KAJIAN SENYAWA DERIVAT FLOROTANIN *Ecklonia cava* SEBAGAI KANDIDAT ANTI SARS-CoV-2 BERDASARKAN PENDEKATAN *MOLECULAR DOCKING*

SKRIPSI

diajukan untuk memenuhi sebagian dari syarat memperoleh gelar Sarjana Sains
Program Studi Kimia

oleh

Maudy Shintia
NIM 1605479

PROGRAM STUDI KIMIA

DEPARTEMEN PENDIDIKAN KIMIA

FAKULTAS PENDIDIKAN MATEMATIKA DAN ILMU PENGETAHUAN ALAM

UNIVERSITAS PENDIDIKAN INDONESIA

BANDUNG

2020

KAJIAN SENYAWA DERIVAT FLOROTANIN *Ecklonia cava* SEBAGAI KANDIDAT ANTI SARS-CoV-2 BERDASARKAN PENDEKATAN *MOLECULAR DOCKING*

Oleh

Maudy Shintia

Sebuah skripsi yang diajukan untuk memenuhi sebagian syarat memperoleh gelar Sarjana Sains Program Studi Kimia

Universitas Pendidikan Indonesia

Agustus 2020

MAUDY SHINTIA

KAJIAN SENYAWA DERIVAT FLOROTANIN *Ecklonia cava* SEBAGAI KANDIDAT ANTI SARS-CoV-2 BERDASARKAN PENDEKATAN *MOLECULAR DOCKING*

disetujui dan disahkan oleh pembimbing:

Pembimbing I

Heli Siti Halimatul Munawaroh, Ph.D

NIP. 197907302001122002

Pembimbing II

Gun Gun Gumilar, S.Pd., M.Si.

NIP. 197906262001121001

Mengetahui

Ketua Departemen Pendidikan Kimia FPMIPA UPI

Dr. Hendrawan, M.Si.

NIP. 196309111989011001

ABSTRAK

COVID-19 (*Coronavirus Disease 2019*) yang disebabkan oleh SARS-CoV-2 (*Severe Acute Respiratory Syndrome Coronavirus* 2) telah mendorong banyak peneliti untuk melakukan eksplorasi senyawa kandidat anti-SARS-CoV-2. Senyawa derivat florotanin, terutama diekol dari makroalga coklat *Ecklonia cava* dilaporkan memiliki potensi sebagai anti-SARS-CoV yang secara genomik memiliki kemiripan hingga 86% dengan SARS CoV-2. Pada penelitian ini dilakukan *screening* potensi senyawa derivat florotanin dari *Ecklonia cava* sebagai kandidat anti-SARS-CoV-2, menggunakan simulasi *molecular docking* terhadap tiga reseptor yang berperan penting pada COVID-19, yaitu M^{pro} SARS-CoV-2, RBD SARS-CoV-2 dan ACE2. Tahapan penelitian yang dilakukan meliputi preparasi protein menggunakan Autodock Tools 1.5.6, validasi metode *docking*, optimasi dan preparasi ligan menggunakan MOPAC dan Autodock Tools 1.5.6, *molecular docking* menggunakan Autodock Vina 4.2, serta visualisasi sisi pengikatan dan interaksi molekuler dengan menggunakan *Biovia Discovery Studio* 2020. Hasil penelitian menunjukkan bahwa diekol memiliki afinitas pengikatan tertinggi jika dibandingkan dengan senyawa derivat florotanin lainnya dan kandidat obat komersial. Afinitas pengikatan diekol dengan M^{pro}, RBD SARS-CoV-2 dan ACE2, berurut-turut sebesar 9,0 *kkal/mol*, 7,5 *kkal/mol* dan -7,9 *kkal/mol.* Afinitas pengikatan diekol dengan M^{pro}, RBD SARS-CoV-2 dan ACE2 berturut-turut 1,07; 1,17; 1,27 kali lipat lebih tinggi dibandingkan nelfinavir dan mencapai 1,50; 1,49; 1,47 kali lipat lebih tinggi dibandingkan klorokuin, serta 1,48; 1,40; 1,44 kali lipat lebih tinggi dibandingkan hidroksiklorokuin. Semua senyawa derivat florotanin dan kandidat obat komersial berinteraksi dengan M^{pro} dan RBD SARS-CoV-2 pada sisi pengikatan yang sama, sedangkan pada ACE2 tidak semua berikatan pada sisi yang sama. Interaksi diekol dengan ketiga reseptor tersebut melibatkan ikatan hidrogen, interaksi hidrofobik dan gaya Van der Waals. Berdasarkan hasil simulasi ditunjukkan bahwa senyawa derivat florotanin, terutama diekol diprediksi memiliki potensi sebagai senyawa anti-SARS-CoV-2. Uji *in vitro* dan *in vivo* perlu dilakukan untuk mengetahui efektivitas senyawa derivat florotanin sebagai anti-SARS-CoV-2 secara empirik.

Kata Kunci: COVID-19, *Ecklonia cava*, florotanin, *molecular docking*, SARS-CoV-2.

ABSTRACT

COVID-19 (*Coronavirus Disease 2019*) *which caused by* SARS-CoV-2 *(Severe Acute Respiratory Syndrome Coronavirus 2) has been growing interests among researchers to explore functional compounds for anti-*SARS-CoV-2. *Phlorotannin derivatives, particularly dieckol derived from brown macroalgae Ecklonia cava has been reported to exhibit the potential as anti-*SARS-CoV, *which has 86% of genomic similarity with* SARS-CoV-2. *In this study, a molecular docking simulation was carried out to screen the potential of phlorotannin derivatives derived from Ecklonia cava as anti-*SARS-CoV-2 *candidates. Molecular docking simulation was performed between Phlorotannin derivatives derived from Ecklonia cava with three significant receptors of* COVID-19 *i.e.* M^{pro} SARS-CoV-2, RBD SARS-CoV-2, *and* ACE2. *Research stages include preparation of protein using* Autodock Tools 1.5.6, *docking methods validation, optimization and preparation of ligand using* MOPAC *and* Autodock Tools 1.5.6, *molecular docking using* Autodock Vina 4.2, *and visualization of the binding site and molecular interactions using Biovia Discovery Studio*. *The results show that dieckol has the highest binding affinity compared to either phlorotannin derivatives and commercial drug candidates. The binding affinity of dieckol with* M^{pro} SARS-CoV-2, RBD SARS-CoV-2, *and* ACE2 *were* 9.0 *kcal/mol;* 7.5 *kcal/mol; and* -7.9 *kcal/mol, respectively. The binding affinity of dieckol with* M^{pro}, RBD SARS-CoV-2, *and* ACE2 *were* 1.07; 1.17; 1.27 *times higher than nelfinavir,* 1.50; 1.49; 1.47-*times higher than those of the chloroquine, and* 1.48; 1.40; 1.44 *times higher compared to hydroxychloroquine. Phlorotannin derivatives and commercial drugs binds to the same active site of* M^{pro} *and* RBD SARS-CoV-2, *but on a different binding site of* ACE2. *Molecular interactions of dieckol with three receptors involves hydrogen bonds, hydrophobic interactions and van der Waals forces. Molecular docking simulation suggested that phlorotannin derivatives, particularly dieckol, has potential as anti-*SARS-CoV-2. *In vitro and in vivo study has to be conducted in order to explore the efficacy of phlorotannin derivatives as anti-*SARS-CoV-2 *empirically***.**

Keywords: COVID-19, *Ecklonia cava, phlorotannin, molecular docking,* SARS-CoV-2.

DAFTAR ISI

DAFTAR PUSTAKA

Adem, S., Eyupoglu, V., Sarfraz, I., Rasul, A., & Ali, M. (2020). Identification of potent COVID-19 main protease (Mpro) inhibitors from natural polyphenols: An in silico strategy unveils a hope against CORONA Sevki. *PREPRINTS (Www.Preprints.Org), March 2020*. https://doi.org/10.20944/preprints201810.0478.v1

Ajay, & Murcko, M. A. (1995). Computational Methods to Predict Binding Free Energy in Ligand-Receptor Complexes. *Journal of Medicinal Chemistry*, *38*(26), 4953–4967. https://doi.org/10.1021/jm00026a001

Al-Bari, A. A. (2014). Chloroquine analogues in drug discovery: New directions of uses, mechanisms of actions and toxic manifestations from malaria to multifarious diseases. *Journal of Antimicrobial Chemotherapy*, *70*(6), 1608–1621. https://doi.org/10.1093/jac/dkv018

Artan, M., Li, Y., Karadeniz, F., Lee, S. H., Kim, M. M., & Kim, S. K. (2008). Anti-HIV-1 activity of phloroglucinol derivative, 6,6′-bieckol, from Ecklonia cava. *Bioorganic and Medicinal Chemistry*, *16*(17), 7921–7926. https://doi.org/10.1016/j.bmc.2008.07.078

Baudoux, P., Carrat, C., Besnardeau, L., Charley, B., & Laude, H. (1998). Coronavirus pseudoparticles formed with recombinant M and E proteins induce alpha interferon synthesis by leukocytes. *Journal of Virology*, *72*(11), 8636–8643. https://doi.org/10.1128/JVI.72.11.8636-8643.1998

Belouzard, S., Millet, J. K., Licitra, B. N., & Whittaker, G. R. (2012). Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses*, *4*(6), 1011–1033. https://doi.org/10.3390/v4061011

Berg John L. Tymoczko, & Jeremy, L. S. (2007). *Biochemistry 6th Edition (Sixth Ed.)*. W.H. Freeman and Company. https://www.ncbi.nlm.nih.gov/books/NBK21154/

Chappell, M. C., Marshall, A. C., Alzayadneh, E. M., Shaltout, H. A., & Diz, D. I. (2014). Update on the angiotensin converting enzyme 2-angiotensin (1-7)-Mas receptor axis: Fetal programing, sex differences, and intracellular pathways. *Frontiers in Endocrinology*, *5*(JAN), 1–13. https://doi.org/10.3389/fendo.2013.00201

Chen, Y. W., Yiu, C. P. B., & Wong, K. Y. (2020). Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CLpro) structure: Virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates. *F1000Research*, *9*, 1–17. https://doi.org/10.12688/f1000research.22457.1

Cleaves, H. J. (Jim). (2011). *Steric Effect BT - Encyclopedia of Astrobiology* (M. Gargaud, R. Amils, J. C. Quintanilla, H. J. (Jim) Cleaves, W. M. Irvine, D. L. Pinti, & M. Viso (eds.); p. 1598). Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-642-11274-4_1517

Coleman, R. G., Carchia, M., Sterling, T., Irwin, J. J., & Shoichet, B. K. (2013). Ligand Pose and Orientational Sampling in Molecular Docking. *PLOS ONE*, *8*(10), e75992. https://doi.org/10.1371/journal.pone.0075992

Cox, M., & Nelson, D. (2008). Lehninger Principles of Biochemistry. In *Wh Freeman* (Vol. 5). https://doi.org/10.1007/978-3-662-08289-8

Dassault Systèmes Biovia Corp. (2016). *Discovery Studio Visualizer v. 17.2.0.16349*.

De Clercq, E. (2004). Antiviral drugs in current clinical use. *Journal of Clinical Virology : The Official Publication of the Pan American Society for Clinical Virology*, *30*(2), 115—133. https://doi.org/10.1016/j.jcv.2004.02.009

de Groot, R. J., Baker, S. C., Baric, R. S., Brown, C. S., Drosten, C., Enjuanes, L., Fouchier, R. A. M., Galiano, M., Gorbalenya, A. E., Memish, Z. A., Perlman, S., Poon, L. L. M., Snijder, E. J., Stephens, G. M., Woo, P. C. Y., Zaki, A. M., Zambon, M., & Ziebuhr, J. (2013). Middle East Respiratory Syndrome Coronavirus (MERS-CoV): Announcement of the Coronavirus Study Group.

Journal of Virology, *87*(14), 7790–7792. https://doi.org/10.1128/jvi.01244-13

de Haan, C. A. M., Kuo, L., Masters, P. S., Vennema, H., & Rottier, P. J. M. (1998). Coronavirus Particle Assembly: Primary Structure Requirements of the Membrane Protein. *Journal of Virology*, *72*(8), 6838–6850. https://doi.org/10.1128/jvi.72.8.6838-6850.1998

de Haan, C. A. M., & Rottier, P. J. M. (2005). Molecular Interactions in the Assembly of Coronaviruses. *Advances in Virus Research*, *64*(January), 165–230. https://doi.org/10.1016/S0065-3527(05)64006-7

Devaux, C. A., Rolain, J. M., Colson, P., & Raoult, D. (2020). New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *International Journal of Antimicrobial Agents*, *December 2019*, 105938. https://doi.org/10.1016/j.ijantimicag.2020.105938

Devaux, C. A., Rolain, J. M., & Raoult, D. (2020). ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. *Journal of Microbiology, Immunology and Infection*, *53*(3), 425–435. https://doi.org/10.1016/j.jmii.2020.04.015

Ghosh, R., Chakraborty, A., Biswas, A., & Chowdhuri, S. (2020). Evaluation of green tea polyphenols as novel corona virus (SARS CoV-2) main protease (Mpro) inhibitors–an in silico docking and molecular dynamics simulation study. *Journal of Biomolecular Structure and Dynamics*, *0*(0), 1–13. https://doi.org/10.1080/07391102.2020.1779818

Głowacki, E. D., Irimia-Vladu, M., Bauer, S., & Sariciftci, N. S. (2013). Hydrogen-bonds in molecular solids-from biological systems to organic electronics. *Journal of Materials Chemistry B*, *1*(31), 3742–3753. https://doi.org/10.1039/c3tb20193g

Gorbalenya, A. E., Baker, S. C., Baric, R. S., de Groot, R. J., Drosten, C., Gulyaeva, A. A., Haagmans, B. L., Lauber, C., Leontovich, A. M., Neuman, B. W., Penzar, D., Perlman, S., Poon, L. L. M., Samborskiy, D. V., Sidorov, I. A., Sola, I., &

Ziebuhr, J. (2020). The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nature Microbiology*, *5*(4), 536–544. https://doi.org/10.1038/s41564-020-0695-z

Gralinski, L. E., & Menachery, V. D. (2020). Return of the coronavirus: 2019-nCoV. *Viruses*, *12*(2), 1–8. https://doi.org/10.3390/v12020135

Gui, M., Song, W., Zhou, H., Xu, J., Chen, S., Xiang, Y., & Wang, X. (2017). Cryo-electron microscopy structures of the SARS-CoV spike glycoprotein reveal a prerequisite conformational state for receptor binding. *Cell Research*, *27*(1), 119–129. https://doi.org/10.1038/cr.2016.152

Guiry, M.D. & Guiry, G. M. (2020). *AlgaeBase.* World-Wide Electronic Publication. https://www.algaebase.org

Guo, Y. R., Cao, Q. D., Hong, Z. S., Tan, Y. Y., Chen, S. D., Jin, H. J., Tan, K. Sen, Wang, D. Y., & Yan, Y. (2020). The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak- A n update on the status. *Military Medical Research*, *7*(1), 1–10. https://doi.org/10.1186/s40779-020-00240-0

Gwathmey, T. M., Shaltout, H. A., Nixon, P. A., O'shea, T. M., Rose, J. C., Washburn, L. K., & Chappell, M. C. (2008). Gender differences in urinary ACE and ACE2 activities in adolescents. *The FASEB Journal*, *22*(S1), 940.6-940.6. https://doi.org/10.1096/fasebj.22.1_supplement.940.6

Hasan, C., & Mehmet, O. (2020). Comparison of Clinically Approved Molecules on SARS-CoV-2 Drug Target Proteins: A Molecular Docking Study. *ChemRxiv*, *1*. https://doi.org/10.26434/chemrxiv.12090828.v1

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, *395*(10223), 497–506.

https://doi.org/10.1016/S0140-6736(20)30183-5

Jaghoori, M. M., Bleijlevens, B., & Olabarriaga, S. D. (2016). 1001 Ways to run AutoDock Vina for virtual screening. *Journal of Computer-Aided Molecular Design*, *30*(3), 237–249. https://doi.org/10.1007/s10822-016-9900-9

Jeffrey, G. A. (1997). An Introduction to Hydrogen Bonding By George A. Jeffrey (University of Pittsburgh). Oxford University Press: New York and Oxford. 1997. ix + 303 pp. $60.00. ISBN 0-19-509549-9. In *Oxford* (Vol. 120, Issue 22). Oxford. https://doi.org/10.1021/ja9756331

Jung, W. K., Heo, S. J., Jeon, Y. J., Lee, C. M., Park, Y. M., Byun, H. G., Choi, Y. H., Park, S. G., & Choi, I. L. W. (2009). Inhibitory effects and molecular mechanism of dieckol isolated from marine brown alga on COX-2 and iNOS in microglial cells. *Journal of Agricultural and Food Chemistry*, *57*(10), 4439–4446. https://doi.org/10.1021/jf9003913

Kang, K. A., Lee, K. H., Chae, S., Zhang, R., Jung, M. S., Lee, Y., Kim, S. Y., Kim, H. S., Joo, H. G., Park, J. W., Ham, Y. M., Lee, N. H., & Hyun, J. W. (2005). Eckol isolated from Ecklonia cava attenuates oxidative stress induced cell damage in lung fibroblast cells. *FEBS Letters*, *579*(28), 6295–6304. https://doi.org/10.1016/j.febslet.2005.10.008

Kang, K. A., Lee, K. H., Park, J. W., Lee, N. H., Na, H. K., Surh, Y. J., You, H. J., Chung, M. H., & Hyun, J. W. (2007). Triphlorethol-A induces heme oxygenase-1 via activation of ERK and NF-E2 related factor 2 transcription factor. *FEBS Letters*, *581*(10), 2000–2008. https://doi.org/10.1016/j.febslet.2007.04.022

Kjellman, F.R. & Petersen, J. V. (1885). Om Japans Laminariaceer. *Vega-Expeditionens Vetenskapliga Iakttagelser. Stokholm 4*, 255–280.

Kumar, R., Singh, C., Saifi, A., Kumar, S., & Kumar, B. (2020). Corona Virus, Precaution and Some Treatments. *American Journal of Biomedical Research*, *8*(1), 15–18. https://doi.org/10.12691/ajbr-8-1-3

Lan, J., Ge, J., Yu, J., Shan, S., Zhou, H., Fan, S., Zhang, Q., Shi, X., Wang, Q., Zhang, L., & Wang, X. (2020). Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*, *581*(7807), 215–220. https://doi.org/10.1038/s41586-020-2180-5

Li, F. (2016). Structure, Function, and Evolution of Coronavirus Spike Proteins. *Annual Review of Virology*, *3*(1), 237–261. https://doi.org/10.1146/annurev-virology-110615-042301

Liu, J., Cao, R., Xu, M., Wang, X., Zhang, H., Hu, H., Li, Y., Hu, Z., Zhong, W., & Wang, M. (2020). Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discovery*, *6*(1), 6–9. https://doi.org/10.1038/s41421-020-0156-0

Lukitaningsih, E., Wisnusaputra, A., & Sudarmanto, B. S. A. (2009). SCRINING IN SILICO ACTIVE COMPOUND OF Pachyrrhizus erosus AS ANTITIROSINASE ON Aspergillus oryzae (COMPUTATTIONAL STUDY WITH HOMOLOGY MODELING AND MOLECULAR DOCKING). *Majalah Obat Tradisional (Traditional Medicine Journal)*, *20*(1), 7–15.

Maegawa, M., Yokohama, Y., & Aruga, Y. (1987). Critical light conditions for young Ecklonia cava and Eisenia bicyclis with reference to photosynthesis. *Hydrobiologia*, *151*(1), 447–455. https://doi.org/10.1007/BF00046166

Mauthe, M., Orhon, I., Rocchi, C., Zhou, X., Luhr, M., Hijlkema, K. J., Coppes, R. P., Engedal, N., Mari, M., & Reggiori, F. (2018). Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion. *Autophagy*, *14*(8), 1435–1455. https://doi.org/10.1080/15548627.2018.1474314

McBride, R., van Zyl, M., & Fielding, B. C. (2014). The coronavirus nucleocapsid is a multifunctional protein. *Viruses*, *6*(8), 2991–3018. https://doi.org/10.3390/v6082991

Mengist, H. M., Fan, X., & Jin, T. (2020). Designing of improved drugs for COVID-

19: Crystal structure of SARS-CoV-2 main protease Mpro. *Signal Transduction and Targeted Therapy*, *5*(1), 2–3. https://doi.org/10.1038/s41392-020-0178-y

Mingo, R. M., Simmons, J. A., Shoemaker, C. J., Nelson, E. A., Schornberg, K. L., D'Souza, R. S., Casanova, J. E., & White, J. M. (2015). Ebola Virus and Severe Acute Respiratory Syndrome Coronavirus Display Late Cell Entry Kinetics: Evidence that Transport to NPC1 + Endolysosomes Is a Rate-Defining Step . *Journal of Virology*, *89*(5), 2931–2943. https://doi.org/10.1128/jvi.03398-14

Mirza, M. U., & Froeyen, M. (2020). Structural elucidation of SARS-CoV-2 vital proteins: Computational methods reveal potential drug candidates against main protease, Nsp12 polymerase and Nsp13 helicase. *Journal of Pharmaceutical Analysis*. https://doi.org/10.1016/j.jpha.2020.04.008

Moitessier, N., Englebienne, P., Lee, D., Lawandi, J., & Corbeil, C. R. (2008). Towards the development of universal, fast and highly accurate docking/scoring methods: A long way to go. *British Journal of Pharmacology*, *153*(SUPPL. 1), 7–26. https://doi.org/10.1038/sj.bjp.0707515

Morse, J. S., Lalonde, T., Xu, S., & Liu, W. R. (2020). Learning from the Past: Possible Urgent Prevention and Treatment Options for Severe Acute Respiratory Infections Caused by 2019-nCoV. *ChemBioChem*, *21*(5), 730–738. https://doi.org/10.1002/cbic.202000047

Muchtaridi, M., Dermawan, D., & Yusuf, M. (2018). Molecular docking, 3D structure-based pharmacophore modeling, and ADME prediction of alpha mangostin and its derivatives against estrogen receptor alpha. *Journal of Young Pharmacists*, *10*(3), 252–259. https://doi.org/10.5530/jyp.2018.10.58

Neuman, B. W., Kiss, G., Kunding, A. H., Bhella, D., Baksh, M. F., Connelly, S., Droese, B., Klaus, J. P., Makino, S., Sawicki, S. G., Siddell, S. G., Stamou, D. G., Wilson, I. A., Kuhn, P., & Buchmeier, M. J. (2011). A structural analysis of M protein in coronavirus assembly and morphology. *Journal of Structural Biology*, *174*(1), 11–22. https://doi.org/10.1016/j.jsb.2010.11.021

Nieto-Torres, J. L., DeDiego, M. L., Verdiá-Báguena, C., Jimenez-Guardeño, J. M., Regla-Nava, J. A., Fernandez-Delgado, R., Castaño-Rodriguez, C., Alcaraz, A., Torres, J., Aguilella, V. M., & Enjuanes, L. (2014). Severe Acute Respiratory Syndrome Coronavirus Envelope Protein Ion Channel Activity Promotes Virus Fitness and Pathogenesis. *PLoS Pathogens*, *10*(5). https://doi.org/10.1371/journal.ppat.1004077

Ohashi, H., Watashi, K., Saso, W., Shionoya, K., Iwanami, S., Hirokawa, T., Shirai, T., Kanaya, S., Ito, Y., Kim, K. S., Nishioka, K., Ando, S., Ejima, K., Koizumi, Y., Tanaka, T., Aoki, S., Kuramochi, K., Suzuki, T., Maenaka, K., … Wakita, T. (2020). Multidrug treatment with nelfinavir and cepharanthine against COVID-19. *BioRxiv*, 1–16. https://doi.org/10.1101/2020.04.14.039925

Pal Singh, I., & Bharate, S. B. (2006). Phloroglucinol compounds of natural origin. *Natural Product Reports*, *23*(4), 558–591. https://doi.org/10.1039/b600518g

Palese, L. L. (2020). *The Structural Landscape of SARS-CoV-2 Main Protease : Hints for Inhibitor Search . 1*. https://doi.org/10.26434/chemrxiv.12209744.v1

Pantsar, T., & Poso, A. (2018). Binding affinity via docking: Fact and fiction. *Molecules*, *23*(8), 1DUMMY. https://doi.org/10.3390/molecules23081899

Parhizgar, A. R. (2017). Introducing new antimalarial analogues of chloroquine and amodiaquine: A narrative review. *Iranian Journal of Medical Sciences*, *42*(2), 115–128.

Park, J. Y., Kim, J. H., Kwon, J. M., Kwon, H. J., Jeong, H. J., Kim, Y. M., Kim, D., Lee, W. S., & Ryu, Y. B. (2013). Dieckol, a SARS-CoV 3CLpro inhibitor, isolated from the edible brown algae Ecklonia cava. *Bioorganic and Medicinal Chemistry*, *21*(13), 3730–3737. https://doi.org/10.1016/j.bmc.2013.04.026

Patil, R., Das, S., Stanley, A., Yadav, L., & Sudhakar, A. (2010). Optimized hydrophobic interactions and hydrogen bonding at the target-ligand interface leads the pathways of Drug-Designing. *PLoS ONE*, *5*(8). https://doi.org/10.1371/journal.pone.0012029

Paton, N. I., Lee, L., Xu, Y., Ooi, E. E., Cheung, Y. B., Archuleta, S., Wong, G., & Smith, A. W. (2011). Chloroquine for influenza prevention: A randomised, double-blind, placebo controlled trial. *The Lancet Infectious Diseases*, *11*(9), 677–683. https://doi.org/10.1016/S1473-3099(11)70065-2

Pepper, I. L. (2019). Biotic Characteristics of the Environment. In *Environmental and Pollution Science* (3rd ed.). Elsevier Inc. https://doi.org/10.1016/b978-0-12-814719-1.00005-7

Pillaiyar, T., Manickam, M., Namasivayam, V., Hayashi, Y., & Jung, S. H. (2016). An overview of severe acute respiratory syndrome-coronavirus (SARS-CoV) 3CL protease inhibitors: Peptidomimetics and small molecule chemotherapy. *Journal of Medicinal Chemistry*, *59*(14), 6595–6628. https://doi.org/10.1021/acs.jmedchem.5b01461

Pinzi, L., & Rastelli, G. (2019). Molecular docking: Shifting paradigms in drug discovery. *International Journal of Molecular Sciences*, *20*(18). https://doi.org/10.3390/ijms20184331

Plewczynski, D., Łaźniewski, M., Grotthuss, M. Von, Rychlewski, L., & Ginalski, K. (2011). VoteDock: Consensus docking method for prediction of protein-ligand interactions. *Journal of Computational Chemistry*, *32*(4), 568–581. https://doi.org/10.1002/jcc.21642

Polyansky, A., Zubac, R., & Zagrovic, B. (2012). Estimation of Conformational Entropy in Protein–Ligand Interactions: A Computational Perspective. *Methods in Molecular Biology (Clifton, N.J.), 819*, 327–353. https://doi.org/10.1007/978-1-61779-465-0_21

Prieto Martínez, F. D., Arciniega, M., & Medina-Franco, J. L. (2018). Molecular docking: current advances and challenges. *TIP Rev.Esp.Cienc.Quím.Biol*, *21*(May), 0–23. https://doi.org/10.22201/fesz.23958723e.2018.0.143

Ragan, M. A. and Glombitza, K. W. (1986). *Handbook of Physiological Methods.* Cambridge University Press.

Rodríguez-Morales, A. J., MacGregor, K., Kanagarajah, S., Patel, D., & Schlagenhauf, P. (2020). Going global – Travel and the 2019 novel coronavirus. *Travel Medicine and Infectious Disease*, *33*. https://doi.org/10.1016/j.tmaid.2020.101578

Rohan R. Narkhede, Rameshwar S. Cheke, Jaya P Ambhore, S. D. S. (2020). The Molecular Docking Study of Potential Drug Candidates Showing Anti-COVID-19 Activity by Exploring of Therapeutic Targets of SARS-CoV-2. *Eurasian Journal of Medicine and Oncology*, *4*(3), 185–195. https://doi.org/10.14744/ejmo.2020.31503

Romanelli, F., Smith, K., & Hoven, A. (2005). Chloroquine and Hydroxychloroquine as Inhibitors of Human Immunodeficiency Virus (HIV-1) Activity. *Current Pharmaceutical Design*, *10*(21), 2643–2648. https://doi.org/10.2174/1381612043383791

Rossignol, J.-F. (2014). Nitazoxanide: a first-in-class broad-spectrum antiviral agent. *Antiviral Research*, *110*, 94–103. https://doi.org/10.1016/j.antiviral.2014.07.014

Ryu, Y. B., Jeong, H. J., Yoon, S. Y., Park, J.-Y., Kim, Y. M., Park, S.-J., Rho, M.-C., Kim, S.-J., & Lee, W. S. (2011). Influenza Virus Neuraminidase Inhibitory Activity of Phlorotannins from the Edible Brown Alga Ecklonia cava. *Journal of Agricultural and Food Chemistry*, *59*(12), 6467–6473. https://doi.org/10.1021/jf2007248

Savarino, A., Gennero, L., Sperber, K., & Boelaert, J. R. (2001). The anti-HIV-1 activity of chloroquine. *Journal of Clinical Virology*, *20*(3), 131–135. https://doi.org/10.1016/S1386-6532(00)00139-6

Savarino, Andrea, Di Trani, L., Donatelli, I., Cauda, R., & Cassone, A. (2006). New insights into the antiviral effects of chloroquine. *Lancet Infectious Diseases*, *6*(2), 67–69. https://doi.org/10.1016/S1473-3099(06)70361-9

Schoeman, D., & Fielding, B. C. (2019). *Coronavirus envelope protein : current knowledge*. *0*, 1–22.

Shen, K., Yang, Y., Wang, T., Zhao, D., Jiang, Y., Jin, R., Zheng, Y., Xu, B., Xie, Z., Lin, L., Shang, Y., Lu, X., Shu, S., Bai, Y., Deng, J., Lu, M., Ye, L., Wang, X., Wang, Y., & Gao, L. (2020). Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. *World Journal of Pediatrics*, *0123456789*. https://doi.org/10.1007/s12519-020-00343-7

Shereen, M. A., Khan, S., Kazmi, A., Bashir, N., & Siddique, R. (2020). COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. *Journal of Advanced Research*, *24*, 91–98. https://doi.org/10.1016/j.jare.2020.03.005

Siti Halimatul Munawaroh, H., Gumilar, G. G., Nurjanah, F., Yuliani, G., Aisyah, S., Kurnia, D., Wulandari, A. P., Kurniawan, I., Ningrum, A., Koyande, A. K., & Show, P.-L. (2020). In-vitro molecular docking analysis of microalgae extracted phycocyanin as an anti-diabetic candidate. *Biochemical Engineering Journal*, *161*, 107666. https://doi.org/https://doi.org/10.1016/j.bej.2020.107666

Sohrabi, C., Alsafi, Z., O'Neill, N., Khan, M., Kerwan, A., Al-Jabir, A., Iosifidis, C., & Agha, R. (2020). World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *International Journal of Surgery*, *76*(February), 71–76. https://doi.org/10.1016/j.ijsu.2020.02.034

Stobart, C. C., Sexton, N. R., Munjal, H., Lu, X., Molland, K. L., Tomar, S., Mesecar, A. D., & Denison, M. R. (2013). Chimeric Exchange of Coronavirus nsp5 Proteases (3CLpro) Identifies Common and Divergent Regulatory Determinants of Protease Activity. *Journal of Virology*, *87*(23), 12611–12618.

https://doi.org/10.1128/jvi.02050-13

Su, S., Wong, G., Shi, W., Liu, J., Lai, A. C. K., Zhou, J., Liu, W., Bi, Y., & Gao, G. F. (2016). Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses. *Trends in Microbiology*, *24*(6), 490–502. https://doi.org/10.1016/j.tim.2016.03.003

Sun, P., Lu, X., Xu, C., Sun, W., & Pan, B. (2020). Understanding of COVID-19 based on current evidence. *Journal of Medical Virology*, *92*(6), 548–551. https://doi.org/10.1002/jmv.25722

Tortorici, M. A., & Veesler, D. (2019). Structural insights into coronavirus entry. In *Advances in Virus Research* (1st ed., Vol. 105). Elsevier Inc. https://doi.org/10.1016/bs.aivir.2019.08.002

Trott, Oleg & Olson, A. J. (2010). Autodock vina: improving the speed and accuracy of docking. *Journal of Computational Chemistry*, *31*(2), 455–461. https://doi.org/10.1002/jcc.21334.AutoDock

Utomo, R. Y., Ikawati, M., & Meiyanto, E. (2020). Revealing the Potency of Citrus and Galangal Constituents to Halt SARS-CoV-2 Infection. *Preprints.Org*, *2*(March), 1–8. https://doi.org/10.20944/preprints202003.0214.v1

Wan, Y., Shang, J., Graham, R., Baric, R. S., & Li, F. (2020). Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. *Journal of Virology*, *94*(7), 1–9. https://doi.org/10.1128/jvi.00127-20

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong, Y., Zhao, Y., Li, Y., Wang, X., & Peng, Z. (2020). Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA - Journal of the American Medical Association*, 1–9. https://doi.org/10.1001/jama.2020.1585

Warner, F. J., Smith, A. I., Hooper, N. M., & Turner, A. J. (2004). Angiotensin-converting enzyme-2: A molecular and cellular perspective. *Cellular and Molecular Life Sciences*, *61*(21), 2704–2713. https://doi.org/10.1007/s00018-004-4240-7

Wijesekara, I., Yoon, N. Y., & Kim, S. K. (2010). Phlorotannins from Ecklonia cava (Phaeophyceae): Biological activities and potential health benefits. *BioFactors*, *36*(6), 408–414. https://doi.org/10.1002/biof.114

Wipf, P., Skoda, E. M., & Mann, A. (2015). Conformational Restriction and Steric Hindrance in Medicinal Chemistry. *The Practice of Medicinal Chemistry: Fourth Edition*, 279–299. https://doi.org/10.1016/B978-0-12-417205-0.00011-0

Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J. A., Hsieh, C., Abiona, O., Graham, B. S., & Mclellan, J. S. (2020). *Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation*. *1263*(March), 1260–1263.

Wu, C., Liu, Y., Yang, Y., Zhang, P., Zhong, W., Wang, Y., Wang, Q., Xu, Y., Li, M., Li, X., Zheng, M., Chen, L., & Li, H. (2020). Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharmaceutica Sinica B*, *10*(5), 766–788. https://doi.org/10.1016/j.apsb.2020.02.008

Xu, C., Zhu, L., Chan, T., Lu, X., Shen, W., Madigan, M. C., Gillies, M. C., & Zhou, F. (2016). Chloroquine and Hydroxychloroquine Are Novel Inhibitors of Human Organic Anion Transporting Polypeptide 1A2. *Journal of Pharmaceutical Sciences*, *105*(2), 884–890. https://doi.org/10.1002/jps.24663

Xu, Xiaoling, Han, M., Li, T., Sun, W., Wang, D., Fu, B., Zhou, Y., Zheng, X., Yang, Y., Li, X., Zhang, X., Pan, A., & Wei, H. (2020). Effective Treatment of Severe COVID-19 Patients with Tocilizumab. *ChinaXiv*, 1–12.

Xu, Xintian, Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., Zhong, W., & 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

Xu, Z., Peng, C., Shi, Y., Zhu, Z., Mu, K., Wang, X., & Zhu, W. (2020). Nelfinavir was predicted to be a potential inhibitor of 2019-nCov main protease by an integrative approach combining homology modelling, molecular docking and binding free energy calculation. *BioRxiv*, *1201*, 2020.01.27.921627. https://doi.org/10.1101/2020.01.27.921627

Xuan-Yu Meng, Hong-Xing Zhang, Mihaly Mezei, and M. C. (2014). Molecular Docking: A powerful approach for structure-based drug discovery. *Curr Comput Aided Drug Des.*, *23*(1), 1–7. https://doi.org/10.1038/jid.2014.371

Yamamoto, N., Matsuyama, S., Hoshino, T., & Yamamoto, N. (2020). *Nelfinavir inhibits replication of severe acute respiratory syndrome coronavirus 2 in vitro.* https://doi.org/10.1101/2020.04.06.026476

Yan, Y., Zou, Z., Sun, Y., Li, X., Xu, K. F., Wei, Y., Jin, N., & Jiang, C. (2013). Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model. *Cell Research*, *23*(2), 300–302. https://doi.org/10.1038/cr.2012.165

Zaki, A. M., Van Boheemen, S., Bestebroer, T. M., Osterhaus, A. D. M. E., & Fouchier, R. A. M. (2012). Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *New England Journal of Medicine*, *367*(19), 1814–1820. https://doi.org/10.1056/NEJMoa1211721

Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C., Sauerhering, L., Becker, S., Rox, K., & Hilgenfeld, R. (2020). (Mengist et al., 2020). *Science*, *368*(6489), 409–412. https://doi.org/10.1126/science.abb3405

Zhao, Y., Zhao, Z., Wang, Y., Zhou, Y., Ma, Y., & Zuo, W. (2020). Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. *BioRxiv*, 2020.01.26.919985. https://doi.org/10.1101/2020.01.26.919985

Zhou, P., Yang, X. Lou, Wang, X. G., Hu, B., Zhang, L., Zhang, W., Si, H. R., Zhu, Y., Li, B., Huang, C. L., Chen, H. D., Chen, J., Luo, Y., Guo, H., Jiang, R. Di, Liu, M. Q., Chen, Y., Shen, X. R., Wang, X., … Shi, Z. L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, *579*(7798), 270–273. https://doi.org/10.1038/s41586-020-2012-7

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G. F., & Tan, W. (2020). A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine*, *382*(8), 727–733. https://doi.org/10.1056/NEJMoa2001017