The interaction of alpha-mangostin and its derivatives against main protease enzyme in COVID-19 using in silico methods

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Abstract

More than 111 million people worldwide have been affected by the COVID-19 outbreak caused by SARS-CoV-2. The main therapeutic target of COVID-19 is main protease (Mpro). It plays a key role as an enzyme in the SARS-CoV-2 replication and transcription. In this case, the alpha-mangostin potentially has antiviral activity against Mpro by inhibiting this enzyme. Nevertheless, the alpha-mangostin has low solubility and a lack of information about alpha-mangostin activity against the SARS-CoV-2. The aim of this study is to describe the molecular interactions and identify the pharmacokinetics profile between alpha-mangostin and its derivatives. in silico study was conducted by pharmacokinetics and toxicity prediction, molecular docking simulation, and Lipinski’s rule of five. FKS9 has a Gibbs free energy value of -10.5 kcal/mol with an inhibition constant of 36.45 µM and an interaction with amino acid His41 residue. Its human intestinal absorption and Caco-2 values were 95.13% and 47.71% while the plasma protein binding and blood-brain barrier values were 96.66% and 6.99%. FKS9 also has no mutagenic and carcinogenic potential. FKS9 as an alpha-mangostin derivative had the best interaction with the Mpro enzyme and its pharmacokinetic profiles was identified.

Key words: Alpha-mangostin, COVID-19, in silico, main protease

INTRODUCTION

According to the World Health Organization (WHO), more than 111 million confirmed COVID-19 cases have been reported in 216 countries with 2.46 million confirmed deaths.[1] This pandemic is a major and recurrent global public health concern. This outbreak is an emerging infection and rapidly spreading globally.[2] The COVID-19 was caused by the SARS-CoV-2, which is an RNA virus that can spread widely to cause respiratory diseases.[3]

Currently, the primary care for COVID-19 patients is symptomatic therapy. Based on the clinical trials conducted by WHO from around the world, hydroxychloroquine, lopinavir, remdesivir, and interferon have proven ineffective in COVID-19 treatment.[4] These drugs have a tendency to develop acute toxicity and show poor therapeutic results in overcoming COVID-19.[5] As a result, further research related to the discovery of the COVID-19 drug is required to find active compounds that effectively reduce the spread of COVID-19.

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The search for active compounds through natural ingredients is accomplished in the search for parent compounds for COVID-19 therapy. Alpha-mangostin, originated from mangosteen pericarp has the potential to be an alternative agent for COVID-19 therapy. This is supported by previous studies which show that alpha-angostin has activity on the protease enzymes of the HIV.\textsuperscript{[6-9]} HIV protease has a genomic similarity level of 67.5\% compared to SARS-CoV-2’s main protease (Mpro).\textsuperscript{[10]} Therefore, alpha-mangostin is also thought to be able to have the same activity against the Mpro.

Mpro is referred to as an ideal drug target because of its specific presence that is only owned by viruses.\textsuperscript{[11]} This specific existence is able to suppress the side effects that will be accepted by humans because the compounds will only affect the virus.

Behind these potentials, there are several limitations of alpha-mangostin, such as a low pharmacokinetic profile and a lack of information regarding alpha-mangostin activity against SARS-CoV-2.\textsuperscript{[12,13]} Therefore, structural modification of alpha-mangostin is required to obtain alpha-mangostin derivatives with better pharmacokinetic profiles and pharmacological activities.

MATERIALS AND METHODS

Hardware and software
Hardware: A personal computer with Intel\textsuperscript{®} Core\textsuperscript{™} i5-6600 CPU, CPU 3.90 GHz, and 8 GB RAM. Software: The ChemOffice 2010 and ChemDraw Ultra 12.0 programs (PerkinElmer Inc., downloaded at http://www.cambridgesoft.com/) for drawing two-dimensional structures and expressing three-dimensional (3D) structures of the ligands. The AutoDock 4.2.6 and AutoDockTools 1.5.6 programs (The Scripps Research Institute, USA) to conduct molecular docking simulations. Pre-ADMET 2.0 program to predict absorption, distribution, and toxicity profile. The BIOVIA Discovery Studio 2017 R2 Client (Dassault Systems, downloaded from http://www.accelrys.com/) to visualize 3D structures.

Structure acquisition
The 3D structure of Mpro was downloaded from Protein Data Bank (PDB) (http://www.rcsb.org/) with ID code 6 LU7. Mpro was complexed with N3 inhibitor molecule. Separation was performed using BIOVIA Discovery Studio 2017 R2 Client. The 3D structure of the ligands (alpha-mangostin and its derivatives) was drawn and optimized utilizing ChemOffice 2010 and ChemDraw Ultra 12.0 (PerkinElmer Inc.). Nelfinavir was chosen as comparison compound and the structure was downloaded from Pubchem (http://pubchem.ncbi.nlm.nih.gov/).

Pharmacokinetics and toxicity prediction
The pharmacokinetics (absorption and distribution) and toxicity prediction include human intestinal absorption (HIA), Caco2, plasma protein binding (PPB), blood–brain barrier (BBB), Mutagenicity, and Carcinogenicity.

Molecular docking simulation
Ligands and enzyme are prepared using AutodockTools 1.5.6. Polar hydrogen and Kollman charges are added to protein and saved as PDBQT. Gasteiger charges were calculated. The box size is set at $26 \times 52 \times 32$ at the coordinate...
Table 1: Alpha-mangostin and its derivative structures

| Compound | Structure |
|----------|-----------|
| Alpha-mangostin | |
| FKS1 | |
| FKS2 | |
| FKS3 | |
| FKS4 | |
| FKS5 | |
| FKS6 | |
| FKS7 | |
| FKS8 | |
| FKS9 | |
| FKS10 | |

Figure 3: Interaction between FKS9 and main protease

x = −9.732; y = 11.403; and z = 68.925 with a distance of 0.375 Å. The genetic algorithm is set at 100x runs and other parameters are set by default. Autodock 4.2.6 is used to simulate the molecular docking process. The binding affinities of the compounds were studied using Discovery Studio Visualizer.

Lipinski’s rule of five
According to Lipinski’s rule of five (RO5), a reasonable compound for use as an orally active candidate must have no more than one violation of the following criteria: ≤5 hydrogen bond donors, ≤10 hydrogen bond acceptors, molecular weight ≤500, and logP ≤5.¹⁴

RESULTS
The alpha-mangostin structure modification was focused on C1 and C6 atoms which are more reactive than others to improve physicochemical properties, bioavailability, and pharmacological activity of alpha-mangostin. Alpha-mangostin modified compounds shown in the following [Table 1].

Pharmacokinetics and toxicity prediction
Table 2 shows the pharmacokinetic profile of these ligands. It shows the absorption profile of the compound represented by the HIA and Caco-2 values, while the distribution profile is shown by the PPB and BBB values, and the toxicity is represented by mutagenicity and carcinogenicity.

Molecular docking simulation
The molecular docking research control was used to validate the molecular docking parameters. The N3...
Structure of Caco-2 cells was categorized into three groups, administered active substances. The quality of absorption was good in addition, Caco-2 cell modeling is recommended as a method that can be properly absorbed by the intestine. There are three categories, namely HIA 0%–20% (low), 20%–70% (moderate), and >70% (high).

The HIA value of alpha-mangostin and its derivatives is in the range of 90%–99% which indicates that these compounds are strongly bound to plasma proteins so that only a small portion of the drug is in its free form which can then reach the Mpro. Meanwhile, the BBB value of FKS1, FKS2, FKS6, FKS7, and FKS10 values were below 90% so that it could be partitioned much more easily in the blood and drugs would be much easier to distribute to cells.

The degree of binding of the drug to plasma proteins affects the pharmacokinetic and pharmacodynamic properties of the drug. PPB values <90% indicate the drug is strongly bound to protein, whereas PPB values below 90% indicate the drug is weakly bound to plasma proteins so that the drug can be easily partitioned for distribution to cells. PPB values of alpha-mangostin, FKS4, FKS5, FKS7, FKS8, FKS9, FKS11, and FKS12 have PPB values above 90% which indicates that these compounds are strongly bound to plasma proteins so that only a small portion of the drug is in its free form which can then reach the Mpro. Meanwhile, the BBB value of FKS1, FKS2, FKS6, FKS7, and FKS10 values were below 90% so that it could be partitioned much more easily in the blood and drugs would be much easier to distribute to cells.

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has a higher ΔG value than nelfinavir (−9.74 kcal/mol) and alpha-mangostin (−8.58 kcal/mol). This shows that the interactions that occur between FKS9 and Mpro are at a higher level compared to alpha-mangostin and also the comparison compound (nelfinavir). The more negative the ΔG value, the more stable the bonds are. As a result, the ligand-protein affinity is getting better which leads to better activity.

The next parameter is the inhibition constant (Ki). The smaller the Ki, the smaller the doses required to demonstrate pharmacological abilities. The FKS9 has a Ki value of 36.45 μM. This was much smaller than that of nelfinavir (72.09 μM) and alpha-mangostin (511.49 μM).

The analysis of molecular docking results is also important to review the ability of the test ligand to interact with the ligand-binding domain (LBD) of the target protein. Cys145 and His41 are catalytic amino acid residues in LBD so that antagonistic compounds that are able to inhibit LBD by binding with these residues through hydrogen bond interactions cause virus replication to not occur. In this case, The interactions of alpha-mangostin [Figure 1], nelfinavir [Figure 2], and FKS9 [Figure 3] were compared to see compounds with better interactions. FKS9 [Figure 3] is able to interact with Mpro catalytic residue, His41, via hydrogen bond, which indicates that FKS9 has a good potential as an Mpro antagonist in inhibiting SARS-CoV-2 replication compared to alpha-mangostin and nelfinavir.

Lipinski’s rule of five
Based on Table 3, the FKS9 achieves the RO5 with only one violation, namely the logP value that exceeds the requirements (logP <5). Thus, FKS9 can be further investigated in vitro and it is predicted that it can be administered orally with a determinable oral bioavailability.

CONCLUSION
In conclusion, FKS9 as an alpha-mangostin derivative had
the best interaction with the Mpro enzyme as indicated by ∆G and Ki values of −10.5 kcal/mol and 36.45 µM and also an interaction with His41 residue. The pharmacokinetic profile of FKS9 has been known as shown by the HIA and Caco-2 values of 95.13% and 47.71%, these two values indicate that FKS9 can be well absorbed in the intestine and has the ability to penetrate the membrane. The PPB and BBB values of 96.66% and 6.99% indicating the distribution profile of FKS9 in terms of binding to plasma proteins and the ability to penetrate the BBB. FKS9 also has no mutagenic and carcinogenic potential.

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Conflicts of interest
There are no conflicts of interest.

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