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In silico screening of the active compounds of *Syzygium cumini* (L.) Skeels. as anti-coronavirus

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Coronavirus disease-19 (Covid-19) has been pandemic since 2019 and the world is still trying to cope with it. Even though there is a new hope with the invention of the vaccine, the virus has rapid mutation rate. Therefore alternative solutions are necessary and one of them is using the herbs with their active compounds. *Syzygium cumini* (L.) Skeels. is a species of Myrtaceae containing various phytochemical compounds with medicinal activity, such as anti-oxidants, anti-inflammatory, anti-cancer, anti-tumour, anti-diabetes and anti-microbial. Previous studies showed that several compound contained in *S. cumini* had the potential of having anti-coronavirus activities. This study aimed to determine the phytochemical compounds of *S. cumini* and to screen their potential as an anti-coronavirus. The method used in this research were literature study and molecular docking. The results showed that *S. cumini* contained the active compounds of anti-coronavirus, namely betulinic acid, kaempferol, malvidin, myricetin and quercetin. Those compounds are contained in the bark of *S. cumini*.

Keywords: Anti-coronavirus, COVID-19, *Syzygium cumini*.

INTRODUCTION

At the end of 2019, the world was shocked by the outbreak of the Covid-19 disease caused by a new type of coronavirus. This virus was first reported in Wuhan, China, on 1 December 2019 and has spread very rapidly to several countries in the world (Chen et al. 2020). The World Health Organization reported that Covid-19 had infected more than 100 countries with a total of 90,335,008 confirmed cases as of January 2021. In Indonesia, Covid-19 attack has caused 25,246 mortalities and thousands of positive cases added every day (Kementerian Kesehatan Republik Indonesia, 2020). Scientists around the world are working hard to find ways to overcome this pandemic (Anwar et al. 2021). Currently the Covid-19 vaccine has been found, but it is known that there are many new variants of the SARS-CoV-2 appear due to mutations. Efforts to find effective drugs to alleviate symptoms are continuously being made, including by utilizing potential herbal plants. Abdulrahman et al. (2019) stated that herbal plants contain a number of active compounds that are efficacious in treating various diseases.

One of the plant species to be recommended for such purpose is *Syzygium cumini* (L.) Skeels (Myrtaceae) (Mahmoud, 2001). Indonesian call this species “duwet” and its existence is rarely found growing wild (Wijayanti and Setiawan, 2018). According to Ayyanar and Subash-Babu (2012), it contains several metabolites with the

activity to cure various diseases. The local communities of India and Brazil have long used it traditionally to treat diabetes, dysentery and kidney disorders by using its leaves, bark and fruit (Jain et al. 2005; de Albuquerqe et al. 2007).

Empirically, Kusumoto et al. (1995) stated that its extract could inhibit HIV-1 protease activity, making it potential as an anti-virus. Thus, it is possible that it might inhibit the activity of other types of viruses, including coronavirus. Therefore, this study aimed to determine the types and functions of the phytochemical compounds it contains and to screen the anti-coronavirus potential of these compounds in silico. This research is expected to add value to the benefits of *S. cumini*, thereby increasing public awareness to conserve it in order to avoid the threat of extinction.

MATERIALS AND METHODS

This research was conducted from May to June 2020. It began with an inventory of the active compounds of *S. cumini* on the site http://www.knapsackfamily.com/. The three-dimensional structure of its each active compound was obtained from the site https://pubchem.ncbi.nlm.nih.gov/ and saved in structure data file (SDF) format. SDF data for active compounds were then minimized using PyRx software version 0.8 and saved in protein data base (PDB) format. Determination of the coronavirus target protein was carried out by a literature study through the site https://scholar.google.com/. FATSA data for the coronavirus target protein were obtained through the site https://www.ncbi.nlm.nih.gov/protein and their protein structures were acquired using the site https://swissmodel.expasy.org/. The results of structural modeling of each target protein were saved in PDB format and docked with the PDB data of active compounds. The evaluation of the docking results was carried out using Discovery Studio Visualization 2016. The data in this study were then analyzed descriptively.

RESULTS AND DISCUSSION

Based on the literature studies and search results on the site http://www.knapsackfamily.com/, *S. cumini* contains various types of chemical compounds which are found in the roots, bark, leaves, flowers and fruit as in Table 1. Most of the active compounds contained in *S. cumini* have medicinal activities, such as anti-oxidants, anti-inflammatory, anti-cancer, anti-tumour, anti-diabetes and anti-microbial properties.

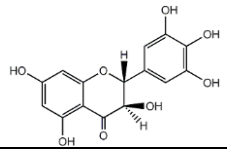
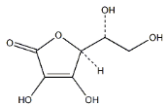
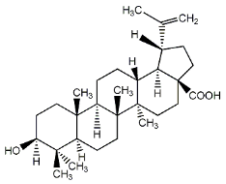
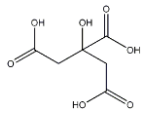
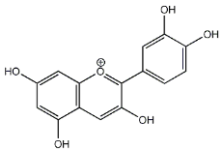
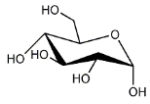
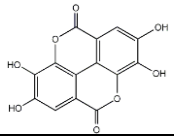
Among those phytochemicals, it is known that four of them had anti-coronavirus activity, namely betulinic acid, kaempferol, myricetin and quercetin. Previous study revealed that they inhibited the replication process of coronavirus by affecting the performance of papain-like protease (PLpro) and 3C-like protease (3CLpro) (Li et al. 2003; Chen et al. 2006; Park et al. 2013; Jo et al. 2020; Yang et al. 2020; Zhang et al. 2020). Both proteins are encoded by coronavirus and play an important role in virus replication (Zhang et al. 2020). Apart of PLpro and 3CLpro, another studies showed that there are other proteins useable as target of in silico screening for anti-coronavirus activity, Spike protein and angiotensin-converting enzyme-2 (ACE2). Spike protein is a part of the coronavirus which has an important role when the virus enters into the host cell (Li, 2016). While ACE2 is a receptor on human alveolar epithelial cells that binds to the coronavirus Spike protein, thus allowing the virus to enter these cells (Kuhn et al. 2006; Wu et al. 2020; Xu et al. 2020; Zhou et al. 2020; Anwar et al. 2021). Thus, these four proteins are suitable as target proteins for in silico studies of the anti-coronavirus activity of certain compounds

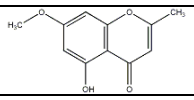
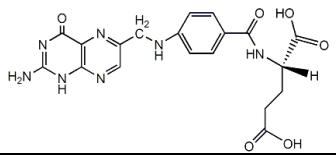
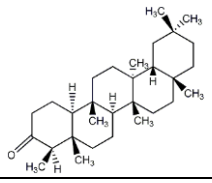
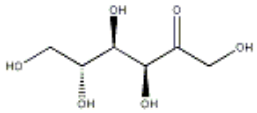
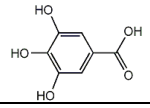
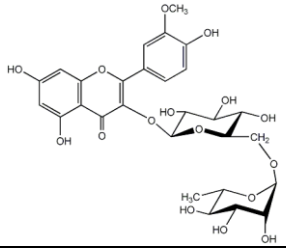
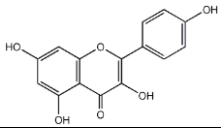
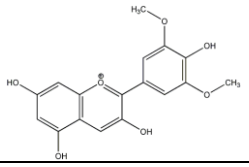
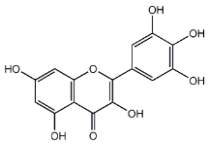
In silico screening showed that there were five compounds contained in *S. cumini* with anti-coronavirus activity. In addition to the four compounds previously mentioned (betulinic acid, kaempferol, myricetin and quercetin), there is one more compound, malvidin, which is also able to interact with ACE2, Spike protein, 3CLpro and PLpro (Table 2). Thus, the five compounds are shown to have anti-coronavirus activity in silico. Based on their binding affinity, the five active compounds had different affinities for each target protein. The ligand binding affinities with the target protein from highest to lowest are as follows: Betulinic acid: Spike protein> ACE2> 3CLpro> PLpro; Kaempferol: Spike protein> PLpro> 3CLpro; Malvidin: Spike protein> ACE2> 3CLpro> PLpro; Myricetin: Spike protein> ACE2> 3CLpro> PLpro; and Quercetin: Spike protein> 3CLpro> ACE2> PLpro.

It is clear that the active compounds in *S. cumini* tend to have stronger interaction with the Spike protein, followed by ACE2, then 3CLpro and PLpro. Thus it reveals that most of those compounds tend to show inhibitory activity of coronavirus infection in the host cell; by interacting with the Spike protein as well as ACE2. As stated by Li (2016), the coronavirus adheres (in adsorption stage) to the host cell via the

interaction between the Spike protein in the virus and the ACE2 receptor on the host cell. The Spike protein binds to the ACE2 receptor through the S1 subunit, then membrane fusion occurs between the virus and the host cell through the S2 subunit (Li, 2016). Therefore, by blocking the binding of ACE2 to the Spike protein could prevent the entry of coronavirus into host cells (Cinatl et al. 2003; Chen and Nakamura, 2004; Yi et al. 2004; Ho et al. 2007; Schwarz et al. 2011; Yang et al. 2020).

Table 1: Phytochemicals of *Syzygium cumini*

Phytochemical	Structure	Part of plant where the phytochemical is found	Function	References
Ampelopsin		flower	antioxidant, anti-bleeding, anti-tumour, hepatoprotective, neuroprotective	Ayyanar and Subash-Babu 2012; Kou and Chen 2012
Ascorbic acid		fruit	anti-oxidant, wound healing, enzyme cofactor for prolyl hydroxylase, inhibits oxidation of LDL	Frei et al. 1996; Litchford 2008; Rucker et al. 2008; Kehrer et al. 2010; Ayyanar and Subash-Babu 2012
Betulinic acid		bark	anti-ploriferative, anti-HIV, anti-cancer, anti-bleeding, anti-malaria	Ayyanar and Subash-Babu 2012; Varsha et al. 2017; Kumar and Dubey 2019
Citric acid		fruit	anti-microbial, anti-oxidant, intermediates in the oxidative metabolism of cells	Poerwono et al. 2001; Soltoft-Jensen and Hensen 2005; Ayyanar and Subash-Babu 2012
Cyanidin		fruit	inhibits UVB, induces COX-2 expression and prostaglandin E2 secretion in epidermal cells by suppressing nuclear factor-κB transactivation and protein-1 activator, inhibits JNK1/2, ERK1/2 and MEK1/2 phosphorilation with MKK4 and Raf-1	Ayyanar and Subash-Babu 2012; Dorman et al. 2016
D-Glucose		fruit	energy source, aerobic and anaerobic respiration, precursors for vitamin C	Ayyanar and Subash-Babu 2012; Shendurse and Khadker 2016
Ellagic acid		bark	anti-carcinogenic, bioactive potential for prevention of chronic diseases and skin aging	Ayyanar and Subash-Babu 2012; Meena et al. 2014; Salimi and Pourahmad 2018
Eugenin		bark	actively against the Herpes virus	Peres 2003; Ayyanar and

				Subash-Babu 2012
Folic acid		fruit	synthesizes and disjoints amino acids, synthesizes DNA/RNA, forms new cells (blood, skin and mucosa cells)	Ayyanar and Subash-Babu 2012; Dugoua 2013
Friedelan-3-one		bark	anti-feedant, anti-bleeding, anti-cancer, hepatoprotective, anti-microbe and anti-candida	Ayyanar and Subash-Babu 2012; Lakshmi and Nair 2017
Fructose		fruit	Increases cell proliferation	Ayyanar and Subash-Babu 2012; Kim et al. 2012
Gallic acid		bark, fruit	anti-oxidant, anti-cancer	Ayyanar and Subash-Babu 2012; Zanwar et al. 2014
Isorhamnetin 3-O-rutinoside		root	anti-microbe	Ayyanar and Subash-Babu 2012; Pereira et al. 2016
Kaempferol		bark, flower	anti-oxidant, anti-bleeding, anti-microbe, anti-diabetes and anti-cancer	Ayyanar and Subash-Babu 2012; Shields 2017
Malvidin		fruit	anti-oxidant, anti-hipertensive, anti-bleeding	Ayyanar and Subash-Babu 2012; Huang et al. 2016
Myricetin		leaf, bark, flower	anti-diabetes, hypolidemi, anti-oxidant, anti-bleeding, anti-carcinogen, anti-virus and induces apoptosis in cancer cells	Ayyanar and Subash-Babu 2012; Jadeja and Devkar 2014; Dorman et al. 2016
Myricetin 3-robinobioside		root	anti-oxidant, anti-bleeding, anti-mutagenic and anti-carcinogenic	Vaishnava et al. 1992; Panche et al. 2016

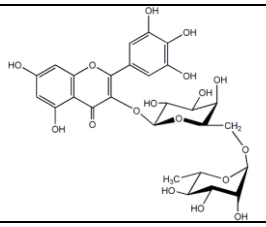
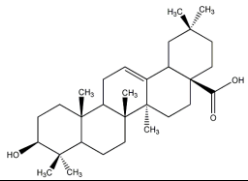
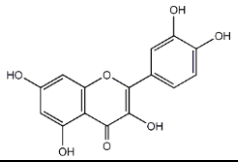
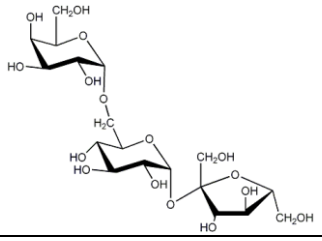
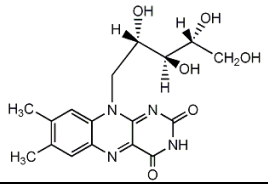
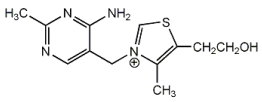
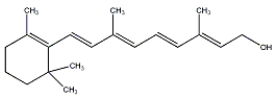
				
Oleanolic acid		flower	anti-oxidant, anti-tumour, anti-bleeding, anti-diabetes and anti-microbe	Ayyanar and Subash-Babu 2012; Ayeleso et al. 2017
Quercetin		leaves, bark, flower	therapeutic, anti-oxidant, anti-bleeding, anti-cancer	Ayyanar and Subash-Babu 2012; Ay et al. 2016
Raffinose		fruit	Plays role in abiotic pressure tolerance, as an acceptor for galactosyl residue from galactynol results in stachyose tetrasaccharide	Chibbar and Baga 2003; Ayyanar and Subash-Babu 2012
Riboflavin		fruit	Coenzyme in energy, precursor for cofactor stabilization of MTHFR, FAD	Ayyanar and Subash-Babu 2012; Miller and Peters 2015; Guilliams 2018
Thiamine		fruit	Cofactor for decarboxylation of 2-oxoacids, optimizes the function of nervous system function and repairs myelin sheath, transketolase, dehydrogenase piruvate and α-ketoglutarat, biosyntesis of neurotransmitter, nucleic acid, fatty acid, steroid and complex carbohydrate	Ayyanar and Subash-Babu 2012; de la Monte et al. 2016; Crook 2019
Vitamin A		fruit	Maintains cell function for growth, epithelium strength, produces erythrocytes maintains the function of immune and reproduction system.	Ayyanar and Subash-Babu 2012; Abrams et al. 2014

Table 2: Docking results of active compounds of *Syzygium cumini* as anti-coronavirus

Ligand	Binding affinity (kcal/mol)			
	ACE2	3CLPro	PLpro	Spike
Betulinic acid	-10,0	-9,2	-6,8	-10,3
Kaempferol	-8,2	-7,7	-8,1	-8,3
Malvidin	-7,6	-7,5	-6,6	-8,3
Myricetin	-8,2	-8,1	-7,3	-8,4
Quercetin	-8,1	-8,2	-8,0	-9,1

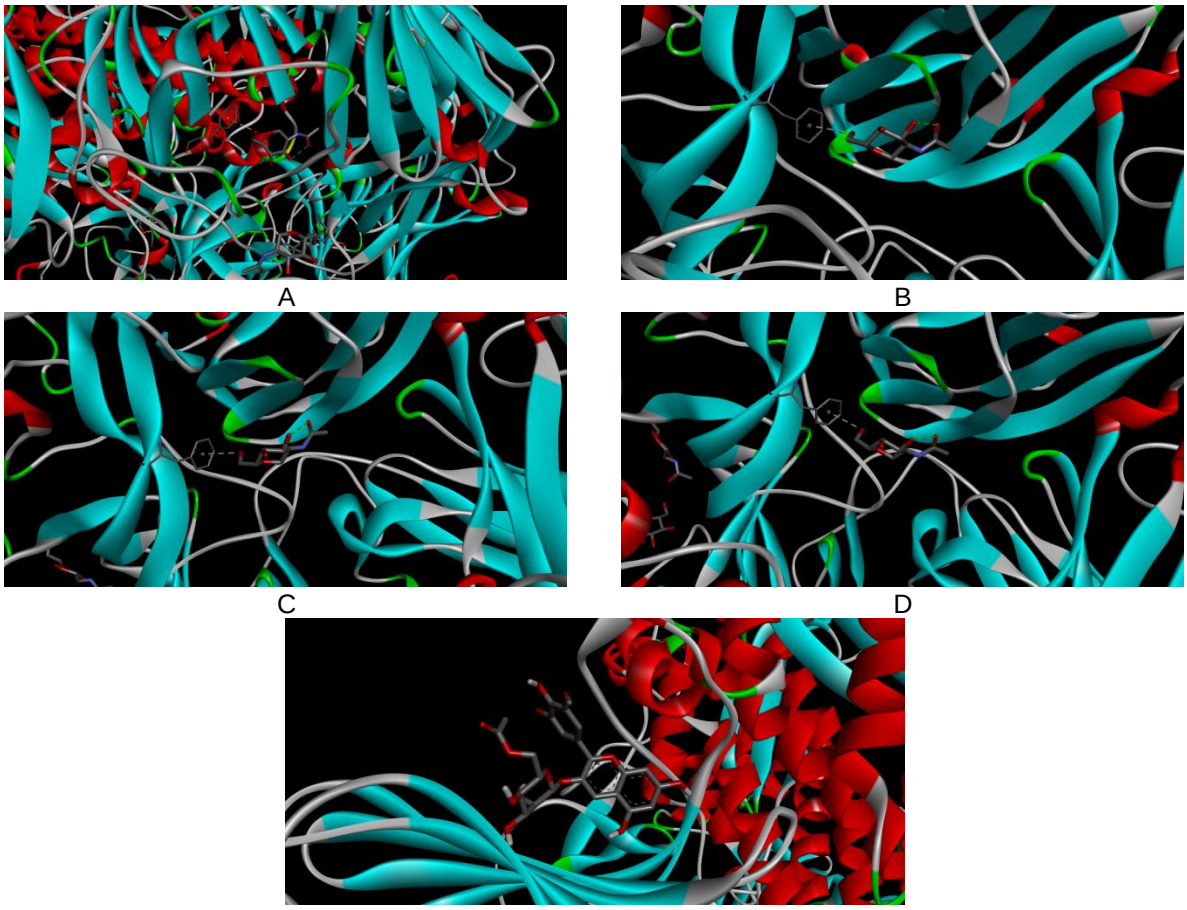


Figure 1: Interaction of active compounds of *S. cumini* and Spike protein; betulinic acid (A), kaempferol (B), myricetin (C), quercetin (D) and malvidin (E)

Hence if the active compounds of *S. cumini* have the ability to interact with the both proteins, they possess the anti-coronavirus potential through this mechanism.

In addition, based on the level of interaction with the Spike protein, the active compounds with the strongest interactions are betulinic acid (-10.3 kcal/mol), followed by quercetin (-9.1 kcal/mol), myricetin (-8.4 kcal/mol), kaempferol (-8.3 kcal/mol) and malvidin (-8.3 kcal/mol). The analysis using Discovery Studio Visualization 2016 shows that the interactions between the five compounds and the Spike protein occur because two kinds of chemical bonds are formed, hydrogen bonds and non-hydrogen bonds. In betulinic acid, quercetin, myricetin and kaempferol, the type of chemical bond formed is the hydrogen bond in amino acid PHE A: 420 (Figure 1A-D). However, in malvidin, the interactions are formed due to four hydrogen bonds and three non-hydrogen bonds. Hydrogen bonds interact with amino acids THR C: 55, SER

C: 172 and SER C: 118 (Figure 1E), while non-hydrogen bonds interact with amino acids SER C: 118, ALA C: 76 and TYR C: 88. Although the number of bonds formed in malvidin is more than the other four compounds, the binding affinity is the lowest and is equivalent to that of kaempferol, -8.3 kcal/mol. Thus the strength of the hydrogen bond interactions in kaempferol is proportional to the four hydrogen bonds and three non-hydrogen bonds in malvidin.

Although the five active compounds of *S. cumini* are more likely to interact strongly with one of the target proteins, it does not mean that there is no interaction with other target proteins. The difference in binding affinity causes the tendency for the interaction between the active compound and the target protein. As with the interaction on the PLpro, four out of five compounds show the weakest binding affinity. Even so, in silico screening shows that all these compounds interact with the PLpro, so they are still potential to inhibit the replication of the coronavirus. PLpro is a key enzyme in the early stages of infection in which it cleaves the viral polyproteins, eliminates viral and cellular proteins, and inhibits the interferon (IFN) response. Besides, according to Baez-Santos et al. (2015), PLpro in SARS-CoV has an additional function in the trimming the ubiquitin and ISG15 from host cell proteins, thus allowing the coronavirus to avoid the body's immune response. Likewise, 3CLpro contributes in mediating proteolytic processing of polypeptide replication into functional proteins that play an important role in viral replication (Hsu et al. 2004). Thus it strengthens the potential of *S. cumini* as an anti-coronavirus drug. According to Ayyanar and Subhas-Babu (2012), the five anti-coronavirus compounds can be found in the bark of *S. cumini* (Table 1). Hence *S. cumini*'s bark is the most potential part to obtain the active anti-coronavirus compounds. To prove the anti-coronavirus effectiveness of *S. cumini*, further in vitro or in vivo researches are necessary.

CONCLUSION

In silico screening showed that compounds contained in the bark of *S. cumini* such as betulinic acid, kaempferol, malvidin, myricetin and quercetin interact with ACE2, Spike protein, 3CLpro and Plpro. Therefore *S. cumini* has medicinal potential for anti-coronavirus.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

AUTHOR CONTRIBUTIONS

All individuals listed as authors have significantly contributed to the writing of this manuscript. Their responsibilities were as follows: ER and SR designed the research; ER, SR and ERP conducted the molecular docking; ER and ERP analyzed the data obtained; ER and ERF wrote the manuscript; ERF performed the translation; ER had the primary responsibility for the final content of the manuscript; and all the authors read and approved the final manuscript..

REFERENCES

Abdulrahman MD, Ali AM, Khandaker MM, Fatihah HNN, Mat N, 2019. Review on traditional knowledge and utilisation of medicinal plants. Bioscience Research 16(4); 3298–3313.

Abrams S, Brabin BJ, Coulter JBS, 2014. Nutrition-associated Disease. Manson's Tropical Infectious Diseases (Twenty-Third Edition), pp 1151-1167.e2. https://doi.org/10.1016/B978-0-7020-5101-2.00078-9.

Anwar F, Khan M, Rehman N, Akbar F, Ahmad S, Yousaf M, et al., 2021. Review and forecasting on COVID-19 outbreak; An insight to *in silico* candidate drug discovery. Bioscience Research 18(2): 1198–1210.

Ay M, Charli A, Jin H, Anantharam V, Kanthasamy A, Kanthasamy AG, 2016. Quercetin. Nutraceuticals, pp 447-452. https://doi.org/10.1016/B978-0-12-802147-7.00032-2.

Ayeleso TB, Matumba MG, Mukwevho E, 2017. Oleanolic acid and its derivatives: biological activities and therapeutic potential in chronic diseases. Molecules 22(11): 1915. doi: 10.3390/molecules22111915.

Ayyanar M, Subash-Babu P, 2012. *Syzygium cumini* (L.) Skeels: a review of its

phytochemical constituents and traditional uses. Asian Pac J Trop Biomed 2(3): 240–246. doi: 10.1016/S2221-1691(12)60050-1.

Baez-Santos YM, John SES, Mesecar AD, 2015. The SARS-coronavirus papain-like protease: Structure, function and inhibition by designed antiviral compounds. Antiviral Research 115: 21-38. https://doi.org/10.1016/j.antiviral.2014.12.01.

Chen L, Li J, Luo C, et al., 2006. Binding interaction of quercetin-3-β-galactoside and its synthetic derivatives with SARS-CoV 3CL(pro): structure-activity relationship studies reveal salient pharmacophore features. Bioorg Med Chem 14(24): 8295–8306.

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al., 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 359(10223): 507–513.

Chen Z, Nakamura T, 2004. Statistical evidence for the usefulness of Chinese medicine in the treatment of SARS. Phytotherapy research: PTR 18(7): 592–594.

Chibbar RN, Baga M, 2003. Genetic modification of primary metabolism. In Encyclopedia of Applied Plant Sciences, pp 449-459. https://doi.org/10.1016/B0-12-227050-9/00171-X.

Cinatl J, Morgenstem B, Bauer G, Chandra P, Rabenau H, Doerr HW, 2003. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 361(9374): 2045–2046.

Crook MA, 2019. Methods for assessment of thiamine (vitamin B1). In Laboratory Assessment of Vitamin Status, pp 149-164. https://doi.org/10.1016/B978-0-12-813050-6.00006-1.

de Albuquerque UP, de Mederios PM, de Almeida ALS, Monteiro JM, Nito EMFL, de Melo JG, dos Santos JP, 2007. Medicinal plants of the *caatinga* (semi-arid) vegetation of NE Brazil: a quantitative approach. J Ethophamacol 114(3): 325-354.

de la Monte SM, Huse S, Kim M, 2016. Alcoholic beverage and insulin resistance–mediated degenerative diseases of liver and brain: cellular and molecular effects. In Molecular Nutrition and Diabetes, pp 237-251. https://doi.org/10.1016/B978-0-12-801585-8.00019-1.

Dorman G, Flachne B, Hajdu I, Andras CD, 2016. Target identification and polypharmacology of nutraceuticals. In Nutraceuticals Efficacy, Safety and Toxicity, pp 263-286. https://doi.org/10.1016/B978-0-12-802147-7.00021-8.

Dugoua J-J, 2013. Vitamins, minerals, trace elements, and dietary supplements. In Clinical Pharmacology During Pregnancy, pp 367-382. https://doi.org/10.1016/B978-0-12-386007-1.00022-2.

Frei B, Keaney Jr JF, Retsky KL, Chen K, 1996. Vitamins C and E and LDL Oxidation. Vitamins and Hormones, Volume 52, pp 1-34. https://doi.org/10.1016/S0083-6729(08)60405-7.

Guilliams TG, 2018. MTHFR, homocysteine and nutrient needs. In Integrative Medicine (Fourth Edition), pp 395-403.e2. https://doi.org/10.1016/B978-0-323-35868-2.00038-4.

Ho T, Wu S, Chen J, Li C, Hsiang C, 2007. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antiviral Res 74(2): 92–101.

Hsu JT, Kuo CJ, Hsieh HP, et al., 2004. Evaluation of metal-conjugated compounds as inhibitors of 3CL protease of SARS-CoV. FEBS Lett 574(1-3): 116–120.

Huang W, Zhu Y, Li C, Sui Z, Min W, 2016. Effect of blueberry anthocyanins malvidin and glycosides on the antioxidant properties in endothelial cells. Oxidative Medicine and Cellular Longevity 1591803(2016): 1-10. https://doi.org/10.1155/2016/1591803.

Jadeja RN, Devkar RV, 2014. Polyphenols and Flavonoids in Controlling Non-Alcoholic Steatohepatitis. Polyphenols in Human Health and Disease, Volume 1, pp 615-623.

Jain A, Katewa SS, Galav PK, Sharma P, 2005. Medicinal plant diversity of Sitamata wildlife sanctuary Rajasthan India. J Ethnopharmacol 102: 143-157.

Jo S, Kim S, Shin DH, Kim M-S, 2020. Inhibition of SARS-CoV 3CL protease by flavonoids. J Enzyme Inhib Med Chem 35(1): 145–151.

KehrerJP, Robertson JD, Smith CV, 2010. Free Radicals and Reactive Oxygen Species. Comprehensive Toxicology (Second Edition), Volume 1, pp 277-307. https://doi.org/10.1016/B978-0-08-046884-6.00114-7.

Kementerian Kesehatan Republik Indonesia, 2020. Situasi COVID-19. https://www.kemkes.go.id/ Accessed 21 January, 2021.

Kim J, Song G, Wu G, Bazer FW, 2012. Functional roles of fructose. Proc Natl Acad Sci U S A 109(25): E1619-28. doi: 10.1073/pnas.1204298109.

Kou X, Chen N, 2012. Pharmacological potential of ampelopsin in rattan tea. Food Science and Human Wellness 1(1): 14-18. https://doi.org/10.1016/j.fshw.2012.08.001.

Kumar D, Dubey KD, 2019. Hybrid approach for transformation for betulin (an anti-HIV molecule). New and Future Developments in Microbial Biotechnology and Bioengineering, pp 193-203. https://doi.org/10.1016/B978-0-444-63504-4.00015-3.

Kusumoto IT, Nakabayashi T, Kida H, Miyashiro H, Hattori H, Namba T, et al., 1995. Screening of various plant extracts on human immunodeficiency virus type I (HIV-I) protease. Phytother Res 12: 488-493.

Lakshmi M, Nair BR, 2017. GC-MS analysis of the chloroform extract of bark of *Terminalia travancorensis* Wight. and Arn. (Combretaceae). Int J Pharm Sci Res 8(2): 794-98. doi: 10.13040/IJPSR.0975-8232.8(2).794-98.

Li F, 2016. Structure, function, and evolution of coronavirus spike proteins. Annual Review of Virology 3: 237-261. https://doi.org/10.1146/annurev-virology-110615-042301.

Li W, Moore MJ, Vasilieva N, et al., 2003. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 426(6965): 450–454.

Litchford MD, 2008. Nutritional issues in the patient with diabetes and foot ulcers. Levin and O'Neal's the Diabetic Foot (Seventh Edition), pp 199-217. https://doi.org/10.1016/B978-0-323-04145-4.50015-6.

Mahmoud II, Marzouk MS, Moharram FA, El-Gindi MR, Hassan AM, 2001. Acylated flavonol glycosides from *Eugenia jambolana* leaves. Phytochemistry 58: 1239-1244.

Meena F, Meena A, Treton J, 2014. Polyphenols Against Skin Aging. Polyphenols in Human Health and Disease, Volume 1, pp 819-830. https://doi.org/10.1016/B978-0-12-398456-2.00063-3.

Miller RK, Peters P, 2015. Vitamins, minerals and trace elements. In Drugs During Pregnancy and Lactation (Third Edition), pp 493-510. https://doi.org/10.1016/B978-0-12-408078-2.00019-6.

Nakamura Y, Asahi H, Altaf-Ul-Amin M, Kurokawa K, Kanaya S, 2020. KNApSAcK: a comprehensive species-metabolite relationship database. http://www.knapsackfamily.com/KNApSAcK/ Accessed 28 May 2020.

Panche AN, Diwan AD, Chandra SR, 2016. Flavonoids: an overview. J Nutr Sci 5: e47. doi: 10.1017/jns.2016.41.

Park JY, Kim JH, Kwon JM, et al., 2013. Dieckol, a SARS-CoV 3CL(pro) inhibitor, isolated from the edible brown algae *Ecklonia cava*. Bioorg Med Chem 21(13): 3730–3737.

Pereira C, Barros L, Alves MJ, Santos-Buelga C, Ferreira ICFR, 2016. Artichoke and milk thistle pills and syrups as sources of phenolic compounds with antimicrobial activity. Food Funct 7: 3083. DOI: 10.1039/c6fo00512h.

Peres RM, 2003. Antiviral activity of compounds isolated from plants. Pharmaceutical Biology 41(2):107-157. DOI: 10.1076/phbi.41.2.107.14240.

Poerwono H, Higashiyama K, Kubo H, Poernomo AT, Suharjono Sudiana IK, Indrayanto G, Brittain HG, 2001. Citric Acid. Analytical Profiles of Drug Substances and Excipients, Volume 28, pp 1-76. https://doi.org/10.1016/S1075-6280(01)28002-1.

Rucker RB, Morris J, Fascetti AJ, 2008. Vitamins. Clinical Biochemistry of Domestic Animals (Sixth Edition), pp 695-730. https://doi.org/10.1016/B978-0-12-370491-7.00023-4.

Salimi A, Pourahmad J, 2018. Role of natural compounds in prevention and treatment of chronic lymphocytic leukemia. Polyphenols: Prevention and Treatment of Human Disease (Second Edition), pp 195-203. https://doi.org/10.1016/B978-0-12-813008-7.00016-3.

Schwarz S, Wang K, Yu WJ, Sun B, Schwarz W, 2011. Emodin inhibits current through SARS-associated coronavirus 3a protein. Antiviral Res 90(1): 64–69.

Shendurse AM, Khadker CD, 2016. Glucose: properties and analysis. In Caballero, B., Finglas, P., and Toldrá, F. (eds.) The Encyclopedia of Food and Health vol. 3, pp 239-247. Oxford: Academic Press.

Shields M, 2017. Chemotherapeutics. Pharmacognosy, pp 295-313. https://doi.org/10.1016/B978-0-12-802104-0.00014-7.

Soltoft-Jensen J, Hensen F, 2005. New Chemical and biochemical hurdles. Emerging

Technologies for Food Processing, pp 387-416. https://doi.org/10.1016/B978-012676757-5/50017-7.

Trott O, Olson AJ, 2010. Autodock vina: improving the speed and accuracy of docking with a scoring function, efficient optimazion and multithrearing. J Comput Chem 31: 455-461.

Vaishnava MM, Tripathy SK, Gupta KR, 1992. A flavonoid glycoside myricetin 3-o-robinoside from *Syzygium cumini* roots. Fitoterapia 63(3): 259-260.

Varsha K, Sharma A, Kaur A, Madan J, Pandey RS, Jain UK, Chandra R, 2017. Natural plant-derived anticancer drugs nanotherapeutics: a review on preclinical to clinical success. Nanostructures for Cancer Therapy, pp. 775-809. https://doi.org/10.1016/B978-0-323-46144-3.00028-3.

Wijayanti T, Setiawan DC, 2018. Eksplorasi senyawa metabolit sekunder pada kulit batang tanaman duwet (*Syzygium cumini* L.) dengan metode *liquid chromatograph mass spectrometry* (LCMS). Bioma 7(2): 196-210.

World Health Organization, 2020. WHO Coronavirus Disease (COVID-19) Dashboard. https://covid19.who.int/. Accessed: 1 September 2020.

Yang Y, Islam MS, Wang J, Li Y, Chen X, 2020. Traditional Chinese Medicine in the treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): a review and perspective. Int J Biol Sci 16(10): 1708–1717.

Zanwar AA, Badole SL, Shende PS, Hegde MV, Bodhankar SL, 2014. Role of gallic acid in cardiovascular disorders. In Polyphenols in Human Health and Disease, Volume 2, pp 1045-1047. https://doi.org/10.1016/B978-0-12-398456-2.00080-3.

Zhang D-H, Wu K-L, Zhang X, Deng S-Q, Peng B, 2020. In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. Journal of Integrative Medicine 18(2): 152–158.