Moringa

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Molecular docking of *Moringa oleifera* compounds with human ACE2 receptor: for COVID-19 drug candidate

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Abstract

COVID-19 is an infectious disease caused by a new coronavirus called Sars Corona Virus-2 (SARS-CoV-2). SARS-CoV-2 which can infect humans due to an interaction between the Spike glycoprotein (protein S) virus and thse Angiotensin-converting enzyme 2 (ACE2) receptor. *Moringa oleifera* is a plant known as phytomedicines and has excellent benefits. This study aims to identify the physicochemical characteristics of compounds in *M. oleifera* and their potential for blocking interactions between S glycoprotein and ACE2 receptors. ADMET analysis was conducted by using the TCMSP web-based application and evaluated by using the Lipinski and TCMSP criteria. The docking process used the Chimera UCSF program so that the grid box region and its affinity energy values are known. The results showed that phytol compounds have the most

physicochemical characteristics following Lipinski and TCSM criteria and have the lowest affinity energy when interacting with ACE2 receptors. This study concluded that phytol is a compound in *Moringa oleifera* which has the smallest pharmacological effect and has the most potential for preventing interactions between SARS-CoV-2 S protein and ACE2 receptors.

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Keywords: *ACE2 receptors, Moringa oleifera, SARS CoV-2,*

Introduction

The world is rattled by a disease that has symptoms of pneumonia, similar to SARS. This disease first appeared in Wuhan City, Hubei Province, China, at the end of December 2019 (Wong, et al., 2020). In early 2020 the World Health Organization (WHO) referred to it as Corona Virus Disease (COVID-19) (Hui et al., 2020; Bogoch et al., 2020). In March 2020, the World Health Organization settled COVID-19 as a pandemic, and until April 14, 2020, COVID-19 has attacked 213 countries with 1,776,867 confirmed cases, and 111,828 people were reported dead (World Health Organization, 2020b).

COVID-19 is an infectious disease caused by a new coronavirus. Initially, the virus was referred to as the 2019 coronavirus novel (nCoV-2019) (Wong et al., 2020; Lai et al., 2020) and later called the Sars Corona Virus-2 (SARS-CoV-2) (Lai et al. ., 2020; Ghinai et al., 2020; World Health Organization, 2020a). SARS-CoV-2 was thought to be originated from bats which migrated to humans through food in the seafood and wild animal markets (Hui et al., 2020). SARS-CoV-2 attacks the human respiratory tract. People infected with this virus can

show no symptoms, acute respiratory disease, or pneumonia (Lai et al., 2020). This virus is spread from person to person through droplets or direct contact (Lai et al., 2020).

The naming of SARS-CoV-2 due to the characteristics of this virus is similar to the Sars Corona Virus (SARS-CoV) which causes SARS disease and appeared at the end of February 2003 (World Health Organization, 2004). On January 10, 2020, the SARS-CoV-2 genome sequence was released, and on January 20, 2020, it was discovered that the SARS-CoV-2 genome chain sequence is similar to the genome sequence of SARS-CoV (Xu et al., 2020). SARS-CoV-2 is not only similar to SARS-CoV, but also similar to MERS-CoV (the cause of MERS disease) and belongs to the Betacoronavirus group (Elfiky et al., 2017). At present, there are seven different types of coronaviruses (HCoVs) which can infect humans, which are, 229E and NL63 (Alphacoronaviruses), OC43, HKU1, SARS, MERS, and COVID-19 (Betacoronaviruses) (Fehr et al., 2017). SARS-CoV and MERS-CoV are best known HCoV groups (Ibrahim et al., 2020).

Viruses can infect through interaction of viral protein and receptors in the host, as well as SARS-CoV-2. Like SARS-CoV, SARS-CoV-2 can infect humans because of a bond between the Spike glycoprotein (S protein) of the virus and Angiotensin-converting enzyme 2 (ACE2) (Prabakaran et al., 2004). SARS-CoV has S protein on its surface, and most likely, it is also present in SARS-CoV-2 because they have similar genomes. S protein is a large glycoprotein which has a type 1 membrane of the viral envelope (Berend et al., 2003). The S protein of SARS-CoV consists of two subunits, which are the S1 subunit in which it

contains the receptor-binding domain involved with ACE2 and the S2 subunit which mediates the fusion between the virus and cell membrane of the host (Du et al., 2009).

ACE2 is a type I transmembrane protein with extracellular N-terminal domains which contains active sites and short intracellular C-terminal tails (Lambert et al., 2005). ACE2 is an important regulator of the renin-angiotensin system and has recently identified as a major functional receptor for SARS-CoV (Prabakaran et al., 2004; Chen et al., 2010; Hamming et al., 2004; Xiao et al., 2003). ACE2 is present in several human organs, which are heart, kidneys, small intestine, and lungs (Hamming et al., 2004; Donoghue et al., 2000). In the lungs, ACE2 is present in type II pneumocytes (type II alveolar cells) (Chen et al., 2010; Uhal et al., 2013).

The interaction between S protein and the ACE2 receptor is caused by a decrease in ACE2 regulation (Glowacka et al., 2010). That matter can result in increased injury to the lungs. Reduction in ACE2 regulation underlies the pathology of infection (Imai et al., 2005). The interaction between human ACE2 and SARS-CoV-2 S protein has a higher affinity than the interaction between ACE2 and Bat-CoV S protein (Ortega et al., 2020). That matter may be one of the causes of the very rapid spread of the SARS-CoV-2 virus in humans.

Until now, there is no vaccine or a definite cure for COVID-19 disease. That prompted scientists to research to find drug candidates. Phytochemicals in one of a components which are potentially used as medicinal ingredients. Plants which are known to have great benefits, one of which is *Moringa oleifera* (Figure 1). *M. oleifera* is phytomedicine which has various functions, including as an anti-

inflammation (Mbikay, 2012), antimicrobial (Moyo, 2012), antidiabetic (Tende et al., 2011), antioxidants (Qwele et al., 2013), anticancer (Shaban et al., 2012), anticlastogenic (Promkum et al., 2010), and anthelmintic (Novian, 2019).

ADMET aims to determine physicochemical properties and levels of toxicity to humans, and molecular docking aims to determine whether the components of *M. oliefera* can block the interaction between SARS-CoV-2 S protein and ACE2 receptors so that it is potential to use as a candidate for COVID-19 drug. 3D protein structure models were created using the SARS-CoV-2 genome. The docking method can show the SARS-CoV-2 and SARS-CoV models have a strong interaction with the ACE2 receptor, although the order of the two genomes has several differences (Xu et al., 2020; Hamming et al., 2004). Based on this initial report, the next step is investigating compounds which can inhibit interactions between the ACE2 receptor and the S protein from SARS-CoV-2. In this study, the PubMed 3D structure modeled bioactive compounds from *M. oleifera* (Canese & Weis, 2013), and the structure of a protein data bank modeled he ACE2 receptor (Protein Data Bank, 2019). 3D structural models of drug compounds with ACE2 receptors can be used to find candidates for structure-based drugs. A drug search approach by drug therapy is difficult because the COVID-19 outbreak is very fast infecting everyone in the world (Wang et al., 2020). However, to find a drug, clinical trials must be carried out in vitro and in vivo.

In general, this study aims to identify compounds of *M. oleifera*, which has the potential to be inhibitors of ACE2 receptors. The results of this study can indicate the level of toxicity of the *M. oleifera* component in the human body and the

strength of the bond between the *M oleifera* component and the ACE2 receptor, so that it can show whether the *M. oleifera* component is useful as a drug candidate for COVID-19.

Materials and Methods

Tools

The tools used in this study is a set of personal computers with Intel® Core ™ i5-7200U, 4 gigabyte RAM, NVIDIA Ge Force Graphic Card, and Windows 10 Pro 64-bit operating system. The Discovery Studio Client V4.5 is visualizing S protein from SARS-CoV-2 (Studio, 2015). The Angiotensin-converting enzyme 2 (ACE2) receptors (PDB ID: 6m0j) downloading from the PDB database with URL: https://www.rcsb.org/. The 2D structure of the *M. oleifera* plant bioactive compounds tested consisted of 1-Hexadecanol, Hexadecanoic acid, 9-Octadecenamide, Oleic acid, and Phytol is downloaded from Pubchem database with the URL: https://pubchem.ncbi.nlm.nih.gov/. The TCMSP web-based is an application which was used to Pharmacological effect tests with the URL: http://www.tcmspw.com/molecule.php (Ru et al., 2014) and FAFDrugs4 with the URL: https://mobyle.rpbs.univ-paris-diderot.fr/cgi-bin/portal.py?form=FAF-Drugs3#forms::FAF-Drugs4 (Lagorce et al., 2017). The OpenBabelG UI software version 2.3.219 is a software used for the modifying chemical structure (O'Boyle et al., 2011) and visualization of molecular shapes using Discovery Studio Client V4.5 (Studio, 2015). The UCSF Chimera20 program is a software used to do a docking method (Yang et al., 2012).

ADME and Toxicity (ADMET)

The screening results of the bioactive and drug compounds using the TCMSP web-based application were evaluated with five Lipinski (RO5) 22 rules and drug criteria suggested by TCMSP. The drug criteria by Lipinski, are to have a molecular mass of less than 500 Dalton; high lipophilicity (expressed as log P less than 5), less than 5 hydrogen bond donors; less than 10 hydrogen bond acceptors and molar endurance between 40-130. The composition of drugs must be a good compound. The good compound follows TCMSP must obey the basic rules of the drug. The basic rules of the drug are oral bioavailability (OB), penetration to the brain (BBB), the half-life of the drug (HL), molecular polarity (TPSA), and the number of rotations (RBN) (Ru et al., 2014). The TCMSP criteria are followed at http://www.tcmspw.com/load_intro.php?id=29.

Molecular Docking

The docking process used the Chimera UCSF program. The docking approach using the Chimera UCSF program can provide the best conformational pose at the binding site of the protein-ligand complex. The docking procedure consists of the following two steps: (1) identifying and selecting the protein region as the active site for docking and (2) the docking process for the best ligand candidate to the chosen site. Interactions between all potential bioactive compounds and drug compounds with ACE2 receptors (PDB ID: 2AJF) were calculated by the confirmed binding site. Then UCSF Chimera calculated the energy affinity between the conformation of the protein and the ligand. Furthermore, comparing the affinity energy with the energy from positive control compounds. The smaller the value of its affinity, the bioactive compound is more stable and has the potential to become a drug compound.

Results and Discussion

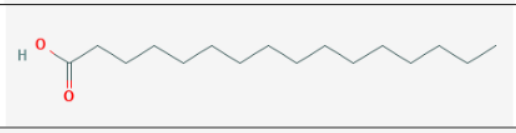
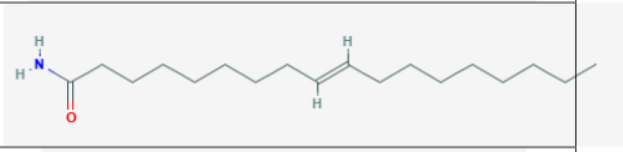
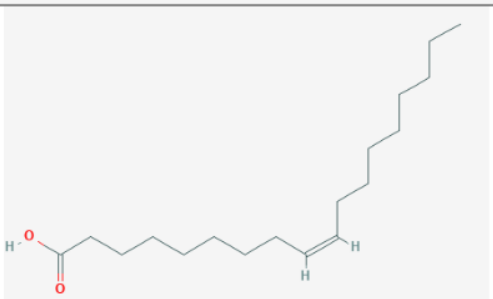
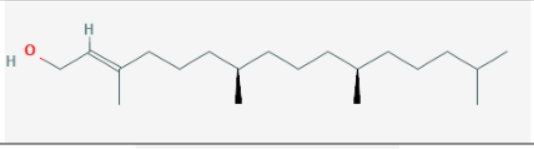
Moringa oleifera is a soft woody plant which grows low (Figure 1) and, for centuries, has been used as a source of nutrition, medicine, and industry (Chollom S. C, 2012). There are various active compounds in the ethanol extract of *M. oleifera* leaves, including 1-Hexadecanol, Hexadecanoic acid, 9-Octadecenamide, Oleic acid, and Phytol (Novian, 2019; Vats & Gupta, 2017; PM Aja et al., 2014).

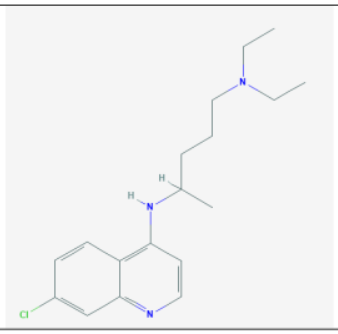
Figure 1. Moringa oleifera leaf
(Source: Personal Documentation)

The ACE2 receptor is the primary SARS-CoV-2 receptor which plays a role in the entry of the virus into the host cell. SARS-CoV-2 is known to have many gene similarities with SARS-CoV. Like SARS-CoV, SARS-CoV-2 also has a protein spike (S protein) which is known from the 3D structure of the receptor-binding domain which maintains the shape of Van Der Wals (Zhang et al., 2020). S protein in SARS-CoV-2 has a stronger bond with ACE2 receptors in humans (Wan, Shang, Graham, Baric, & Li, 2020). In this study, the ACE2 receptor with code 6m0j (PDB ID) and the ligands are 1-Hexadecanol, Hexadecanoic acid, 9-

Octadecenamide, Oleic acid, and Phytol which were found in *M. oleifera*. This study also used the drug compounds Fafipiravir and Chloroquine as comparative ligands (positive controls). The chemical structure of the 2 D ligand used in this study is in Table 1.

Table 1. The Name of Ligand Compounds and their 2 Dimensional Structure

No.	ID	Ligand Compounds	2 Dimensional Structure
1.	2682	*1-Hexadecanol*	
2.	985	*Hexadecanoic acid*	
3.	5353370	*9-octadecenamide*	
4.	445639	*Oleic acid*	
5.	5280435	*Phytol*	
6.	492405	* *Favipiravir*	

No.	ID	Ligand Compounds	2 Dimensional Structure
7.	2719	*Chloroquine	

*: drugs compounds as a comparative (positive control)
Source: https://pubchem.ncbi.nlm.nih.gov

The selection of ligands was screened based on Lipinski criteria. The Lipinski criteria estimate the solubility and permeability developed through experimental and computational approaches (Lipinski et al, 1997). So if the selected ligand has met the Lipinski criteria, it is assumed that the ligand has potential to enter the cell membrane of the body, and the body can absorb that. The Lipinski criteria explain that absorption or permeability will be bad if the number of proton donor hydrogen bonds > 5, the number of proton acceptor groups> 10, molecular weight> 500 grams/mol, and log calculated P (ClogP)> of 5 (or MlogP> 4.15) (Lipinski et al., 1997).

The ligands used in this study are compounds in *M. oleifera*, ligand selection also followed on the criteria of the traditional Chinese medicine systems pharmacology database and analysis platform (TCMSP). TCMSP aims to accelerate drug discovery from herbal ingredients and an efficient pharmacological system platform which represents the convergence of pharmacochemical information, ADME properties, drug similarity, drug targets, related diseases, and tissue interactions, whose needs are very urgent (Ru et al.,

2014). Analysis of absorption, distribution, metabolism, elimination (ADME), and acceptable toxicology properties to determine whether the selected ligands meet Lipinski and TCMSP criteria.

Web-based application TCMSP and FAFDrugs4 calculated the ADME value and toxicity of a compound based on molecular properties, which are molecular weight (MW), partition coefficient between octanol and water, lipophilicity (AlogP), hydrogen bond donor (Hdon), hydrogen bond acceptor (Hacc), oral bioavailability (OB), compound penetration into the brain (BBB), drug similarity (DL), molecular polarity (TPSA), rotation amount (RBN), drug half-life (HL) and LogP relationship with tPSA (3/75). The results of ADME and the toxicity of bioactive compounds and positive control compounds are present in Table 2.

Tabel 2. The results of ADME and the toxicity of bioactive compounds and positive control compounds

Compound Name (Ligan)	***Physical and Chemical Properties***										
	MW	**AlogP**	**Hdon**	**Hacc**	**OB (%)**	**BBB**	**DL**	**TPSA**	**RBN**	**HL (jam)**	**3/75**
1-Hexadecanol	242,50**	6,45	1**	1**	13,32	1,07	0,08	20,23*	14	0*	Warning
Hexadecanoic acid	256,48**	6,37	1**	2**	19,30	1,00	0,10	37,30*	14	0*	Warning
9-Octadecenamide	281,54**	6,23	2**	2**	31,20*	1,07	0,14	43,09*	15	4,84	Warning
Oleic acid	282,52**	6,84	1**	2**	33,13*	0,78	0,14	37,30*	15	4,99	Warning
Phytol	296,6**	7,34	1**	1**	33,82*	0,85	0,13	20,23*	13	2,34*	warning
Favipiravir°	157.1**	0.56**	3**	5**	good	-	-	88.84	-	-	good
Klorokuin°	142.54**	0.84**	0**	2**	30.46*	0.11*	0.04	38,91*	0*	-2,16*	warning

* : according to TCMPS criteria
** : as per Lipinski criteria
° : medicinal compounds
- : there is no data on the TCMSP web

Table 2 shows that the ligands used in molecular docking simulations in this study met many Lipinski and TCMPS criteria, so they proceeded to the molecular docking stage. Molecular docking is the main tool in the structure of biology which functions in finding potential drug compounds through computer assistance (Morris, Garrett M., 2008). Ligand compounds are docked with ACE2 receptors using the UCSF Chimera program. Docking is done to tether each ligand to the receptor at certain tethering coordinates. The active site is Docking can predict the major binding model between ligands and proteins from known three-dimensional structures (Morris, Garrett M., 2008). The active site of the ACE2 receptor can be identified by docking, which is presented in Figure 2. The active side serves as a reaction site between the ACE2 receptor and the ligand.

The ACE2 active site in the docking simulation is x coordinate -21.626, y coordinate is -34.686, and z coordinate is -15.468 with each dimension 126 A. The active site serves as a site for the reaction between the ligand and the ACE2 receptor. The physical and chemical properties of the ligand compounds used in the molecular docking simulation are shown in Table 1. The visualization shows that there is no difference in the 3D structure conformation of the receptor before docking and after the determination of the active-side receptors grid box. Conformation of 3D structures is essential because it is closely related to the function of a receptor. If the structure changes, the receptor function will change. Molecular docking also obtained the value of energy affinity from the results of the receptor and ligand interactions which occur at the active site. The affinity energy values between the receptor and ligands are presented in Table 3.

Table 3 shows that the phytol bioactive compound has the lowest affinity when it binds to the ACE2 receptor. When compared with the comparative ligand, the phytol bioactive compound has a lower energy affinity than the favipiravir and cloroquine drug compound. Phytol thus has the most stable receptor and ligand interactions so that it can have the potential to block the interaction between S protein and the ACE2 receptor.

Affinity Energy is a parameter of conformational stability between ligands and receptors. Ligands and receptors which interact will tend to be in low energy conditions, and these conditions make the molecules in a stable state, so the lower the affinity energy interaction between the ligand and the receptor, the more stable it will be. Molecular interactions in ligands and receptors include electrostatic interactions, hydrophobic interactions, and hydrogen bonds, which contribute to the affinity energy values of ligands and receptors. The interactions which occurred are hydrogen bonds, hydrophobic interactions, and electrostatic interactions in the tethering area.

Based on ADME and Toxicity analysis (Table 2), phytol is phytochemical compounds of the *M. oleifera,* which has the lowest pharmacological effect. That is because phytol has the most physicochemical properties which met to Lipinski and TCMSP criteria. So phytol is the most rules of drug compounds compared to other phytochemical compounds. The pharmacological effect of the phytol is higher when compared to favipiravir drug compounds, but lower when compared to chloroquine drug compounds. The phytol compound has an MW of less than 500, which is 296.6, Hdon is less than 5, which is 1, Hacc is less than 10, is 1, OB is more than 30%, 33.82%, TPSA is less than 60, is 20.23, and drug half-life is

less from 4 hours which is 2.34 hours. However, Phytol compound also has a weakness because it has a lipofility (AlogP) of more than 5, 7.34, the penetration of compounds into the brain is higher than 0.3, 0.85, the similarity of the drug is less than 0.18, 0.13, the number of rotations is more than 10, 13, and AlogP's relationship with TPSA (3/75) is a warning. Favipiravir drug compound has a weakness in terms of molecular polarity (TPSA) of more than 60, and this can cause it to dissolve too easily in the body so that the effectiveness of the drug is less than optimal. Chloroquine compound has a weakness in AlogP's relationship with TPSA (3/75), which is a warning. It shows that medicinal compounds have high toxicity, so their use must be careful. ADME drug properties and toxicity are important for the final clinical success of drug candidates (Albert PLi, 2001). Drugs that fulfill these properties will have good bioavility so that they can be absorbed by the intestine and are also safe for consumption.

Phytol is a naturally occurring diterpene alcohol molecule which can be extracted from green plants (Olofsson et al., 2014). Phytol is one of the compounds contained in the leaves of *M. oleifera* (P. M. Aja et al., 2014; Vats & Gupta, 2017). Phytol is a compound which has the potential to be used as an antiviral in simplex virus type 1 (HSV-1) at various stages of infection (Susana et al., 2012).

A virus can infect a host due to interactions with receptors. The first step to infecting is the virus must pass through the host cell membrane. Viruses can fuse with membranes with the help of special proteins which can bind to the receptors on the membrane (Berend et al, 2003) and are followed by changes in the conformation of the viral protein (Dimitrov, 2004) likewise with SARS-CoV-

2 which infects humans because of the interaction between S protein and ACE2 receptors. S protein is a type I transmembrane protein and class I fusion protein consisting of different N-terminal (S1) and C-terminal (S2) domains, which mediate the binding of receptors and fusion of viral cells. The location of ACE2 receptors is in type 2 alveolar epithelial cells so that these cells can function as an invading SARS-CoV-2 reservoir (Zhang et al., 2020).

After contacting the ACE2 receptor, the S protein undergoes conformational changes which expose the fusion of peptides embedded in the S2 domain and induce repeated reorganization of large S2 heptads into circular coils (Li et al., 2006). This conformational change brings the virion membrane into an apposition close to the cellular membrane for subsequent fusion (Li et al., 2006). After the fusion occurs, genetic material will enter and replicate. This process ends with the transfer of viral genomes in the host cell (Dimitrov, 2004). ACE2 not only functions as a viral receptor but also works to protect the lungs from injury. The interaction between ACE2 and SARS-CoV-2 results in the downregulation of the ACE2 receptor resulting in severe lung injury (Zhang et al., 2020).

Based on molecular docking simulations (Table 3), we can find out that the phytol compounds found in *M. oleifera* are capable of binding to ACE2 receptors. Interaction between phytol compounds and ACE2 receptors can prevent interactions between S protein and ACE2 receptors. Phytol compounds can compete with S protein to prevent the entry of viruses into cells. It can reduce the spread of the virus and protect the lungs from injury (Zhang et al., 2020).

Conclusion

Phytol is a compound in *Moringa oleifera* which has the lowest pharmacological effect and has the most potential to block interactions between Spike glycoprotein of SARS-CoV-2 and ACE2 receptors. The pharmacological effect based on ADMET analysis, which showed that phytol has the most physicochemical characteristics, according to Lipinski and TCSM criteria. The potential blocking is shown from Molecular Docking, which is known that the interaction between phytol and ACE2 receptors has the lowest affinity energy.

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References

Aja, P. M., Nwachukwu, N., Ibiam, U. A., Igwenyi, I. O., Offor, C. E., & Orji, U. O. (2014). Chemical constituents of Moringa oleifera leaves and seeds from Abakaliki, Nigeria. *Am J Phytomedicine Clin Ther*.

Albert PLi. (2001). Screening for human ADME/Tox drug properties in drug discovery. *Drug Discovery Today*, *6*(7), 357–366. https://doi.org/https://doi.org/10.1016/S1359-6446(01)01712-3

Berend Jan Bosch, Ruurd van der Zee, Cornelis A. M. de Haan, P. J. M. R. (2003). The Coronavirus Spike Protein Is a Class I Virus Fusion Protein: Structural and Functional Characterization of the Fusion Core Complex. *JOURNAL OF VIROLOGY*, *77*(16), 8801–8811. https://doi.org/10.1128/JVI.77.16.8801

Bogoch, I. I., Watts, A., Thomas-Bachli, A., Huber, C., Kraemer, M. U. G., & Khan, K. (2020). Pneumonia of Unknown Etiology in Wuhan, China: Potential for International Spread Via Commercial Air Travel. *Journal of Travel Medicine*. https://doi.org/10.1093/jtm/taaa008

Canese, K., & Weis, S. (2013). PubMed: The bibliographic database. *The NCBI*

Handbook.

Chen, I.-Y., Chang, S. C., Wu, H.-Y., Yu, T.-C., Wei, W.-C., Lin, S., … Chang, M.-F. (2010). Upregulation of the Chemokine (C-C Motif) Ligand 2 via a Severe Acute Respiratory Syndrome Coronavirus Spike-ACE2 Signaling Pathway. *Journal of Virology*, *84*(15), 7703–7712. https://doi.org/10.1128/jvi.02560-09

Chollom S. C. (2012). Investigation of aqueous extract of Moringa oleifera lam seed for antiviral activity against newcastle disease virus in ovo. *Journal of Medicinal Plants Research*, *6*(22), 3870–3875. https://doi.org/10.5897/jmpr12.394

Christopher A. Lipinski, Franco Lombardo, Beryl W.Dominy, P. J. F. (1997). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*, *23*(1–3), 3–25. https://doi.org/https://doi.org/10.1016/S0169-409X(96)00423-1

Dimitrov, D. S. (2004). Virus entry: Molecular mechanisms and biomedical applications. *Nature Reviews Microbiology*, *2*(2), 109–122. https://doi.org/10.1038/nrmicro817

Donoghue, M., Hsieh, F., Baronas, E., Godbout, K., Gosselin, M., Stagliano, N., … Acton, S. (2000). A Novel Angiotensin-Converting Enzyme–Related Carboxypeptidase (ACE2) Converts Angiotensin I to Angiotensin 1-9. *Circ Res*, *87*(5), e1–e9. https://doi.org/https://doi.org/10.1161/01.RES.87.5.e1

Du, L., He, Y., Zhou, Y., Liu, S., Zheng, B. J., & Jiang, S. (2009). The spike protein of SARS-CoV - A target for vaccine and therapeutic development. *Nature Reviews Microbiology*, *7*(3), 226–236. https://doi.org/10.1038/nrmicro2090

Elfiky, A. A., Mahdy, S. M., & Elshemey, W. M. (2017). Quantitative structure-activity relationship and molecular docking revealed a potency of anti-hepatitis C virus drugs against human corona viruses. *Journal of Medical Virology*. https://doi.org/10.1002/jmv.24736

Fehr, A. R., Channappanavar, R., & Perlman, S. (2017). Middle East Respiratory Syndrome: Emergence of a Pathogenic Human Coronavirus. *Annual Review of Medicine*. https://doi.org/10.1146/annurev-med-051215-031152

Ghinai, I., McPherson, T. D., Hunter, J. C., Kirking, H. L., Christiansen, D., Joshi, K., … Layden, J. E. (2020). First known person-to-person transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the USA. *The Lancet*, *2*(Cdc), 1–8. https://doi.org/10.1016/s0140-6736(20)30607-3

Glowacka, I., Bertram, S., Herzog, P., Pfefferle, S., Steffen, I., Muench, M. O., … Pohlmann, S. (2010). Differential Downregulation of ACE2 by the Spike Proteins of Severe Acute Respiratory Syndrome Coronavirus and Human Coronavirus NL63. *Journal of Virology*, *84*(2), 1198–1205. https://doi.org/10.1128/jvi.01248-09

Hamming, I., Timens, W., Bulthuis, M. L. C., Lely, A. T., Navis, G. J., & van Goor, H. (2004). Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *Journal of Pathology*, *203*(2), 631–637. https://doi.org/10.1002/path.1570

Hui, D. S., I Azhar, E., Madani, T. A., Ntoumi, F., Kock, R., Dar, O., … Petersen, E. (2020). The continuing 2019-nCoV epidemic threat of novel

coronaviruses to global health — The latest 2019 novel coronavirus outbreak in Wuhan, China. *International Journal of Infectious Diseases*. https://doi.org/10.1016/j.ijid.2020.01.009

Ibrahim, I. M., Abdelmalek, D. H., Elshahat, M. E., & Elfiky, A. A. (2020). COVID-19 Spike-host cell receptor GRP78 binding site prediction. *Journal of Infection*. https://doi.org/https://doi.org/10.1016/j.jinf.2020.02.026

Imai, Y., Kuba, K., Rao, S., Huan, Y., Guo, F., Guan, B., … Penninger, J. M. (2005). Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature*, *436*(7047), 112–116. https://doi.org/10.1038/nature03712

Lagorce, D., Bouslama, L., Becot, J., Miteva, M. A., & Villoutreix, B. O. (2017). FAF-Drugs4: Free ADME-tox filtering computations for chemical biology and early stages drug discovery. *Bioinformatics*. https://doi.org/10.1093/bioinformatics/btx491

Lai, C.-C., Liu, Y. H., Wang, C.-Y., Wang, Y.-H., Hsueh, S.-C., Yen, M.-Y., … Hsueh, P.-R. (2020). Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. *Journal of Microbiology, Immunology and Infection*, *2*(xxxx). https://doi.org/10.1016/j.jmii.2020.02.012

Lai, C. C., Shih, T. P., Ko, W. C., Tang, H. J., & Hsueh, P. R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *International Journal of Antimicrobial Agents*, *55*(3), 105924. https://doi.org/10.1016/j.ijantimicag.2020.105924

Lambert, D. W., Yarski, M., Warner, F. J., Thornhill, P., Parkin, E. T., Smith, A. I., … Turner, A. J. (2005). Tumor necrosis factor-α convertase (ADAM17) mediates regulated ectodomain shedding of the severe-acute respiratory syndrome-coronavirus (SARS-CoV) receptor, angiotensin-converting enzyme-2 (ACE2). *Journal of Biological Chemistry*, *280*(34), 30113–30119. https://doi.org/10.1074/jbc.M505111200

Li, W., Wong, S.-K., Li, F., Kuhn, J. H., Huang, I.-C., Choe, H., & Farzan, M. (2006). Animal Origins of the Severe Acute Respiratory Syndrome Coronavirus: Insight from ACE2-S-Protein Interactions. *Journal of Virology*, *80*(9), 4211–4219. https://doi.org/10.1128/jvi.80.9.4211-4219.2006

Mbikay, M. (2012). Therapeutic potential of Moringa oleifera leaves in chronic hyperglycemia and dyslipidemia: A review. *Frontiers in Pharmacology*. https://doi.org/10.3389/fphar.2012.00024

Morris, Garrett M., M. L.-W. (2008). *Methods Molecular Biology: Molecular Modeling of Proteins*. (A. Kukol, Ed.). Switzerland: Humana Press. https://doi.org/https://doi.org/10.1007/978-1-59745-177-2_19

Moyo. (2012). Antimicrobial activities of Moringa oleifera Lam leaf extracts. *African Journal of Biotechnology*. https://doi.org/10.5897/ajb10.686

Novian, D. R. (2019). Potensi Anthelmintik Moringa Oleifera Sebagai Inhibitor Mitochondrial Rhodoquinol-Fumarate Reductase Dari Ascaris Suum Menggunakan Metode Docking Anthelmintic Potential Of Moringa Oleifera As Inhibitor Mitochondrial Rhodoquinol-Fumarate Reductase From Asc, *5*(2), 106–114. https://doi.org/https://doi.org/10.31603/pharmacy.v5i2.3000

O'Boyle, N. M., Banck, M., James, C. A., Morley, C., Vandermeersch, T., & Hutchison, G. R. (2011). Open Babel: An Open chemical toolbox. *Journal of*

Cheminformatics. https://doi.org/10.1186/1758-2946-3-33

Ortega, J. T., Serrano, M. L., Pujol, F. H., & Rangel, H. R. (2020). Role of changes in SARS-CoV-2 spike protein in the interaction with the human ACE2 receptor: An in silico analysis. *Excli J*, *19*, 410–417. https://doi.org/10.17179/excli2020-1167

Othman, H., Bouslama, Z., Brandenburg, J.-T., Rocha, J. da, Hamdi, Y., Ghedira, K., … Hazelhurst, S. (2020). In silico study of the spike protein from SARS-CoV-2 interaction with ACE2: similarity with SARS-CoV, hot-spot analysis and effect of the receptor polymorphism. *BioRxiv*. https://doi.org/10.1101/2020.03.04.976027

P. M. Aja, N. Nwachukwu, U. A. Ibiam, I. O. Igwenyi, C. E. Offor, U. O. O. (2014). Chemical constituents of Moringa oleifera leaves and seeds from Abakaliki, Nigeria. *American Journal of Phytomedicine and Clinical Theraupetics*, *2*(3).

Peter Olofsson, Malin Hultqvist, Lars I. Hellgren, R. H. (2014). *Phytol: A Chlorophyll Component with Anti-inflammatory and Metabolic Properties: Recent Advances in Redox Active Plant and Microbial Products*. Switzerland: Springer, Dordrecht. https://doi.org/https://doi.org/10.1007/978-94-017-8953-0_13

Prabakaran, P., Xiao, X., & Dimitrov, D. S. (2004). A model of the ACE2 structure and function as a SARS-CoV receptor. *Biochemical and Biophysical Research Communications*, *314*(1), 235–241. https://doi.org/10.1016/j.bbrc.2003.12.081

Promkum, C., Kupradinun, P., Tuntipopipat, S., & Butryee, C. (2010). Nutritive evaluation and effect of Moringa oleifera pod on clastogenic potential in the mouse. *Asian Pacific Journal of Cancer Prevention*.

Protein Data Bank. (2019). RCSB PDB: Homepage.

Qwele, K., Hugo, A., Oyedemi, S. O., Moyo, B., Masika, P. J., & Muchenje, V. (2013). Chemical composition, fatty acid content and antioxidant potential of meat from goats supplemented with Moringa (Moringa oleifera) leaves, sunflower cake and grass hay. *Meat Science*. https://doi.org/10.1016/j.meatsci.2012.11.009

Ru, J., Li, P., Wang, J., Zhou, W., Li, B., Huang, C., … Yang, L. (2014). TCMSP: A database of systems pharmacology for drug discovery from herbal medicines. *Journal of Cheminformatics*, *6*(13), 1–6. https://doi.org/10.1186/1758-2946-6-13

Shaban, A., Mishra, G. M., Nautiyal, R., Srivastava, S., Tripathi, K., Chaudhary, P., & Verma, S. K. (2012). In vitro cytotoxicity of Moringa oleifera against different human cancer cell lines. *Asian Journal of Pharmaceutical and Clinical Research*.

Studio, D. (2015). Dassault Systemes BIOVIA, Discovery Studio Modelling Environment, Release 4.5. *Accelrys Software Inc*.

Susana Santoyo, Laura Jaime, Merichel Plaza, Miguel Herrero, Irene Rodriguez-Meizoso, E. I. & G. R. (2012). Antiviral compounds obtained from microalgae commonly used as carotenoid sources. *Journal of Applied Phycology*, *24*, 731–741. https://doi.org/https://doi.org/10.1007/s10811-011-9692-1

Tende, J. A., Ezekiel, I., Dikko, A. A., & Goji, A. D. T. (2011). Effect of

Ethanolic Leaves Extract of Moringa oleifera on Blood Glucose Levels of Streptozocin-Induced Diabetics and Normoglycemic Wistar Rats. *Br. J. Pharm. Toxicol.*

Uhal, B. D., Dang, M., Dang, V., Llatos, R., Cano, E., Abdul-hafez, A., … Molina-molina, M. (2013). Cell cycle dependence of ACE-2 explains downregulation in idiopathic pulmonary fibrosis. *European Respiratory Journal*, *42*(IDIOPATHIC PULMONARY FIBROSIS), 198–210. https://doi.org/10.1183/09031936.00015612

Vats, S., & Gupta, T. (2017). Evaluation of bioactive compounds and antioxidant potential of hydroethanolic extract of Moringa oleifera Lam. from Rajasthan, India. *Physiology and Molecular Biology of Plants*, *23*(1), 239–248. https://doi.org/10.1007/s12298-016-0407-6

Volford, A. (2015). MarvinSketch. *Chem Axon MarvinSketch*.

Wan, Y., Shang, J., Graham, R., Baric, R. S., & Li, F. (2020). Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. *Journal of Virology*, *94*(7), 1–9. https://doi.org/10.1128/jvi.00127-20

Wang, C., Horby, P. W., Hayden, F. G., & Gao, G. F. (2020). A novel coronavirus outbreak of global health concern. *The Lancet*. https://doi.org/10.1016/S0140-6736(20)30185-9

Wong, M. C., Cregeen, S. J. J., Ajami, N. J., & Petrosino, J. F. (2020). Evidence of recombination in coronaviruses implicating pangolin origins of nCoV-2019. *BioRxiv Preprint*, 2020.02.07.939207. https://doi.org/10.1101/2020.02.07.939207

World Health Organization. (2004). Severe Acute Respiratory Syndrome (SARS). Retrieved March 30, 2020, from https://www.who.int/csr/sars/en/

World Health Organization. (2020a). Coronavirus disease (COVID-19) outbreak – Emergency Use Listing Procedure (EUL) announcement. Retrieved March 29, 2020, from https://www.who.int/health-topics/coronavirus#tab=tab_1

World Health Organization. (2020b). Coronavirus disease (COVID-19) Pandemic. Retrieved March 28, 2020, from https://www.who.int/emergencies/diseases/novel-coronavirus-2019

Xiao, X., Chakraborti, S., Dimitrov, A. S., Gramatikoff, K., & Dimitrov, D. S. (2003). The SARS-CoV S glycoprotein: Expression and functional characterization. *Biochemical and Biophysical Research Communications*. https://doi.org/10.1016/j.bbrc.2003.11.054

Xu, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., … Hao, P. (2020). Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Science China Life Sciences*, *63*(3), 457–460. https://doi.org/10.1007/s11427-020-1637-5

Yang, Z., Lasker, K., Schneidman-Duhovny, D., Webb, B., Huang, C. C., Pettersen, E. F., … Ferrin, T. E. (2012). UCSF Chimera, MODELLER, and IMP: An integrated modeling system. *Journal of Structural Biology*. https://doi.org/10.1016/j.jsb.2011.09.006

Zhang, H., Penninger, J. M., Li, Y., Zhong, N., & Slutsky, A. S. (2020). Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Medicine*, *46*(4), 586–590. https://doi.org/10.1007/s00134-020-05985-9

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