lauric acid, linoleic acid, myristic acid, oleic acid, and palmitic acid, with oleic acid as a dominant substance. Molecular docking analysis showed that linoleic acid has the best interaction to the receptors with the lowest binding affinity to 3CLpro (6LU7), Spike protein (6VXX), PLpro (6WX4), RdRp (6M71), E protein (5X29), and Spike Ectodomain Structure (6VYB) of -4.9, -5.8, -4.7, -4.3, -5.3 and -5.5 kcal/mol, respectively. The finding suggests that the binding of linoleic acid to the SARS-CoV-2 protein and enzyme may cause impairment of viral attachments to host cells, thus reducing infectivity in COVID-19 patients.

1. Introduction
The end of 2019 saw the rise of a new pneumonia case in Wuhan, China. A few days later, China's health authorities confirmed that this case was related to coronavirus disease infection, hereinafter known as COVID-19 [1]. The first clinical report showed that 13 out of 14 (92%) COVID-19 patients had comorbidities [2], such as cardiovascular, diabetes, hypertension, and chronic obstructive pulmonary disease. Subsequent findings reported that 64 of the 138 cases (46.4%) of COVID-19 patients had known comorbidity. Other findings also prove that COVID-19 patients admitted to the ICU have high comorbidity of approximately 72.2%. This fact shows that comorbidity is a risk factor for patients of COVID-19 [3]. Therefore, a systematic risk evaluation or management is needed, not only for comorbidity but also risk management for the underlying disease in COVID-19 patients. Globally, at least 7900 deaths have been directly linked to COVID-19 and will continue to increase every day, as a vaccine has yet to be found to eradicate this virus.
The search for an effective cure against this disease continues to be conducted, through finding or synthesizing new active compounds. This work is handling by the expert whilst the pandemic is still ongoing by the pathogens. The alternative way to find a cure is by testing compounds that already have drug activity against the pathogens. It has been known that natural products have been widely reported having that activity to be antimicrobial [4,5], antibacterial [6–8], antifogfilm [9], antioxidant [10,11], and even antiviral [12]. The natural products are mostly found in plants as metabolites in almost plant parts [13]. It produces by itself through metabolism [14], or by endophyte [15,16]. The natural product is also preferred to be drugs in offering a safer, low side effect and green chemistry materials[17,18].

Fatty acid can be obtained naturally from animal and plant [19], coconut (Cocos nucifera) is one of a natural product as sources of fatty acid. In Aceh Province, coconut meat is traditionally used to produce fermented-coconut namely Pliek U. This process also produce a secondary product called Pliek U oil [20]. Earlia et al., reported that Pliek U oil contained capric acid, caprylic acid, lauric acid, linoleic acid, myristic acid, oleic acid, and palmitic acids, with oleic acid as a dominant substance [21,22], whereas the fatty acid content in Pliek U oil has a potential to be used as a pharmacy resource. Several studies reported that fatty acid affecting to bacterial and fungi, but limited reports focus on antiviral agents. Oleic acid reported has moderate antiviral activity against tobacco mosaic virus [23]. Fatty acids are one of the compounds reported to have reasonably good antiviral activity [24].

There are several essential protein targets for the COVID-19 therapy including PLpro, 3CLpro, E protein, Spike (S) glycoprotein, C-terminal RNA binding domain (CRBD), N-terminal RNA binding domain (NRRBD), helicase and RdRp[25]. Some bioactive compounds have been plainly predicted as therapeutic agent candidates for COVID-19 infection. The potential of fatty acid in case of therapeutic agent for SARS-CoV-2 protein and enzyme are still limited reports. Recent in silico studies have shown that fatty acids have very stable interactions with receptor proteins from bond energy and structural orientation [22]. These are well potential for fatty acid to be tested as the antiviral against SARS-CoV-2. The resources of fatty acid are widely found on palm type such as coconut. As a product from fermented coconut, Pliek U oil should be contained much fatty acid.

The interaction of a chemical compound with receptor proteins is generally carried out through a spectroscopic approach, such as UV-Vis, sensors, lasers, and electromagnetics [26,27]. However, this method requires a lot of time and money. Therefore, a fast, inexpensive approach through computational methods, both virtual and in silico or molecular docking, is needed for an alternative in regard to the urgency related to COVID-19 research. In this study, a molecular docking study was carried out between the fatty acids contained in Pliek U against the SARS-CoV-2 protein and enzyme.

2. Material and methods

2.1. Molecular docking

2.1.1. Ligand determination. The compounds (ligands) used in the molecular docking study are fatty acid compounds contained in PUO and EPUOE in the form of capric acid, caprylic acid, lauric acid, linoleic acid, myristic acid, oleic acid, and palmitic acid.

2.1.2. Receptor determination. The nine SARS-CoV-2 proteins selected as receptors were: Main protease (Mpro) / 3CLpro (Protein Data Bank (PDB) code, PDB: 6LU7); Spike glycoprotein (S) (PDB code: 6VXX); and PLpro (PDB code: 6WX4); RdRp (PDB code: 6M71); Protein E (PDB code: 5X29); Nsp15 (PDB code: 2H85); Complex Nsp7,8,12 (PDB code: 6NUR); Receptor-binding domain, RBD (PDB code: 6YLA) and Spike ectodomain structure, SES (PDB code: 6VYB).

2.1.3. Preparation of ligands and receptors. The three-dimensional (3D) structure of the nine SARS-CoV-2 proteins as receptors was taken from the Protein Data Bank, PDB (http://www.rcsb.org/pdb) downloaded as files in pdb format. Files are stored in special folders for docking treatment. The file was opened using BIOVIA Discovery Studio Visualizer 2020. Water molecules and ligands attached to the receptors were removed, and the receptors were stored in pdb (name: receptor) format. Furthermore,
Autodock Tools [28] was then used, and polar hydrogen atoms were added to the receptors. The file was then saved in the pdbqt format (name: receptor.pdbqt).

The ligand structure was obtained from the PubChem website (http://pubchem.ncbi.nlm.nih.gov). The search was performed by entering the name of the ligand in the search option. The file of each ligand was then downloaded and saved. Files were downloaded in sdf format and then stored in a particular folder for docking treatment. Files are converted to pdb format using Open Babel [29] and saved in pdb format (name: ligand). The pdb-format ligands were opened using Autodock Tools. Torque adjustment was made by detecting the root and adjusting as desired. The file was then saved in the pdbqt format (name: ligand.pdbqt).

2.1.4. Active site determination. The location of amino acids as active sites at the receptors where the ligands will interact can be determined using the Autodock Tools. By arranging it on a three-dimensional map, a grid box was then created in the receptor regions where the ligands interact. The determination of this map can be based on the type of docking used. The three-dimensional map was made as wide as the receptor size, ensuring ligands to be docking to all parts of the receptors (blind docking). In 3CLpro docking, for example, the binding site is known to be the protein, so the three-dimensional map is only made as wide as the docked area (targeted docking).

2.1.5. Receptor-ligand docking. Docking was done using Autodock Vina [30]. The ligands and receptors saved in pdbqt format were copied to the Autodock Vina file to the docking folder. Then vina configuration file was typed into notepad and saved with the name 'conf.txt.' The Vina program was then run through the command prompt which was directed to the to-be-docked folder with the formula below. The docking results were then obtained from the output in a notepad format.

\[
vina \text{ –config } \text{conf.txt –log log.txt.} \tag{1}\]

2.1.6. Analysis and visualization. The docking calculation result was shown from the output in notepad format. The docking ligand confirmation was then determined by selecting the pose with the highest affinity (the most negative Gibbs free energy). The results of the visualization of three-dimensional (3D) and two-dimensional (2D) structures from the results of docking calculations were carried out using BIOVIA Discovery Studio Visualizer 2020. Previously, the highest affinity selection was carried out using the vina program which was run through the command prompt which was directed to the docking calculation results folder, with the formula:

\[
vina\text{_split –input out.pdbqt} \tag{2}\]

Furthermore, the respective affinity values of the ligands were obtained in the pdbqt format. The files of receptors and ligands with the highest affinity in the pdbqt format were opened using the BIOVIA Discovery Studio Visualizer 2020. This enables the authors to see the interaction between ligands and receptors in the form of three-dimensional (3D) structures and show 2D diagrams for two-dimensional (2D) structures. Both files are saved in image files format.

3. Result
The content of fatty acid compounds from the analysis of Pliek U oil using GC-MS can be seen in Table 1 [21]. The results of the molecular docking analysis in the form of binding affinity between ligands (fatty acid compounds) with nine protein and enzyme receptors from SARS-CoV-2 can be seen in Table 2. The results of the binding affinity analysis show that several fatty acids from Pliek U oil have various binding values against some SARS-CoV-2 enzymes and proteins.

The image of code A shows the results of the docking analysis showing the interaction between ligands (fatty acids) and amino acid residues from the SARS-CoV-2 protein in the form of a three-dimensional (3D) structure. The image of the code B shows the results of the docking analysis showing
the types of interactions that occur between ligands (fatty acids) and amino acid residues of the SARS-CoV-2 protein in two-dimensional (2D) form. Visualization results in 3D and 2D are performed based on the selection of poses with the highest affinity (most negative Gibbs free energy) of each fatty acid against the nine enzymes and SARS-CoV-2 protein.

**Table 1.** The results of the analysis of *Pliek U* oil using GC-MS [21].

| No | Common Name     | Chemical Structure                  | C:D  |
|----|-----------------|-------------------------------------|------|
| 1  | Caprylic acid   | CH₃(CH₂)₆COOH                       | 8:0  |
| 2  | Capric acid     | CH₃(CH₂)₈COOH                       | 10:0 |
| 3  | Lauric acid     | CH₃(CH₂)₁₀COOH                      | 12:0 |
| 4  | Myristic acid   | CH₃(CH₂)₁₂COOH                      | 14:0 |
| 5  | Palmitic acid   | CH₃(CH₂)₁₄COOH                      | 16:0 |
| 6  | Oleic acid      | CH₃(CH₂)₇CH=CH(CH₂)₇COOH            | 18:1 |
| 7  | Linoleic acid   | CH₃(CH₂)₄CH=CHCH=CH(CH₂)₇COOH       | 18:2 |

**Figure 1.** Molecular docking positions: Linoleic acid (A) and Palmitic acid (B) to the 3CL\textsuperscript{pro} receptor.

**Figure 2.** Caprylic acid's molecular docking position to the PL\textsuperscript{pro} receptor.

**Figure 3.** Caprylic acid's molecular docking position against the Receptor Binding Domain (RBD).
Figure 4. Molecular docking position: Capric acid (A), Caprylic acid (B), Lauric acid (C), Linoleic acid (D), Myristic acid (E), Oleic acid (F), Palmitic acid (G) to receptors ectodomain structure.

Table 2. Binding affinity between ligands (fatty acids from Pliek U) and some SARS-CoV-2 receptors.

| Ligand C:D | PubChem CID | Binding affinity (Kcal/mol) | SARS-CoV-2 Receptor |
|------------|-------------|-----------------------------|---------------------|
|            |             | M<sup>Pro</sup> | S Pro | P<sub>LD<sup>Pro</sup> | RdRp | E Pro | Nsp<sub>15</sub> | Nsp<sub>7,8,12</sub> | SES | RBD |
| 8:0 (FR)   | 379         | -3.8           | -3.8  | -4.2           | -3.9 | -4.0 | -3.8             | -3.8             | -4.5 | -4.0 |
| 8:0 (NMD)  | 379         | -4.1           | -4.7  | -3.7           | -4.2 | -4.5 | -3.7             | -4.4             | -4.5 | -4.4 |
| 10:0 (FR)  | 2969        | -4.1           | -4.2  | -4.3           | -3.6 | -4.4 | -3.8             | -4.1             | -4.0 | -4.9 |
| 10:0 (NMD) | 2969        | -3.8           | -4.3  | -3.3           | -4.4 | -3.2 | -3.7             | -4.7             | -4.7 | -3.9 |
| 12:0 (MUF) | 3893        | -4.4           | -5.0  | -4.2           | -3.4 | -4.6 | -4.0             | -3.8             | -5.1 | -4.1 |
| 12:0 (MD)  | 3893        | -4.5           | -4.4  | -4.2           | -3.7 | -4.5 | -4.1             | -3.8             | -5.0 | -4.3 |
| 14:0 (SM)  | 11005       | -4.3           | -5.3  | -4.3           | -3.7 | -4.9 | -3.6             | -3.5             | -5.2 | -4.0 |
| 14:0 (CPM) | 11005       | -3.9           | -3.7  | -3.5           | -4.1 | -4.7 | -3.5             | -4.1             | -4.4 | -3.9 |
| 16:0 (FR)  | 985         | -4.5           | -5.0  | -4.2           | -3.5 | -4.4 | -3.6             | -3.7             | -4.8 | -4.1 |
| 16:0 (NMD) | 985         | -3.9           | -4.5  | -3.8           | -3.8 | -4.1 | -3.8             | -4.7             | -4.4 | -4.4 |
| 18:1 (SM)  | 445639      | -4.5           | -3.2  | -3.7           | -4.1 | -4.9 | -3.9             | -4.9             | -4.5 | -4.2 |
| 18:1 (CPM) | 445639      | -4.6           | -4.7  | -4.0           | -3.4 | -4.9 | -3.9             | -3.6             | -4.8 | -4.1 |
| 18:2 (MD)  | 5280450     | -4.5           | -5.8  | -4.4           | -4.3 | -5.3 | -4.4             | -4.2             | -5.0 | -4.8 |
| 18:2 (MUF) | 5280450     | -4.9           | -5.4  | -4.7           | -3.8 | -4.7 | -4.6             | -4.3             | -5.5 | -4.3 |
4. Discussion

4.1. GC-MS analysis

Pliek U oil (PUO) and Pliek U oil ethanol extract (EPUOE) were analyzed using GC-MS. GC-MS is an instrument used for separation and identification. The results of GC were obtained in the form of chromatographic peaks, and MS will be obtained in the form of a mass spectrum. The compound results obtained from the analysis of Pliek U oil (PUO) and Pliek U oil ethanol extract (EPUOE) were caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, oleic acid, and linoleic acid [21].
4.2. Molecular docking

The binding affinity results show that linoleic acid ligands have the highest binding affinity compared to other ligands at the 3CLpro receptor (PDB code: 6LU7), Spike protein (PDB code: 6VXX), PL.pro (PDB code: 6WX4), RdRp (PDB code: 6M71), protein E (PDB code: 5X29), and Spike Ectodomain Structure (PDB code: 6VYB) with an energy binding affinity of -4.9, -5.8, -4.7, -4.3, -5.3, and -5.5 kcal/mol. At the 6NUR receptor, the oleic acid ligand has the highest binding affinity value of -4.9 kcal/mol. At the 6YLA receptor, the capric acid ligand has the highest binding affinity value of -4.9 kcal/mol. Gibbs's energy theory states that the greater or more negative the energy produced from the bonds between the ligands and the receptors are, the more stable the bonds [21]. The higher or more negative ΔG value generated during the interaction of ligands and receptors, the stronger the ligand complex bonds with the receptors. This is due to compounds with receptors having stability and strength of non-covalent interactions, enabling easier entrance to cells and cause cells to die because they interfere with DNA replication or cellular metabolic processes [31].

Molecular docking results were visualized in three-dimensional (3D) and two-dimensional (2D) structures from the results of docking calculations carried out using the BIOVIA Discovery Studio Visualizer 2020. The interactions that occur were in the form of hydrogen bonds, hydrophobic interactions, electrostatic interactions, and unfavorable acceptors. Hydrogen bonds are interactions between hydrogen atoms (H), which are covalently bonded with atoms such as fluorine (F), nitrogen (N), and oxygen (O). The more hydrogen bonds with amino acid residues are formed, the stronger the bonds will be (Glowacki et al., 2013). Based on the 2D structure, hydrogen bonds are obtained in the interaction between capric acid and Spike Ectodomain Structure, caprylic acid and spike protein, caprylic acid and Spike Ectodomain Structure, caprylic acid and Receptor Binding Domain, lauric acid and Spike protein, lauric acid, and Spike Ectodomain Structure, lauric acid and protein E, linoleic acid and Spike Ectodomain Structure, myristic acid and Spike Ectodomain Structure, oleic acid and Spike Ectodomain Structure, oleic acid and E protein, palmitic acid, and 3CLpro, as well as palmitic acid and spike protein. Most hydrogen bonds are found in palmitic acid fatty acids interacting with 3CLpro, namely the amino acid residues of Cys A: 145, Leu A: 141, and Ser A: 144. In addition, the most hydrogen bonds occur in the Spike Ectodomain Structure protein (PDB code: 6VYB).

Hydrophobic interactions are interactions that tend to avoid the liquid environment and gather in the globular protein structure [32]. Included in hydrophobic interactions are pi-Sigma and alkyl or pi-alkyl [33]. Hydrophobic interactions are amino acid residues that are nonpolar and tend to form groups in the interior of the protein so that they can prevent or block the protein from coming into contact with water [34]. Based on the 2D structure, hydrophobic interactions were obtained on the tethering between the Spike Ectodomain Structure receptor with caprylic acid ligands, caprylic acid, lauric acid, linoleic acid, myristic acid, oleic acid and palmitic acid (Figure 4), E protein with caprylic acid ligands, lauric acid, linoleic acid, myristic acid, and oleic acid (Figure 5), as well as spike proteins that bind to caprylic acid, lauric acid, myristic acid, oleic acid and palmitic acid ligands (Figure 6). Also, the bond between the PL.pro receptor and the Receptor Binding The respective domains that each bind to caprylic acid ligands (Figure 2 and Figure 3), as well as bonds between linoleic acid and palmitic acid ligands to the 3CLpro receptor (Figure 1).

Electrostatic interactions are interactions that occur between atoms that are not covalent due to differences in polarity; thus, the interactions that occur are weak and loose but have the potential to inhibit the intended receptors because of the large number of bonds [35]. Included in electrostatic interactions are salt bridges and van der waals bonds [36]. Based on the 2D structure, electrostatic interactions were obtained in the interactions between linoleic acid and palmitic acid ligands against the 3CLpro receptor (Figure 1), the bond between the PL.pro receptor and the Receptor Binding Domain, each of which binds to caprylic acid ligands (Figures 2 and 3), Spike Ectodomain receptors Structure with caprylic acid ligands, caprylic acid, lauric acid, linoleic acid, myristic acid, oleic acid and palmitic acid (Figure 4), protein E with caprylic acid ligands, lauric acid, linoleic acid, myristic acid, and oleic acid (Figure 5), as well as the spike protein which binds to the ligands of caprylic acid, lauric acid, myristic acid, oleic acid and palmitic acid (Figure 6).
Unfavorable Donor to Donor bond is a bond that shows the repulsive force between two molecules. The formation of this bond can reduce the stability of other types of bonds, affecting the stability of the ligands that will be used as drug candidates [37].

According to [38], the binding site area of the 3CLpro enzyme is located between the aspartate catalytic residue, which contains other supporting sub-units, the residue is located at Asp-A: 25, Thr-A: 26, Gly- A: 27 and His-A: 41. The linoleic acid ligand that binds to these receptors precisely binds to one of these residues. This proves that the ligand is predicted to be able to inhibit the performance of this receptor with maximum results.

Spike glycoprotein (S protein) receptors, both in the form of closed state (6VXX) and open state (6VYB) are receptors that are associated with the human ACE2 (hACE2) receptors; thus they do not have a target structure equipped with inhibitors in the Protein Data Bank (PDB). Inhibition occurs on the surface between the two receptors (S protein and hACE2) so that the binding site area is no longer the residue is located at Asp

5. Conclusion
GC-MS analysis showed that the PUO and EPUOE contained fatty acids (according to the order of Table 1) with oleic acid as a dominant substance. Based on the results of molecular docking, the poses with the highest affinity (most negative Gibbs free energy), are the linoleic acid fatty acids interacting with the 3CLpro receptor (PDB code: 6LU7), Spike protein (PDB code: 6VXX), PLpro (PDB code: 6WX4), RdRp (PDB code: 6M71), protein E (PDB code: 5X29), and Spike Ectodomain Structure (PDB code: 6VYB) with the affinity binding of -4.9, -5.8, -4.7, -4.3, -5.3, and -5.5 kcal/mol, respectively.

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