



# Molecular Docking Approach of Natural Compound from Herbal Medicine in Java against Severe Acute Respiratory Syndrome Coronavirus-2 Receptor

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## Abstract

**Edited by:** Ksenija Bogoeva-Kostovska  
**Citation:** Yueniwati Y, Syaban MFR, Faratisha IFD, Yunita KC, Kurniawan DB, Putra GMA, Erwan NE. Molecular Docking Approach of Natural Compound from Herbal Medicine in Java against Severe Acute Respiratory Syndrome Coronavirus-2 Receptor. Open Access Maced J Med Sci. 2021 Dec 09; 9(A):1181-1186. https://doi.org/10.3889/oamjms.2021.6963

**Keywords:** Natural compound; Herbal medicine; Angiotensin-converting enzyme-2 receptor; Severe acute respiratory syndrome coronavirus-2; Molecular docking  
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E-mail: yuyun@ub.ac.id  
**Received:** 06-Aug-2021  
**Revised:** 20-Aug-2021  
**Accepted:** 02-Dec-2021

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**Funding:** This research did not receive any financial support

**Competing Interests:** The authors have declared that no competing interests exist  
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**BACKGROUND:** Indonesia's diversity of natural resources presents an intriguing opportunity for the exploration of potential herbal medicines. Numerous compounds, both purified and crude, have been reported to exhibit antiviral activity. The angiotensin-converting enzyme 2 (ACE-2) receptor may be a therapeutic target for severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection. We used a search engine to search for herbal medicines with ACE-2 inhibitory activity to predict the potential inhibition of natural compounds (i.e., theaflavin, deoxypodophyllotoxin, galliccatechin, allacin, quercetin, annonamine, Curcumin, 6-gingerol, and cucurbitacin B) to SARS-CoV2-ACE-2 complex.

**AIM:** This research conducted to search potential compound against COVID-19 receptor.

**METHODS:** We performed molecular docking analysis using the ACE-2 receptor protein target from Protein Data Bank. Protein stabilization was carried out to adjust to the body's physiology, carried out using Pymol by removing water atoms and adding hydrogen atoms. Ligands of active compounds from natural resources were selected and downloaded from the PubChem database, then optimized by Pymol software.

**RESULTS:** The complexes of the tested ligands compounds and ACE-2 receptors, which have a bond strength smaller than the control, were selected for analysis. It was discovered in this study that the aflavin, deoxypodophyllotoxin, galliccatechin, curcumin, and cucurbitacin B had a higher bond affinity than the control ligands XX5. This binding pocket interaction is also the same for all ligands.

**CONCLUSION:** It is hoped that this study would serve as a starting point for future research into possible treatment candidates for SARS-CoV-2.

## Introduction

Angiotensin-converting enzyme 2 (ACE-) is a homolog of ACE that was discovered in 2000 [1]. ACE-2 is a glycoprotein of type 1 integral membrane that contains 805 amino acids and is composed of two domains: carboxyl and catalytic. The catalytic domain of ACE-2 contains an active domain called the zinc metalloprotein domain. ACE-2 expression is found in the heart, lungs, liver, and intestines [1], [2]. ACE-2 functions physiologically in two distinct ways: as a dependent peptidase and as an independent peptidase. Dependent peptidase participates in the metabolism of angiotensin by converting it to angiotensin peptide 1–9 and then to angiotensin II peptide 1–7. Meanwhile, the function as independent peptidase is related to amino acids absorptions in intestines [3].

ACE-2 has been proved as the receptor of severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2) [4]. A study in 2020 showed that SARS-CoV-2 infects a cell with ACE-2 expression, but not to other SARS-expressed receptors commonly attached to coronaviruses, such as dipeptidyl peptidase 4 and aminopeptidase N [4]. Furthermore, another study showed that the binding affinity of SARS-CoV-2 spike glycoprotein toward ACE-2 receptor was 10 times bigger than those of the common coronaviruses receptors mentioned above [5]. The viruses could invade the cell through the ACE-2 receptor during internalization, a process when a receptor enters a cell along with the virus [6].

No drug has been noted to bind to ACE2 receptor to inhibit SARS-CoV-2 and ACE2 complex [7]. One of the measures that could successfully compete with endogenous ACE2 is soluble ACE2 or an Fc domain fused to ACE2 that may act as a decoy to direct SARS-CoV-2 away from endogenous ACE2 and itself bind the invading virus. The soluble form floats in the bloodstream and may act as a competitive interceptor

of SARS-CoV-2 from binding to the full length ACE2 anchored in the cell membrane. In a clinical study, human recombinant soluble ACE2 (hrsACE2) can significantly block initial stages of SARS-CoV-2 infection [8].

The most promising ACE2 therapy against COVID-19 is the drug APN01, which mimics the protein ACE2. The drug works by confusing the coronavirus, so it attaches to the drug instead of the ACE2 protein in the human cell. Positive evidence is emerging from small clinical trials on the effectiveness of APN01 in COVID-19 patients, especially those that are hospitalized [9].

Chloroquine (CQ) has a broad-spectrum action against viruses such as Dengue, Chikungunya, HIV, Hepatitis A, etc. CQ can inhibit a pre-entry step of the viral cycle by interfering with viral particles binding to their cellular cell surface receptor. In *in-vitro* and in experimental mouse model, CQ is an effective inhibitor of the replication of the SARS-CoV1 by blocking SARS-CoV1 fusion with and entry into the host cell through interfering with the glycosylation of the ACE2 receptor and the S protein. CQ impaired the terminal glycosylation of ACE2, suggesting that the variations in its glycosylation status might result in the ACE2–SARS CoV interaction being less efficient and therefore inhibit virus entry when the cells are treated with CQ. Furthermore, it was shown that the recombinant SARS-CoV S protein downregulates ACE2 expression. Based on its profile, it may be hypothesized that CQ also interferes with ACE2 receptor glycosylation thus preventing SARS-CoV2 binding to target cells. Earlier in the pandemic, CQ is one of promising drugs against the new SARS-CoV-2 coronavirus that causes COVID-19 [10], [11].

However, CQ shows potentially life-threatening cardiac side effects due to its quinidinic-like properties. Ongoing clinical trials listed in Chinese, European, and US clinical trial registries, with a large variety found in the design or endpoint. However, the result is potentially more subjective and more subject to bias than an objective one like death. To date, no published data support the use of CQ in COVID19 [12].

Indonesia has abundant natural resources to be explored as potential regiments through active compounds screening and development. Those kinds of regiments are possibly natural and semi synthetics [13], [14], [15]. The utilization of Indonesian herbs has become a cultural belief for many centuries in traditional medicine and has been passed down through the generations [16], [17], [18]. Herbal medicines and medicinal plant-based natural compounds have been shown to be potential for antiviral drugs, including coronavirus, herpes simplex virus, influenza virus, human immunodeficiency virus, hepatitis B and C viruses, SARS, and MERS [19].

Molecular docking is a method that uses chemometrics to visualize molecular and intermolecular forces to identify and predict receptor- ligand complexes [20]. This method is now widely used in drug discovery research [21]. Most drugs must interact with specific membrane molecules called receptors. Molecular docking has shown great promise as a new tool for discovering novel small molecule drugs with high protein targeting potential. *In silico* drug design interactions can predict the ligand-target protein interaction mechanism and the bond energy that occurs [22], [23]. Based on the concepts above, this study was conducted to identify the potential herbal medicines through *in silico* approach as the candidate for treating the transmission of COVID-19.

## Materials and Methods

### *Herbal medicine search*

We employ various active chemicals that are extensively included in herbal medicine plants found in Java. The active chemicals that we utilize in this investigation include Theaflavin, Deoxypodophyllotoxin, Gallic acid, Gallic acid gallate, Allicin, Quercetin, Annonamine, Curcumin, 6-Gingerol, Curcubitacin B [24], [25]. We chose these compounds because they are frequently found in herbal plants in Java that are frequently used by the general population. Apart from Theaflavin, Deoxypodophyllotoxin, Gallic acid gallate, Allicin, Quercetin, Annonamine, Curcumin, and 6-gingerol, Curcubitacin B has been shown in several studies to have antiviral activity [26], [27], [28], [29].

### *Ligand and protein preparation*

The 3D structure of each phytochemical substance was downloaded from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) or ChemSpider (<http://www.chemspider.com>) and then was saved in SDF format. Furthermore, the energy of the test ligand compound is minimized in ordered to get an ideal bond interaction effect using Open Babel. The compound XX5 (ChemID 395128) was used as a control ligand following pre [29] various research as an ACE-2 receptor Inhibitor [30]. Protein ACE-2 receptor which was obtained from Protein Data Bank web server (<https://www.rcsb.org/>). Protein stabilization was carried out to adjust to the body's physiology, carried out using Pymol by removing water atoms and adding hydrogen atoms [23].

The computational docking method was used to determine the orientation and conformation of ligands at protein-binding sites, as well as the strength of their bond. Specific docking was performed to ascertain

the interaction between the protein ACE-2 and the ligands mentioned previously. The software used to determine the ligand-binding affinity was PyRx 0.95. The coordinates of the bond's center were determined in previous studies [30]. The prediction of bond strength was done with grid box can be seen in Table 1. The grid box and dimension position get from the previous study [30].

**Table 1: Molecular docking coordinate**

Center_X	Center_Y	Center_Z	Size_X (Å)	Size_Y (Å)	Size_Z (Å)
45.27	8.21	32.65	30	30	30

### Pharmacokinetic profile

SwissADME (<http://www.swissadme.ch/index.php>) was used to determine the pharmacokinetic profile of the tested ligands compounds by entering the simplified molecular-input line-entry system (SMILES) formula for each active substance. SMILES data were retrieved from the PubChem database. Lipinski's Rule of Five analysis was conducted to determine the compound's pharmacokinetic properties [31].

### Visualization binding interaction

To determine the chemical bonds formed, we analyzed molecular interactions on molecular complexes generated through docking simulations using the Discovery Studio software version 16. 1. 0. Numerous chemical bonds were visualized in two-dimensional structures, including hydrogen, hydrophobic, Pi-Alkyl, Van der Waals, and electrostatic [32]. PyMol structural selection and coloring software was used to illustrate the complex three-dimensional structure of the mooring simulation results. The complexes of the tested ligand compounds and ACE-2 receptors, which have a bond strength smaller than the control, were selected for analysis.

## Results and Discussion

### Herbal medicine source

The ligands obtained from PubChem was Theaflavin (CID: 135403798), Deoxyphylloxytoxin (CID: 345501), Gallic acid (CID: 345501), Gallic acid (CID: 345501),

199472), Allicin (CID: 65036), Quercetin (CID: 5280343), Annonamine (CID: 56929881), Curcumin (CID: 969516), 6-Gingerol (CID: 969516), and Cucurbitacin B (CID: 5281316) with a molecular weight as shown in (Table 2). This active compound found in herb medicine in java such as Black tea, Propolis, Eucalyptus leaf, Allium sativum, Moringa oleifera, soursop, Curcuma longa and Zingiber officinale [29], [33], [34], [35], [36], [37], [38], [39]. The target proteins were identified in the PDB database with protein data bank code 1R4L. A sample was aligned in the laboratory using the X-ray method. ACE-2 receptor structure had a resolution of 3Å. Meanwhile, the protein resolution *in silico* represents the clarity of the atomic distance between amino acid residues when presented in the software; the higher the value, the more described the molecular visualization [30]. The compound XX5 (ChemID 395128) was used as a control ligand and download as sdf file.

### Pharmacokinetic analysis of test ligand compounds

Absorption, Distribution, Metabolism, and Excretion (ADME) is the study of how administered substances interact with the body over the course of their exposure. ADME is an important study to know how drugs will be administered to get an optimal therapeutic effect. This study calculated candidate drugs for ACE-2 inhibitors by SwissADME and PreAdmet. Druglikeness analysis based on Lipinski Rule of 5 (LR5). Lipinski's criteria 'Rule of Five' is used to evaluate the absorption ability and permeability of oral regimen. The drugs are identified as excellent in absorption ability and permeability if they meet that 'Rule of Five,' which is described as molecule mass ≤500 g/mol, LogP value ≤5, amount of hydrogen bond acceptor ≤10, and hydrogen bond donor ≤5 [40]. However, Lipinski specifies that the rule of 5 applies only to compounds that are not active transporter substrates. When the rule of 5 was developed, there was very little information available about drug transporters [31].

According to our findings as shown in Table 2, the ADME of three compounds found in nine herbal medicines does not meet LR5. Cucurbitacin B violates the first rule by having a molecule mass greater than 500 g/mol, whereas Gallic acid Gallate and Theaflavin violate three rules by having a molecule mass greater

**Table 2: The pharmacokinetic profile of ligand compounds**

Compound	Molecular weight	Hydrogen donor	Hydrogen acceptor	cLogP	Lipinski criteria
Theaflavin	564.49 g/mol	9	12	1.07	No
Deoxyphylloxytoxin	398.41 g/mol	0	7	3.08	Yes
Gallic acid Gallate	458.37 g/mol	8	11	1.01	No
Allicin	162.72 g/mol	0	1	1.61	Yes
Quercetin	302.24 g/mol	5	7	1.23	Yes
Annonamine	296.38 g/mol	1	2	1.53	Yes
Curcumin	368.38 g/mol	2	6	3.03	Yes
6-Gingerol	294.39 g/mol	2	4	3.13	Yes
Cucurbitacin B	558.70 g/mol	3	8	3.19	No

than 500 g/mol, a hydrogen bond acceptor greater than 10, and a hydrogen bond donor greater than 5. In addition, Theaflavin, Deoxypodophyllotoxin, Gallocatechin gallate, Allicin, Quercetin, Annonamie, Curcumin, and 6-gingerol met the requirements for LR5.

### Binding affinity interaction

Molecular docking is frequently used to understand how a small-molecule ligand recognize and interact with macromolecule, which is important in pharmaceutical research and drug discovery by placing a ligand (molecule) into a preferred specific region of receptor (DNA/protein) to form a stable complex of potential efficacy and specificity [41]. PyRx software was used to estimate binding energy, the molecular docking algorithm searches for all possible binding conformations and scores ligand-receptor complexes using a specific scoring function based on the molecular mechanism. Prediction of binding energy is accomplished by calculating the physical-chemical properties of the ligand-receptor complex using mathematical equations; a low (negative) energy indicates a stable complex and a high probability of forming a binding interaction [42].

Our natural compounds have binding energies ranging from 4.3 to  $-10.9$  kcal/mol, with the top five candidates having the lowest score when compared to the control ligand, indicating the highest binding affinity: Theaflavin ( $-10.9$  kcal/mol), Gallocathecin gallate ( $-10.7$  kcal/mol), Cucurbitacin B ( $-10.6$  kcal/mol), Deoxypodophyllotoxin ( $-9.6$  kcal/mol), Curcumin ( $-9.4$  kcal/mol) as shown in (Figure 1). Due to theaflavin's low binding energy, it will have a strong interaction with the ACE-2 receptor. Theaflavin, Gallocathecin gallate, Cucurbitacin B, Deoxypodophyllotoxin, and Curcumin were analyzed to determine their molecular interactions with the ACE-2 receptor.

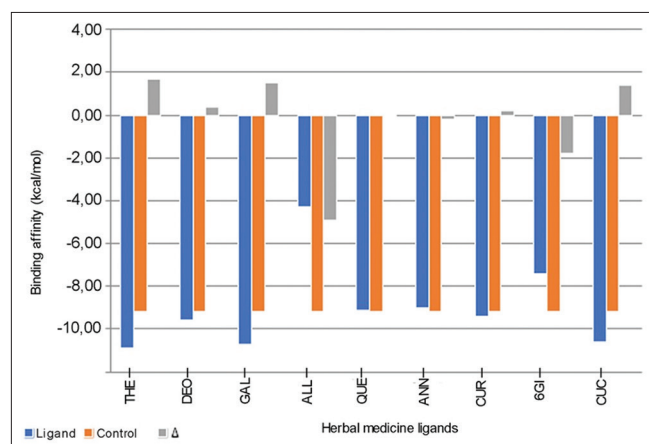


Figure 1: The result of molecular docking of herbal medicine ligands compared to control ligand

### Molecular docking interaction

There is another type to evaluate scoring function by physical event involved in the formation of the ligand-receptor complex [43]. The interaction between the control ligand (XX5) and the ACE-2 receptor-binding complex occurs through the formation of two hydrogen bonds at Arg273 and Pro346 and 11 hydrophobic bonds with a binding affinity of approximately  $-9.2$  kcal/mol.

We analyze the chemical compounds with the lowest bond energies to determine the molecular interactions and the types of bonds formed using the Discovery Studio software. As shown in Figure 2, Theaflavin, Gallocathecin gallate, Cucurbitacin B, Deoxypodophyllotoxin, and Curcumin have the same binding pocket interaction compared with control. Theaflavin forms a hydrogen bond at His354 and a hydrophobic bond at His374, Pro346, and Arg273 with an electrostatic bond. In contrast, ligand XX2 forms hydrogen bond interaction with Pro346 and hydrophobic bond with His345.

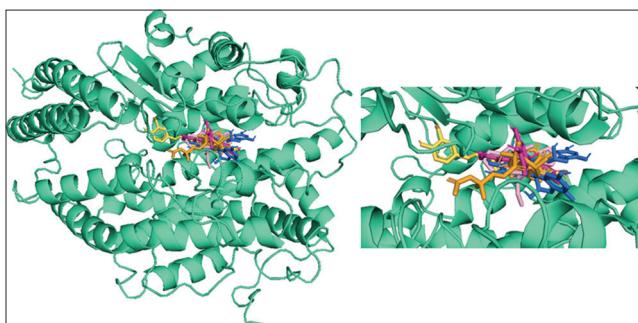


Figure 2: Binding site of angiotensin-converting enzyme 2 receptor to Theaflavin (Blue) and Gallocatechin (Magenta), Cucurbitacin B (Orange), Deoxypodophyllotoxin, Cucurmin (yellow)

Deoxypodophyllotoxin forms a hydrogen bond at His345, Arg273 and His 505, while hydrophobic bond at His374, Pro346, and Arg273 with electrostatic interaction. In contrast, the control ligand forms Arg273 as hydrogen bond and His505 as Hydrophobic bond interaction. Gallocatechin gallate had similar amino acid interactions. There was hydrogen bond (His345, Tyr515, Glu402), hydrophobic bond (Pro346), electrostatic bond (Glu375, Arg273), and Unfavorable donor-donor (His374). This interaction had the same interaction amino acid residues but different kinds of binding interaction with control. Curcumin forms a hydrogen bond at His505, Arg273 and His345, while hydrophobic bonds at Tyr510, Tyr347 and 378. Curcumin had the same type of binding interaction at Arg273 as hydrogen bond, while Tyr510, Thr347, His378 as hydrophobic bond. At last, Cucurbitacin B was only the same in one amino acid residue at His345, but the type of interaction binding was different from control as shown in (Figure 3). The type of interactions is important in triggering protein biological responses, such as activation and inhibition [44], [45]. Hence, the ligands have potential as drugs candidate for

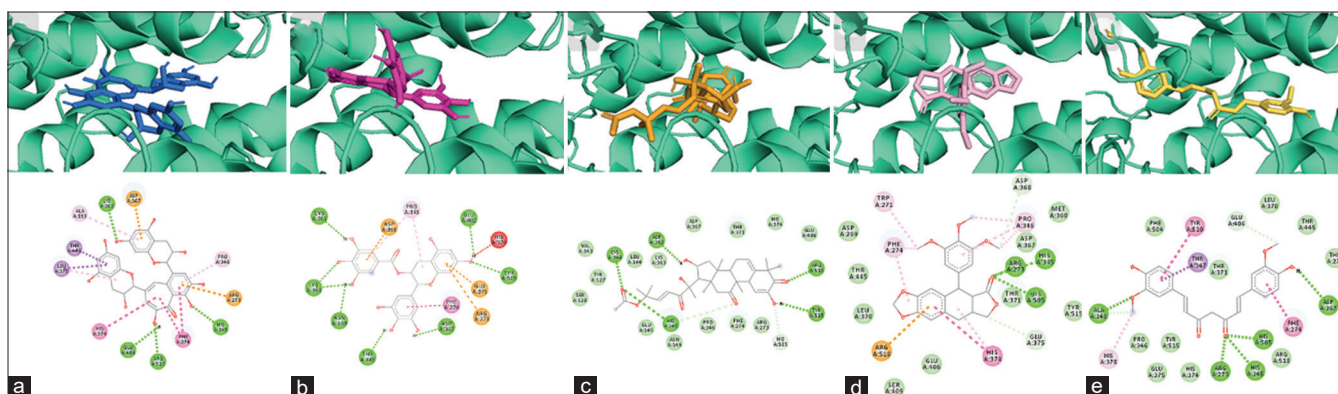


Figure 3: Interaction visualization between Ligands and angiotensin-converting enzyme 2 Receptor. (a) Theaflavin, (b) Gallocathecin, (c) Curcubitacin B, (d) Deoxypodophyllotoxin, (e) Curcumin

COVID-19. The findings of this study can be used as a baseline for future research as a potential therapeutic candidate against SARS-CoV-2.

## Conclusion

In sum, the results of the molecular docking analysis indicated Theaflavin, Deoxypodophyllotoxin, Gallocatechin, Curcumin, and Cucurbitacin B have promising as candidate drugs for COVID-19. It is suggested that additional research be conducted to determine the biological effects on ACE-2 receptors.

## References

1. Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. *J Biol Chem*. 2000;275(43):33238-43. <http://doi.org/10.1074/jbc.M002615200>  
PMid:10924499
2. Turner AJ, Hooper NM. The angiotensin-converting enzyme gene family: Genomics and pharmacology. *Trends Pharmacol Sci*. 2002;23(4):177-83. [http://doi.org/10.1016/s0165-6147\(00\)01994-5](http://doi.org/10.1016/s0165-6147(00)01994-5)  
PMid:11931993
3. Camargo SM, Singer D, Makrides V, Huggel K, Pos KM, Wagner CA, et al. Tissue-specific amino acid transporter partners ACE2 and collectrin differentially interact with hartnp mutations. *Gastroenterology*. 2009;136(3):872-82. <http://doi.org/10.1053/j.gastro.2008.10.055>  
PMid:19185582
4. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet*. 2020;395(10229):1054-62. [http://doi.org/10.1016/S0140-6736\(20\)30566-3](http://doi.org/10.1016/S0140-6736(20)30566-3)  
PMid:32171076
5. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*. 2020;367(6483):1260-3. <http://doi.org/10.1126/science.abb2507>  
PMid:32075877
6. Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care*. 2020;24(1):422. <http://doi.org/10.1186/s13054-020-03120-0>  
PMid:32660650
7. Poduri R, Joshi G, Jagadeesh G. Drugs targeting various stages of the SARS-CoV-2 life cycle: Exploring promising drugs for the treatment of Covid-19. *Cell Signal*. 2020;74:109721. <http://doi.org/10.1016/j.cellsig.2020.109721>  
PMid:32711111
8. Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell*. 2020;181(4):905-13.e7. <http://doi.org/10.1016/j.cell.2020.04.004>  
PMid:32333836
9. APN01 Our Work on a Potential Drug Candidate for COVID-19 Treatment APEIRON Biologics. Available from: <https://www.apeiron-biologics.com/our-work-on-a-potential-drug-candidate-for-covid-19>. [Last accessed on 2021 Aug 19].
10. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: What to expect for COVID-19? *Int J Antimicrob Agents*. 2020;55(5):105938. <http://doi.org/10.1016/j.ijantimicag.2020.105938>  
PMid:32171740
11. Chen L, Chen H, Dong S, Huang W, Chen L, Wei Y, et al. The effects of chloroquine and hydroxychloroquine on ACE2-related coronavirus pathology and the cardiovascular system: An evidence-based review. *Function*. 2020;1:zqaa012.
12. Rebeaud ME, Zores F. SARS-CoV-2 and the use of chloroquine as an antiviral treatment. *Front Med*. 2020;7:184. <http://doi.org/10.3389/fmed.2020.00184>  
PMid:32391371
13. Gbenou JD, Ahounou JF, Akakpo HB, Laleye A, Yayi E, Gbaguidi F, et al. Phytochemical composition of *Cymbopogon citratus* and *Eucalyptus citriodora* essential oils and their anti-inflammatory and analgesic properties on Wistar rats. *Mol Biol Rep*. 2013;40(2):1127-34. <http://doi.org/10.1007/s11033-012-2155-1>  
PMid:23065287
14. Harvey AL, Edrada-Ebel R, Quinn RJ. The re-emergence of natural products for drug discovery in the genomics era. *Nat Rev Drug Discov*. 2015;14(2):111-29. <http://doi.org/10.1038/nrd4510>  
PMid:25614221
15. Newman DJ, Cragg GM. Natural products as sources of new drugs over the 30 years from 1981 to 2010. *J Nat Prod*. 2012;75(3):311-35. <http://doi.org/10.1021/np200906s>

- PMid:22316239
16. Elfahmi, Woerdenbag HJ, Kayser O. Jamu: Indonesian traditional herbal medicine towards rational phytopharmacological use. *J Herb Med.* 2014;4:51-73.
  17. Henuk YL. Medicinal plants used in traditional medicine and their roles in Indonesia. *J Plant Pathol Microbiol.* 2017;8:5.
  18. Purwanti E, Mahmudati N, Faradila SF, Fauzi A. Utilization of plants as traditional medicine for various diseases: Ethnobotany study in Sumenep, Indonesia. *AIP Conf Proc* 2020;2231:040024. <https://doi.org/10.1063/5.0002430>
  19. Xian Y, Zhang J, Bian Z, Zhou H, Zhang Z, Lin Z, *et al.* Bioactive natural compounds against human coronaviruses: A review and perspective. *Acta Pharm Sin B.* 2020;10(7):1163-74. <http://doi.org/10.1016/j.apsb.2020.06.002>  
PMid:32834947
  20. Kharisma V, Nugraha A. Computational study of ginger (*Zingiber officinale*) as E6 inhibitor in human papillomavirus Type 16 (HPV-16) infection. *Biochem Cell Arch.* 2020;20:3155-9.
  21. Pagadala NS, Syed K, Tuszynski J. Software for molecular docking: A review. *Biophys Rev.* 2017;9(2):91-102. <http://doi.org/10.1007/s12551-016-0247-1>  
PMid:28510083
  22. Jing Z, Feng H. Studies on the molecular docking and amino acid residues involving in recognition of substrate in proline iminopeptidase by site-directed mutagenesis. *Protein J.* 2015;34(3):173-80. <http://doi.org/10.1007/s10930-015-9611-4>  
PMid:25957260
  23. Syaban MF, Rachman HA, Arrahman AD, Hidayana N, Purna J, Pratama FA. *Allium sativum* as antimalaria agent via falcipain protease-2 inhibitor mechanism: Molecular docking perspective. *Clin Res J Intern Med* 2021;2:6.
  24. Sumarni W, Sudarmin S, Sumarti SS. The scientification of jamu: A study of Indonesian's traditional medicine. *J Phys Conf Ser.* 2019;1321:032057.
  25. EffAR, Rahayu ST, Mahayasih PG. Standardization of Indonesian traditional antihypertensive medicines (Jamu) through the ace inhibitor mechanism. *Pharmacogn J* 2020;12:422-9. <http://doi.org/10.5530/pj.2020.12.65>
  26. Cione E, La Torre C, Cannataro R, Caroleo MC, Plastina P, Gallelli L. Quercetin, epigallocatechin gallate, curcumin, and resveratrol: From dietary sources to human MicroRNA modulation. *Molecules.* 2019;25(1):63. <http://doi.org/10.3390/molecules25010063>  
PMid:31878082
  27. Jang M, Park YI, Cha YE, Park R, Namkoong S, Lee JI, *et al.* Tea polyphenols EGCG and theaflavin inhibit the activity of SARS-CoV-2 3CL-protease *in vitro*. *Evid Based Complement Alternat Med.* 2020;2020:5630838.
  28. Kapoor N, Ghorai SM, Kushwaha PK, Shukla R, Aggarwal C, Bandichhor R. Plausible mechanisms explaining the role of cucurbitacins as potential therapeutic drugs against coronavirus 2019. *Inform Med Unlocked.* 2020;21:100484.  
PMid:33251326
  29. Rouf R, Uddin SJ, Sarker DK, Islam MT, Ali ES, Shilpi JA, *et al.* Antiviral potential of garlic (*Allium sativum*) and its organosulfur compounds: A systematic update of pre-clinical and clinical data. *Trends Food Sci Technol.* 2020;104:219-34. <http://doi.org/10.1016/j.tifs.2020.08.006>  
PMid:32836826
  30. Borlinghaus J, Albrecht F, Gruhlke M, Nwachukwu I, Slusarenko A. Allicin: Chemistry and biological properties. *Molecules.* 2014;19:12591-618.
  31. Joshi T, Joshi T, Sharma P, Mathpal S, Pundir H, Bhatt V, *et al.* *In silico* screening of natural compounds against COVID-19 by targeting Mpro and ACE2 using molecular docking. *Eur Rev Med Pharmacol Sci.* 2020;24(8):4529-36. [http://doi.org/10.26355/eurrev\\_202004\\_21036](http://doi.org/10.26355/eurrev_202004_21036)  
PMid:32373991
  32. Daina A, Michielin O, Zoete V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep.* 2017;7:42717. <http://doi.org/10.1038/srep42717>  
PMid:28256516
  33. Lam WW, Siu SW. PyMOL mControl: Manipulating molecular visualization with mobile devices. *Biochem Mol Biol Educ.* 2017;45(1):76-83. <http://doi.org/10.1002/bmb.20987>  
PMid:27292587
  34. Takemoto M, Takemoto H. Synthesis of theaflavins and their functions. *Molecules.* 2018;23(4):918. <http://doi.org/10.3390/molecules23040918>  
PMid:29659496
  35. Guerram M, Jiang ZZ, Sun L, Zhu X, Zhang LY. Antineoplastic effects of deoxypodophyllotoxin, a potent cytotoxic agent of plant origin, on glioblastoma U-87 MG and SF126 cells. *Pharmacol Rep.* 2015;67(2):245-52. <http://doi.org/10.1016/j.pharep.2014.10.003>  
PMid:25712646
  36. Khaled M, Jiang ZZ, Zhang LY. Deoxypodophyllotoxin: A promising therapeutic agent from herbal medicine. *J Ethnopharmacol.* 2013;149(1):24-34. <http://doi.org/10.1016/j.jep.2013.06.021>  
PMid:23792585
  37. Gamboa-Gómez CI, González-Laredo RF, Gallegos-Infante JA, Mar Larrosa Pérez MD, Moreno-Jiménez MR, Flores-Rueda AG. Antioxidant and angiotensin-converting enzyme inhibitory activity of eucalyptus camaldulensis and litsea glaucescens infusions fermented with kombucha consortium. *Food Technol Biotechnol.* 2016;54(3):367-74. <http://doi.org/10.17113/ftb.54.03.16.4622>  
PMid:27956869
  38. Ko CH, Lau KM, Choy WY, Leung PC. Effects of tea catechins, epigallocatechin, gallic acid, and gallic acid gallate, on bone metabolism. *J Agric Food Chem.* 2009;57(16):7293-7. <http://doi.org/10.1021/jf901545u>  
PMid:19653629
  39. Agrawal PK, Agrawal C, Blunden G. Quercetin: Antiviral significance and possible COVID-19 integrative considerations. *Nat Prod Commun.* 2020;15:1-10.
  40. Wang S, Zhang C, Yang G, Yang Y. Biological properties of 6-gingerol: A brief review. *Nat Prod Commun.* 2014;9:1027-30.  
PMid:25230520
  41. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev.* 2012;64:4-17.
  42. Syaban MF, Erwan NE, Syamsuddin MR, Az Zahra F, Sabila FL. Molecular docking approach of viscosin as antibacterial for methicillin-resistant *Staphylococcus aureus* Via  $\beta$ -lactamase Inhibitor mechanism. *Clin Res J Intern Med.* 2021;2(2):187-92.
  43. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. In: Hempel JE, Williams CH, Hong CC, editors. *Chemical Biology.* New York: Springer; 2015. p. 243-50.
  44. Ferreira L, dos Santos R, Oliva G, Andricopulo A. Molecular docking and structure-based drug design strategies. *Molecules.* 2015;20(7):13384-421. <https://doi.org/10.3390/molecules200713384>  
PMid:26205061
  45. Fu Y, Zhao J, Chen Z. Insights into the molecular mechanisms of protein-ligand interactions by molecular docking and molecular dynamics simulation: A case of oligopeptide binding protein. *Comput Math Methods Med* 2018;2018:3502514. <https://doi.org/10.1155/2018/3502514>