Analysis of flavonoid compounds of Orange (Citrus sp.) peel as anti-main protease of SARS-CoV-2: A molecular docking study

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Abstract. SARS-CoV-2 is a new type of coronavirus that causes COVID-19. This virus was first detected in the city of Wuhan, China, at the end of 2019, and until now, it has become a global pandemic. The FDA recently approved Veklury (remdesivir) for adults and certain pediatric patients who have COVID-19 and are sick enough to require hospitalization. One of the potential drug target candidates for SARS-CoV-2 is the main protease (Mpro). The purpose of this study was to analyze the flavonoid compounds found in orange (Citrus sp.) peel to determine its potential as anti-Mpro through a molecular docking study. The compounds were initially screened for drug-like properties and then docked using Autodock Vina in the PyRx emulator software. The docking results were visualized using the BIOVIA Discovery Visualizer 2020. The result showed that the binding free energy of hesperidin (-8.6 kcal/mol) was higher than nelfinavir (-8.5 kcal/mol). In addition, hesperitin (-7.3 kcal/mol), sakuranetin (-7.1 kcal/mol), isosakuranetin (-7.2 kcal/mol) and tetra-o-methylscutallerin (-6.8 kcal/mol) exhibited lower binding free energy value than control. Based on these results, hesperidin has the potential as an inhibitor of the main protease's SARS-CoV-2.

1. Introduction

Coronavirus Disease-2019 or COVID-19 is an infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus-2 or (SARS-CoV-2), which was first detected in Wuhan City, Hubei Province, China at the end of 2019 [1]. SARS-CoV-2 is a member of a virus with positive RNA containing about 30,000 nucleotides that are replicated by two polyproteins (pp), namely pp1a and pp1ab [2]. In the replication stage, polyproteins go through a cleavage process by two protease enzymes, main protease (Mpro) and papain-like protease (PLpro) [3]. Mpro digests polyproteins to produce a non-structural protein (nsp) at 11 out of a total of 16 locations, including those responsible for the formation of RNA-dependent RNA polymerase (RdRp), which is involved in transcription and replication [4]. Based on this, Mpro is known to play an important role in the virus life cycle and is one of the antiviral candidates in the treatment of SARS-CoV-2.

With a tropical temperature and abundant rainfall, Indonesia's tropical rainforest is home to an abundance of wildlife [5]. The forest provides food, infrastructure, and even therapeutic ingredients to
millions of species of creatures, including humans. Ancient culture made use of natural resources for medical reasons sometimes referred to as a natural product [6]. It is even more popular nowadays because of the advantages of the natural product compared to synthetic material in offering safer, low side effects and green chemistry [7] materials. Many research reported either by in-silico [8,9] or in-vivo that the natural product from the plant contains various medical activities to be antimicrobial [10], antiviral [11], antibacterial [12–14], antibiofilm [15], antioxidant [16,17], and so on.

The natural product is mostly found in the plant, where it is synthesized as a metabolite and stored in its anatomies like root, bark [18], stem, flower, and fruit [19]. Other sources are endophytes, bacteria [20], or fungus [21] that live within plants. The content of metabolites in plants, qualitatively and quantitatively, varies greatly. The variation is caused not only by the type of plant but also by the geological and geographical origins of the plant. The plant that grows in high salinity areas like geothermal [22–24] or limestone contains more various and higher metabolites.

Research for natural-based antivirals against the SARS-CoV-2 virus has a major contribution. Various studies have shown that certain plant secondary metabolites have the potential to have antiviral activity [25], which can help fight the coronavirus through its bioactive content [26]. Oranges fruit (Citrus sp.) can be used in inhibiting beta-coronaviruses, including SARS-CoV-2, as therapeutic agents, for instance, preventive or prophylactic agents [27]. Oranges have a high concentration of flavonoid chemicals in their secondary metabolites, including the citrus fruit-specific hesperidin, naringin, and tangeretin components. These compounds are present in whole fruit but are more abundant in the skin [28].

Computer-assisted drug discovery is currently being conducted [29,30], especially in the discovery and development of COVID-19 drugs [31,32]. The use of three-dimensional structure information for biological targets in several computational approaches such as molecular docking which is use to see energy bonding, molecular interactions and conformational changes of the structure of the test compound or ligand [33,34]. This research aims to identify and analyze the flavonoid compounds in the orange peel that have the potential inhibitory effect on the M\textsuperscript{pro} of SARS-CoV-2 through molecular docking studies. The flavonoid compounds that are evaluated must adhere to the Lipinski Rule of Five (RO5) in order to determine if they possess chemical and physical characteristics that make them suitable for oral administration by examining their solubility or permeability during the absorption process [35]. Comparison with the antiviral protease inhibitor nelfinavir was evaluated by examining the binding free energy(ΔG) in the in silico calculation using Autodock Vina in PyRx emulator software. Additionally, the interaction between ligands and macromolecules and amino acid residues was examined using the Biovia Discovery Visualizer 2020.

2. Methods

2.1. Determination of ligands

The selection of plant-derived compounds as ligands was based on Hernandez, et al., [36]. They conducted a study on secondary metabolites in oranges (Citrus sinensis) and discovered 54 flavonoid class molecules distributed throughout the fruit, particularly the peel. The compounds were checked for their availability and preliminary screening for physical and chemical properties on Pubchem https://pubchem.ncbi.nlm.nih.gov using the compound names as the keyword. If the compounds were available, then the three-dimensional structures were downloaded and saved in .sdf format. Based on that, several compounds have been chosen, including tetra-o-methylscutellarin, sakuranetin, hesperitin isosakuranetin dan hesperidin. The compounds were evaluated if they complied the Lipinski rule of Five (RO5) using the SWISSADME predictor (http://www.swissadme.ch).

2.2. Preparation of the receptor

The small resolution M\textsuperscript{pro} structure was downloaded from the Protein Data Bank (PDB ID: 6LU7) and saved in .pdb format. This macromolecule was separated from its native ligand (N3 inhibitor) using the Discovery Visualizer 2020.
2.3. Validation of target protein-ligand complex structures
To validate the molecular docking process, the M\textsuperscript{pro} macromolecule was docked with its native ligand in two ways: blind docking and specific docking. This step was conducted to ensure that the docking system remained within the active site of binding [37]. Blind docking results indicated that the active site of the enzyme was situated between the coordinates x = -8.583981, y = 16.125963 and z = 66.739111, while the specific docking resulted in coordinates x = -10.524278, y = 12.178833, z = 69.749296. These results indicated that the grid-boxes resulting from the specific docking and blind docking were slightly different. This shows that the docking took place on the active side of M\textsuperscript{pro}, implying that the subsequent docking procedure will produce optimal outcomes.

2.4. Molecular docking
This molecular docking was performed using Autodock Vina in the PyRx emulator software. Molecular docking was carried out in the grid-box with the following coordinates: x = -10.711837, y = 12.411388 and z = 68.831286, with the dimensions of 25 x 25 x 25 Å. The analysis of molecular docking was assessed based on the binding free energy ($\Delta G_{\text{bind}}$) and the interaction of ligands with amino acid residues of M\textsuperscript{pro} using the BIOVIA Discovery Visualizer 2020.

3. Results and discussion
The 6LU7 macromolecule has two main chains where the main protease is in the A chain, which is composed of 306 amino acids. The 6LU7 also has a second or native ligand in the C chain. This ligand is an N3 inhibitor or Michael acceptor inhibitor, which is known as the M\textsuperscript{pro} inhibitor in other coronaviruses such as SARS-CoV and MERS-CoV and is a strong candidate as an antiviral agent in bronchitis viral infection [38]. Compounds found in the orange peel that was evaluated as candidate inhibitors of M\textsuperscript{pro} in the study included tetra-O-methylscutellarin, sakuranetin, hesperitin, hesperidin and isosakuranetin [36]. Each of these compounds was pharmacokinetically evaluated using the RO5 parameter. The Lipinski Rule contains the stipulation that a compound has more than 5 Hydrogen bond donors, 10 Hydrogen bond acceptors, a molecular weight greater than 500 g mol, and a partition coefficient or Log P (CLogP) value greater than 5 (or Moriguchi Log P / MlogP.4.15), the compound has the potential to be weakly absorbed in the gastrointestinal tract because it is unable to pass through the cell membrane using a passive diffusion mechanism [39]. Based on the Lipinski Rule of Five (RO5) test, it was found that one of the five test compounds did not meet Lipinski's rules, namely Hesperidin which has 3 violations with a molecular weight $>500$ g/mol, hydrogen bond acceptor $>10$ and hydrogen donors $>5$ so it does not meet the rules and indicates that Hesperidin will be weakly absorbed in the gastrointestinal tract based on its physicochemical properties [40]. Hesperitin, Isosakuranetin, Sakuranetin, and Tetra-O-Methylscutallerin, complying with Lipinski's rules, are known to have good solubility in the gastrointestinal system so that they can be candidates in the development of new drugs presented in Table 1.

The main protease is a homodimer, an enzyme composed of two identical subunits with a form of arrangement perpendicular to each other, namely Subunit A and Subunit B [41]. The main structure of proteases is divided into three domains, Domain I, which consists of a series of 8 to 101 amino acid residues, Domain II with 102 to 184 amino acid residues, while Domain III is composed of 201 to 303 amino acid residues. CoV-2 has two catalytic agents or catalytic dyads, Cystein: 145 and Histidin: 41, which exist between the gaps in Domain I and Domain II make a bound place to carry out its function in binding the substrate [2]. The dyad catalyst is activated through the binding of the polyprotein substrate itself, which contributes to its proteolysis catalytic reaction. Therefore the protein that enters the active site at a different position from the natural substrate should not have lower energy and result in no reaction of the main protease enzyme [42].
Table 1. Lipinski rule of five (RO5) of SARS-CoV-2 Mpro potential inhibitor.

| No | Compounds                     | Molecular formula | Molecular weight (<500 g/mol) | H-bond acceptor (<10) | H-bond donor (<5) | Log P (<5) | Solubility | Violations | Meet RO5 Criteria |
|----|-------------------------------|-------------------|------------------------------|-----------------------|-------------------|------------|------------|------------|------------------|
| 1  | Tetra-O-Methylscutellarin     | C_{19}H_{18}O_{6} | 342.34                       | 6                     | 0                 | 3.01       | Moderately soluble | 0          | Yes              |
| 2  | Sakuranetin                   | C_{16}H_{14}O_{5} | 286.28                       | 5                     | 2                 | 2.25       | Soluble    | 0          | Yes              |
| 3  | Hesperitin                    | C_{16}H_{14}O_{6} | 302.28                       | 6                     | 3                 | 1.91       | Soluble    | 0          | Yes              |
| 4  | Isosakuranetin                | C_{16}H_{14}O_{5} | 286.28                       | 5                     | 2                 | 2.25       | Soluble    | 0          | Yes              |
| 5  | Hesperidin                    | C_{20}H_{20}O_{15} | 610.56                      | 15                    | 8                 | -1.06      | Soluble    | 3          | No               |
| 6  | Nelfinavir                    | C_{12}H_{14}N_{3}O_{5} | 567.78                  | 5                     | 4                 | 4.41       | Poorly soluble | 1          | Yes              |

Binding affinity (ΔGbind) is a value that becomes a parameter of ligand and receptor interaction by looking at the energy interacting and its stability in the system, where the smaller (minus) value will indicate the conformation formed by the ligand is stable while the larger the value indicates the less stable conformation. The ΔG relationship in a chemical reaction indicates three things, if the value of ΔG is negative, the reaction will tend to be spontaneous, and the energy to be released is exergonic energy. If ΔG is positive, then the reaction will not occur spontaneously because additional energy is needed into the system to force the reactants to turn into a product, or it is called an endergonic reaction, whereas if ΔG is zero, then both back and forth reactions occur at the same rate or are in an equilibrium system [43].

Molecular docking that is carried out on the test ligands using Autodock Vina will measure the success rate through the bond energy value or ΔG (kcal/mol) in Table 2.

Table 2. Docking analysis of SARS-CoV-2 Mpro potential inhibitor.

| No | Compounds     | Binding affinity (kkal/mol) |
|----|---------------|-----------------------------|
| 1  | Hesperidin    | -8.6                        |
| 2  | Nelfinavir    | -8.5                        |
| 3  | Hesperitin    | -7.3                        |
| 4  | Isosakuranetin| -7.2                        |
| 5  | Sakuranetin   | -7.1                        |
| 6  | Tetra-O-Methylscutellarin | -6.8                     |

Based on Table 2, it can be seen that the test compound that has a higher binding value is Hesperidin with a value of -8.6 kcal/mol compared to the Nelfinavir compound, which has a value of -8.5 kcal/mol. The other four test compounds each have values, Hesperitin -7.3 kcal/mol, Isosakuranetin -7.2 kcal/mol, Sakuranetin -7.1 kcal/mol, and Tetra-O-Methylscutellarin -6.8 kcal/mol. Overall, the interactions that occur in the test ligands against the Main protease (Mpro), as seen from the BIOVIA Discovery Visualizer, are the formation of interactions between test compounds and amino acids through hydrogen bonds, aromatic interactions, and unfavorable acceptor or donor bonds.

The interaction that occurs between the Hesperidin compound and the main protease (Mpro) SARS-CoV-2 as the ligand that has the highest binding value occurs at eleven amino acid residues where seven hydrogen bonds are formed. Hydrogen bonding is the interaction between positively charged hydrogen atoms (H+) and unpaired electrons from other atoms that occur in the same molecule (intermolecular) or different molecules (intramolecular). Hydrogen bonds are generally longer and weaker than covalent bonds in the same atom [43]. Hydrogen bonding not only mediates drug bonding with receptors but also affects physicochemical properties such as solubility and absorption, so it is very important in drug
development [44]. Hydrogen bonds occur on the interactions of hesperidin with amino acid residues Histidine:163 (2.86 Å), Cystein:145 (3.73 Å); Glutamine:189 (2.96 Å); Glycine:143 (3.07 Å); Phenylalanne:140 (2.08 Å); Histidine:172 (2.80 Å) and Glutamic acid:166 (1.86 Å) through its glycon group from hesperidin. The type and distance of the bonds also affect the strength of the bond energy that is formed, where the closer the bonds are, the stronger the bonds are formed. Bond distances of more than 3 Å tend to give weak bond strength [45]. Hesperidin has many hydrogen interactions, which affect its solubility in water. It is very soluble so that it has hydrophilic characteristics according to the rules of the Lipinski Rule of Five.

Furthermore, aromatic-aromatic interactions, which are non-covalent reactions, are important because they participate in the interactions between ligands and proteins [46]. Aromatic interactions occur between π bonds with other groups. A π (phi) bond is a covalent bond in two atoms that have single electrons and overlap with two other atomic orbitals, which are also single electrons. The interaction of π bonds can occur between π and π that occurs in Hesperidin which has an aromatic ring with the amino acid Histidine: 41 in its imidazole ring, which is shaped like the letter T (π- π T shaped). Phi bonding interactions can also occur with alkyl or alkane groups which lose one hydrogen group and become a methyl group (-CH3) which occurs in all test compounds.

**Figure 1.** Docking position of (a) Hesperidin (b) Hesperitin (c) Isosakuranetin, (d) sakuranetin, (e) Tetra-o-methylscutalerin, (f) Nelfinavir.
An unfavorable bump can occur due to the unfavorable possibility that will occur when water compounds interact with proteins. If this bond is formed, it will produce more enthalpy and entropy, which is not profitable [47]. This unwanted load transfer can occur in the form of donors and acceptors. The test compounds that experience this event are Hesperitin which occurs as unwanted donors or acceptors in Glutamic Acid: 166 and Leucine: 141. Tallei et al. [26] have conducted the same study using Autodock Vina against Hesperidin and Nelfinavir, showing the results that Nelfinavir with a value of -8.2 kcal/mol and Hesperidin which is -8.3 kcal/mol. The difference in the use of the docking engine results in a different reading of the docking value. This can occur due to the different types of programming algorithm calculations used by the docking machines [48].

4. Conclusion
Molecular docking of five citrus flavonoid compounds (Citrus sp) has binding affinity values, namely Hesperidin (-8.6 kcal/mol), Hesperitin (-7.3 kcal/mol), Isosacuranetin (-7.2 kcal/mol), Sakuranetin (-7.1 kcal/mol), and Tetra-O-Methylscutallerin (-6.8 kcal/mol) while the comparison was Nelfinavir (-8.5 kcal/mol). However, hesperidin does not meet the Lipinski Rule of Five (RO5) testing because it has three violations. Although hesperidin does not meet RO5 criteria, it can still be used as a drug candidate.

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