In-Silico Study of Beta-Sesquiphellandrene as an Inhibitory Natural Compound of Spike Protein in SARS-CoV2

Evitasari, Andi Ariyandy and Sulfahri

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Evitasari [1)], Ariyandy A [2)], Sulfahri[3)]

[1)]Biomedical Sciences, Postgraduate School, Hasanuddin University, Makassar, Indonesia
[2)]Department of Physiology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
[3)]Department of Biology, Faculty of Mathematics and Natural Sciences, Hasanuddin University, Makassar, Indonesia

Email: evitasari975@ymail.com

Abstract

The purpose of this research is to determine the bioactivity of the ginger compound Beta-Sesquiphellandrene as a spike protein inhibitory compound in SARS-CoV2. This research was carried out using molecular docking and the PyRx 0.8 application. The chemical structure of the Beta-Sesquiphellandrene compound used is Beta-sesquiphellandrene ((3R)-3-[(2S)-6-methylhept-5-en-2-yl]-6-methylidenecyclohexene). The spike protein, which was used as the target protein, was obtained from the RSCB-PDB server under the PDB ID 2GHW. When compared to control compounds, the results showed that the Beta-Sesquiphellandrene compound has less potential as a spike protein inhibitory in SARS-Cov-2 (remdesivir). The value of binding affinity Beta-sesquiphellandrene with spike protein was -5.5, while the value of binding affinity Beta-sesquiphellandrene with control compound was -7.3. The AdmetSAR analysis of the Beta-sesquiphellandrene compound revealed that it was not hepatotoxic, whereas the control compound was. The results of the Swissadme analysis of the Beta-sesquiphellandrene compound revealed that Beta-sesquiphellandrene complied with Lipinski's rule, whereas the control compound did not.

Keywords : Beta-Sesquiphellandrene, remdesivir, spike protein, SARS-CoV2, molecular docking

Introduction

Coronavirus disease 2019 (Covid-19) is a disease caused by a virus called SARS-CoV2. This virus causes severe acute respiratory syndrome [(1)]. This disease was first reported in Wuhan, Hubei Province, China in December 2019. At that time, 4 cases of pneumonia of unknown cause were reported [(2)]. This disease is highly contagious and has been declared a pandemic by WHO because it spreads quickly and has been found in many countries [(3)]. This disease causes high mortality rates in many countries [(1)].

Coronavirus (CoV) is a positive-strand RNA virus that has an envelope glycoprotein that plays an important role in viral replication. The spike protein is one of the glycoproteins

associated with the attachment of the virus to the host [4]. The spike protein will attach to the angiotensin-converting enzyme 2 receptor (ACE2) to enter the host. ACE2 is widely expressed in various organs, such as the lungs [5].

Currently, there is no specific anti-viral treatment for Covid -19 [5]. But to date, there have been many studies related to ginger which has a potential effect against SARS-CoV2. Ginger contains eight main compounds detected in essential oils. The main compounds are camphene, sabinene, alpha-curcumene, zingiberene, alpha-farnesene, beta-sesquiphellandrene, neral, and geranial [6]. Beta-Sesquiphellandrene is a compound that functions as an anti-virus [7].

Remdesivir is one of the antiviral drugs currently being used for Covid -19 [1]. However, it cannot be denied that synthetic compounds have side effects on patients. Meanwhile, medicines made from natural ingredients show lower toxic effects and low cost [8]. The purpose of this research is to determine the bioactivity of the ginger compound Beta-Sesquiphellandrene as a spike protein inhibitory compound in SARS-CoV2.

Method

1. Ligand and Control Preparation
   The 3D structures of the ligand (Beta-sesquiphellandrene) and control compound (Remdesivir) were taken from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). PubChem CID for Beta-sesquiphellandrene is 12315492, with molecular weight 204.35g/mol and the Canonical Smile is CC(CCC=C(C)C)C1CCC(=C)C=C1. PubChem CID for Remdesivir is DB14761, with molecular weight 602.6g/mol and the Canonical Smile is CCC(CC)COC(=O)C(C)NP(=O)(OCC1C(C(C(O1)(C#N)C2=CC=C3N2N=CN=C3N)O)O)OC4=CC=CC=C4. The 3D chemical structures of the ligand and control were saved from PubChem, then sketched using Avogadro and Discovery Studio and saved in PDB format.
2. Target Selection
   The protein target used in this study is spike protein (2GHW). This protein target was validated using Uniport (https://www.uniprot.org/), then downloaded using PDB (https://www.rcsb.org/pdb). Once downloaded, the protein target structure was cleaned of water molecules using PyMOL software.
3. Molecular Docking
   Molecular docking of ligand or control with protein target was performed using PyRx 0.8 software. The docking algorithm process uses the Vina Wizard which is integrated with the PyRx 0.8 software [9].
4. Visualization of Ligand and Protein Target Interaction
   Ligands or controls that have interacted with the protein target are then visualized and analyzed using PyMOL software [9].
5. Properties and ADMET Predictions of Ligand and Control
   Physicochemical Properties, Pharmacokinetics, and Druglikeness properties of ligand and control were investigated using predictions from admetSAR (http://lmmd.ecust.edu.cn/) and Swissadme (http://www.swissadme.ch/) [9].

Results

1. Chemical 3D Structure of Ligand and Control

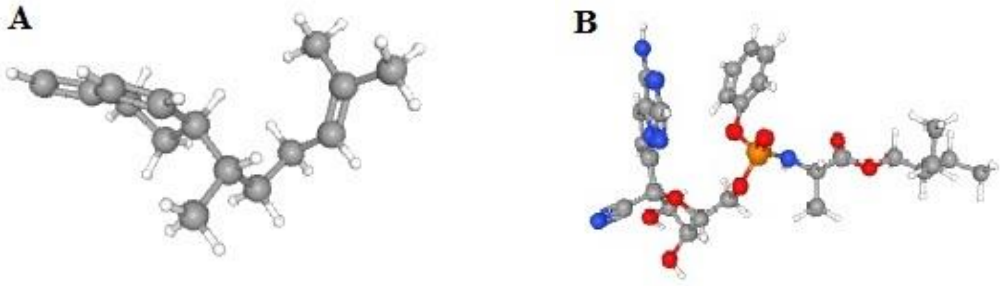

Figure 1. (A) Beta-sesquiphellandrene ((3R)-3-[(2S)-6-methylhept-5-en-2-yl]-6-methylidenecyclohexene); (B) Remdesivir

2. Protein Target After Water Molecule Removed

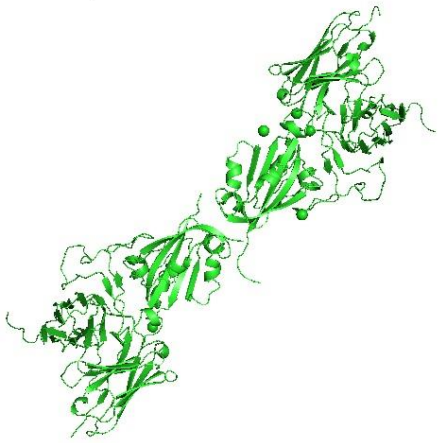

Figure 2. The Spike Protein (2GHW) after water molecule removed

3. Molecular Docking Protein Target (2GHW) with Ligand and Control

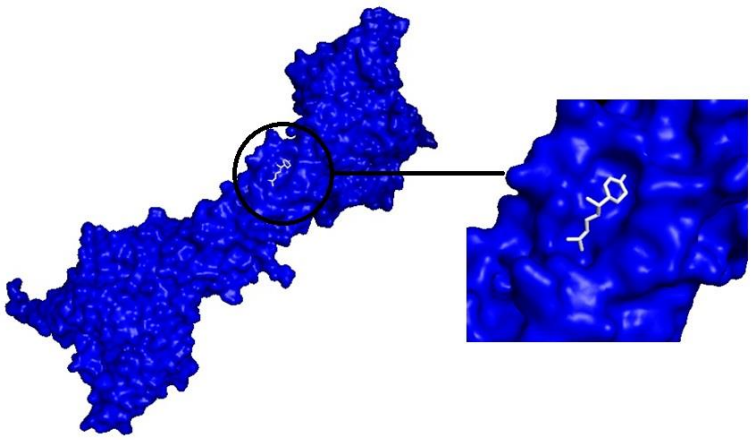

Figure 3. Binding Site of Beta-sesquiphellandrene ((3R)-3-[(2S)-6-methylhept-5-en-2-yl]-6-methylidenecyclohexene) (white) with 2GHW (blue)

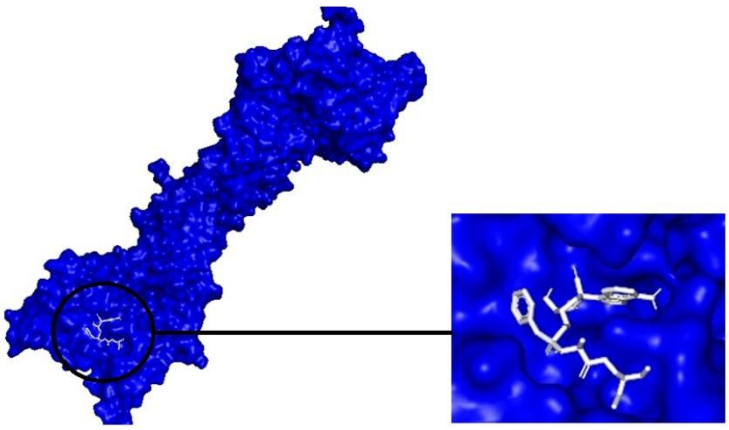

Figure 4. Binding Site of Remdesivir (white) with 2GHW (blue)

Table 1. Binding Affinity of the Spike Protein (2GHW) with ligand and control

Ligand	Binding Affinity (kcal/mol)
Beta-sesquiphellandrene	-5.5
Remdesivir	-7.3

4. Properties and ADMET Predictions of Ligand and Control

Table 2. ADMET Predictions of Ligand (Beta-sesquiphellandrene)

ADMET predicted profile --- Classifications	Value	Probability
Human Intestinal Absorption	+	0.9790
Human oral bioavailability	+	0.5429
Carcinogenicity (binary)	-	0.6714
Ames mutagenesis	-	0.7800
Human either-a-go-go inhibition	+	0.7424
micronuclear	-	1.0000
Hepatotoxicity	-	0.8250

Table 3. ADMET Predictions of Control (Remdesivir)

ADMET predicted profile --- Classifications	Value	Probability
Human Intestinal Absorption	+	0.9135
Human oral bioavailability	-	0.5286
Carcinogenicity (binary)	-	0.9714
Ames mutagenesis	-	0.7400
Human either-a-go-go inhibition	-	0.5000
micronuclear	+	0.9300
Hepatotoxicity	+	0.6750

Table 4. Druglikeness of Beta-sesquiphellandrene from Swissadme Analysis

Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	No; 2 violations: XLOGP3>5, Heteroatoms<2
Bioavailability Score	0.55

Table 5. Druglikeness of Remdesivir from Swissadme Analysis

Druglikeness	
Lipinski	No; 2 violations: MW>500, NorO>10
Ghose	No; 3 violations: MW>480, MR>130, #atoms>70
Veber	No; 2 violations: Rotors>10, TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 3 violations: MW>600, TPSA>150, H-acc>10
Bioavailability Score	0.17

Discussion

One of the active compounds contained in ginger is Beta-Sesquiphellandrene [(6)]. Beta-Sesquiphellandrene is a compound known to function as an anti-virus. Beta-Sesquiphellandrene is a compound that can interact and bind to the spike protein in SARS-CoV2 [(7)].

Spike protein is a glycoprotein found on the surface of SARS-CoV2 and plays an important role in the attachment of the virus to target cells. This protein binds to the ACE2 receptor and causes infection to the host [(5)]. If the spike protein is inhibited by a compound that has the potential to inhibit it, it is suspected that this virus will not be able to infect the host.

Molecular docking research is a computational study that can be used to predict the strength or potential of a compound in interacting with the target protein [(10)]. The result of docking between Beta-Sesquiphellandrene compound with spike protein (2GHW) which has a binding affinity value of -5.5 kcal/mol. Meanwhile, the binding affinity value between remdesivir (control) and spike protein was -7.3 kcal/mol. This means that Beta-Sesquiphellandrene has a lower potential for interaction with spike proteins than remdesivir.

Sometimes, a drug will be taken for a long period. Therefore, the effect of a compound on the body is important [(9)]. The side effects of Beta-Sesquiphellandrene and remdesivir (control) compounds on the body were observed with ADMET predictions. The AdmetSAR analysis of the Beta-sesquiphellandrene compound revealed that it was not hepatotoxic, whereas the control compound was.

Lipinski's rule is used to assess whether a compound has the potential to enter cell membranes and be absorbed by the body [(9)]. The results of the Swissadme analysis of the Beta-sesquiphellandrene compound revealed that Beta-sesquiphellandrene complied with Lipinski's rule, whereas the control compound did not. Beta-sesquiphellandrene bioavailability score was 0.55, while remdesivir had a lower bioavailability score of 0.17.

Conclusion

This study proves that the Beta-sesquiphellandrene compound has a lower potential for interaction with spike proteins than remdesivir. Beta-sesquiphellandrene contained in ginger has the potential as a spike protein inhibitor compound and complies with Lipinski's rules with a bioavailability score of 0.55. Meanwhile, remdesivir does not meet Lipinski's rules and has a lower bioavailability score than Beta-sesquiphellandrene.

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