A Short Overview of *Curcuma aeruginosa* with Curative Potentials Against COVID-19

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COVID-19 (coronavirus disease) is an infectious disease of the respiratory tract caused by SARS-CoV-2. Nature has provided a great source of antiviral compounds, from which innovative products for the treatment of COVID-19 can be produced. One of the medicinal plants that can be developed for the treatment of COVID-19 is *Curcuma aeruginosa* Roxb. Previous studies have found tracheospasmolytic and anti-inflammatory activity of this indigenous Curcuma species. There are 10 chemical compounds from *Curcuma aeruginosa* that have been proven against COVID-19, namely 1,8-cineole (eucalyptol), α-terpineol, β-caryophyllene, β-eudesmol, β-pinene, β-sitosterol, curcumenol, palmitic acid, succinic acid and zingiberene. Further research is needed for *C. aeruginosa* to become a new antiviral drug for the treatment of COVID-19.

Keywords: *Curcuma aeruginosa*, Chemical compounds, COVID-19.

INTRODUCTION

COVID-19 (coronavirus disease) is an infectious disease of the respiratory tract caused by SARS-CoV-2 or known as coronavirus [1]. China reported its first pneumonia case in Wuhan to the World Health Organization (WHO) on December 31, 2019. The virus was identified as 2019-nCoV on January 7, 2020. WHO named the disease COVID-19 and SARS-CoV-2 for the virus on February 11, 2020 [2,3]. Until the end of 2020, the total number of coronavirus cases in the world reached nearly 83 million people, with more than 1.8 million deaths, and people with pre-existing medical conditions such as high blood pressure, cardiovascular disease, or diabetes are more likely to get more serious [6]. With the increasing threat of infection of this virus in humans, the need for new treatment strategies is becoming more evident. There has been no effective vaccine available for COVID-19, so the development of antiviral agents and prevention strategies must be considered. Nature has provided an extraordinary source of antiviral compounds, from which innovative products for the treatment of COVID-19 can be produced [7].

One of the medicinal plants that can be developed for the

fever, cough and shortness of breath. Severe cases of COVID-19 can cause pneumonia, acute respiratory syndrome, kidney failure and even death [4,5]. Most of the infected patients can recover without the need for special treatment. Older adults [10]. Indonesia is a country with a diverse species of Curcuma. There are about 15 indigenous species of Curcuma found in Indonesia, including *C. aeruginosa* [11]. These plants are in the commodities list which are commonly traded in Indonesia's

traditional market [12,13]. This article overviews the chemical compounds derived from *C. aeruginosa* that can be used against COVID-19.

Morphological properties: *C. aeruginosa* is a native tropical plant from Myanmar and commonly found in South-east Asia, including Thailand, Malaysia and Indonesia. It is an unexploited perennial herb from the family *Zingiberaceae* [14]. *C. aeruginosa* known as "temu ireng" in Indonesia or "blue pink ginger" in English [15,16]. The traditional use of *C. aeruginosa* in Indonesia is for postpartum treatments, anti-diabetic, liver disease, tumor or cancer, appetite stimulant, gastritis, asthma, common cold, cough, dysmenorrhea, intestinal worms, fungal infection, mouth sores, obesity, tonic and rheumatoid problems [11,17,18].

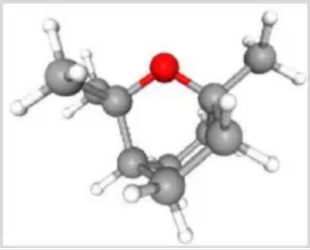
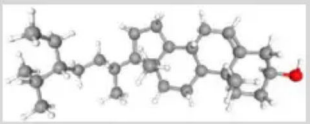
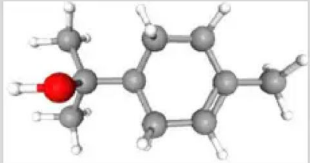
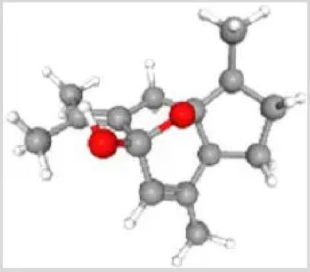
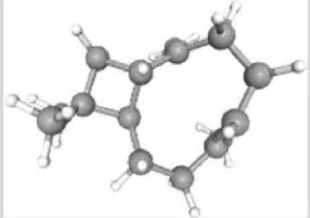
Phytochemical and biological activities: Phytochemical constituents of *C. aeruginosa* are terpenoid, steroid, organic acid, fatty acid, sugar, alkaloid, flavonoid, phenol, glycoside, tannin and saponin [19,20]. Chemically isolated compounds of *C. aeruginosa* are 1,8-cineole (eucalyptol), β-elemene, β-eudesmol, β-pinene, borneol, camphor, caryophyllene, curcumenol, curcumenone, curzerene, curzerenone, cycloisolongifolene, 8,9-dihydro-9-formyl, dehydrocurdione, furanodiene, dihydrocostunolide, furanodienone, furanogermenone, germacrone, isocurcumenol, methenolone, palmitic acid, propiolic acid, sitosterol, succinic acid, terpineol, velleral, (Z)-3-hexenol, Z-α-farnesene, zedoalactone A, zedoalactone B, zedoarol, zedoarondiol and zingiberene [21,22].

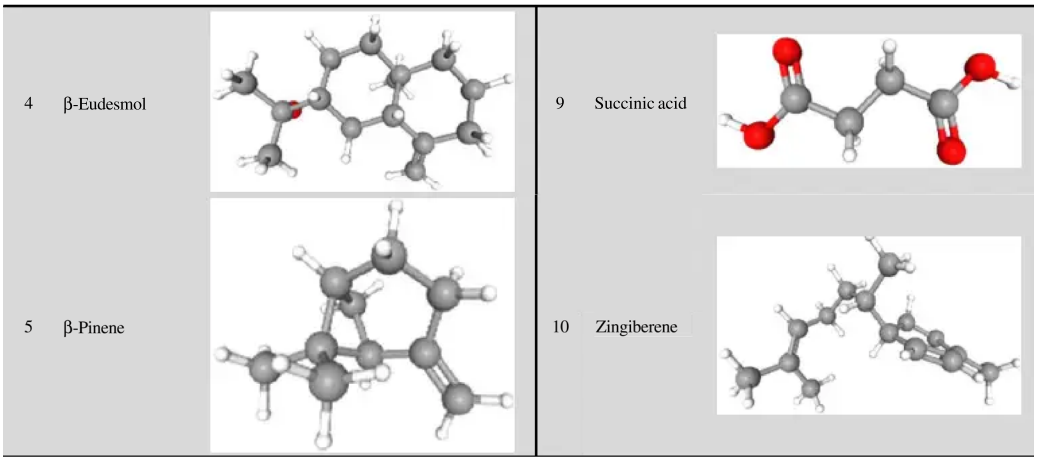
Extracts and essential oils of *C. aeruginosa* show anti-bacterial activity against *Staphylococcus aureus*, *Streptococcus haemolyticus*, *Streptococcus mutans*, *Bacillus cereus*, *Bacillus subtilis*, *Enterococcus faecalis* [23,24], *Salmonella typhi*, *Escherichia coli* [25], *Pseudomonas aeruginosa*, *Vibrio cholera*, *Klebsiella aerogens*, *K. pneumoniae* and *Serratia marcescens* [14]. The essential oil of *C. aeruginosa* also exhibits antifungal activity against *Candida albicans* and *Cryptococcus neoformans* [26].

Chemical compounds against COVID-19: There are 10 isolated compounds from *C. aeruginosa* (Table-1) have been proven against COVID-19, namely 1,8-cineole (eucalyptol), α-terpineol, β-caryophyllene, β-eudesmol, β-pinene, β-sitosterol, curcumenol, palmitic acid, succinic acid and zingiberene.

Recently, My *et al.* [27] isolated the 1,8-cineole (eucalyptol) from *Melaleuca cajuputi* and conducted the molecular docking against angiotensin-converting enzyme 2 (ACE2) protein in the human body as the host receptor for SARS-CoV-2 and main protease (PDB6LU7) of the SARS-CoV-2. The results show

TABLE-1
LIST OF CHEMICAL COMPOUNDS OF *C. aeruginosa* AGAINST COVID-19 [Ref. 39]

No.	Compound	Structure	No.	Compound	Structure
1	1,8-Cineole (Eucalyptol)		6	β-Sitosterol	
2	α-Terpineol		7	Curcumenol	
3	β-Caryophyllene		8	Palmitic acid	



that compound have strong interactions with the amino acids of the ACE2 protein and the main protease PDB6LU7 of SARS-CoV2. These natural ingredients can prevent SARS-CoV-2 from entering the human body [27]. Another study reported that 1,8-cineole may interact directly with the COVID-19 viral membrane and decrease the host inflammatory response [7]. 1,8-Cineole is a volatile compound that has been proven to be safe and effective against COVID-19, so it has the potential to be further developed [28].

The molecular docking results of β-eudesmol against the ACE2 protein and the main protease SARS-CoV-2 showed that this compound can prevent SARS-CoV-2 from entering the body [27]. Similarly, compound isolated from Moroccan medicinal plants reported that β-eudesmol can be an inhibitor against SARS-CoV-2 [29]. A molecular docking study was conducted to examine the potential of β-pinene in functional food against COVID-19. β-Pinene shows an affinity for the main protease receptor SARS-CoV-2, thus becoming a SARS-CoV-2 protease inhibitor [30].

β-Caryophyllene was proposed as an herbal candidate with antiviral activity against SARS-CoV-2 using molecular docking [31,32]. Molecular docking study on β-caryo-phyllene as a compound in functional food shows the SARS-CoV-2 protease inhibitor's effect due to its affinity for the primary protease receptor [30]. Another molecular docking results showed that β-caryophyllene has a weak affinity for ACE2 when compared to captopril, which is an inhibitor of this enzyme [33].

Curcumenol extracted from *Solanum tuberosum* and *Brassica juncea* by *in silico* studies is a selective and potent candidate compared to hydroxychloroquine against COVID-19. Molecular docking was carried out on TMPRSS2, PLpro, SARSCoV2 3CLpro, SARSCoVRdRp, SARSCoV2S and ACE2 as SARS-CoV-2 receptors to prevent COVID19 [34]. In another study, palmitic acid was tested against the HSPA5 substrate-binding domain β (SBDβ), the recognition site for the SARS-CoV-2 spike. The molecular docking results showed the affinity of palmitic acid on HSPA5 SBDβ [35].

β-Sitosterol is a chemical compound which is associated with the antiviral signing pathway for COVID-19 [36]. The molecular docking results show that β-sitosterol is an inhibitor of the SARS-CoV-2 central protease receptor [30]. Another molecular docking results showed that β-sitosterol derived from *Tinospora cordifolia* shows an affinity for the 3CLpro receptor, so it can be developed as a drug to fight SARS-CoV-2 [37]. β-Sitosterol also shows a high affinity for the spike glycoprotein and ACE2. This study showed an excellent pharmacokinetic profile with a low level of toxicity [33]. β-Sitosterol in the Shufeng Jiedu capsule used for the treatment of COVID-19 in Traditional Chinese Medicine (TCM) shows a high affinity for the SARS-CoV-2 gene target [38].

The succinic acid has also been proposed as a potential antiviral candidate for the treatment of COVID-19 based on molecular docking results [39]. α-Terpineol also showed a inhibition of ACE2 protein (SARS-CoV-2 receptor host) and PDB6LU7 (main protease SARS-CoV-2). Thus α-terpineol can prevent SARS-CoV-2 invasion into the human body [27]. Meanwhile, zingiberene exhibits significant binding affinity to the ACE2 receptor, so it can be used to inhibit SARS-CoV-2 [33].

Conclusion

Curcuma aeruginosa is one of the indigenous Curcuma species in Indonesia, which can be developed as a treatment of COVID-19. Ten chemical compounds (1,8-cineole (eucalyptol), α-terpineol, β-caryophyllene, β-eudesmol, β-pinene, β-sitosterol, curcumenol, palmitic acid, succinic acid and zingiberene) isolated from *C. aeruginosa* have shown better binding affinity with ACE2 protein and thus inhibit SARS-CoV-2. However, Further research *in vitro* and *in vivo* is much needed for *C. aeruginosa* to become a new antiviral drug for SARS-CoV-2.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

21. N.S. Dosoky and W.N. Setzer, *Nutrients*, **10**, 1196 (2018); https://doi.org/10.3390/nu10091196
22. N.-S. Mohamad-Fauzi, R.-A. Zainal-Abidin, M.W.A. Zaidan, S. Simoh, A. Zainal and Z.-A. Mohamed-Hussein, *Sains Malays.*, **47**, 2985 (2018); https://doi.org/10.17576/jsm-2018-4712-07
23. N. Akarchariya, S. Sirilun, J. Julsrigival and S. Chansakaowa, *Asian*

2. Z. Wu and J.M. McGoogan, *JAMA*, **323**, 1239 (2020); https://doi.org/10.1001/jama.2020.2648
3. B. Hu, H. Guo, P. Zhou and Z.-L. Shi, *Nat. Rev. Microbiol.*, **19**, 141 (2021); https://doi.org/10.1038/s41579-020-00459-7
4. M. Delikhoon, M.I. Guzman, R. Nabizadeh and A.N. Baghani, *Int. J. Environ. Res. Public Health*, **18**, 395 (2021); https://doi.org/10.3390/ijerph18020395
5. H.A. Rothan and S.N. Byrareddy, *J. Autoimmun.*, **109**, 102433 (2020); https://doi.org/10.1016/j.jaut.2020.102433
6. J. Yang, Y. Zheng, X. Gou, K. Pu, Z. Chen, Q. Guo, R. Ji, H. Wang, Y. Wang and Y. Zhou, *Int. J. Infect. Dis.*, **94**, 91 (2020); https://doi.org/10.1016/j.ijid.2020.03.017
7. A. Hensel, R. Bauer, M. Heinrich, V. Spiegler, O. Kayser, G. Hempel and K. Kraft, *Planta Med.*, **86**, 659 (2020); https://doi.org/10.1055/a-1177-4396
8. S. Paramita, E.B. Moerad, S. Ismail and E. Marliana, *Nusant Biosci.*, **10**, 105 (2018); https://doi.org/10.13057/nusbiosci/n100207
9. S. Paramita, E.B. Moerad, S. Ismail and E. Marliana, *F1000 Res.*, **7**, 1799 (2018); https://doi.org/10.12688/f1000research.16416.1
10. S. Paramita, S. Ismail, E. Marliana and E.B. Moerad, *Eur. Asian J. Biosci.*, **13**, 2389 (2019).
11. D. Subositi and S. Wahyono, *Biodiversitas*, **20**, 1356 (2019); https://doi.org/10.13057/biodiv/d200527
12. B.S. Iskandar, J. Iskandar, B. Irawan and R. Partasasmita, *Biodiversitas J. Biol. Divers.*, **19**, 437 (2018); https://doi.org/10.13057/biodiv/d190211
13. R.V. Shanthi, J. Jumari and M. Izzati, *Biosaintifika J. Biol. Biol. Educ.*, **6**, 61 (2014).
14. S. Jose and T.D. Thomas, *Int. J. Green Pharm.*, **8**, 65 (2014); https://doi.org/10.4103/0973-8258.126828
15. S. Hadijah, M. Hendra and N. Hariani, *Bioprospek J. Ilm. Biol.*, **11**, 19 (2016).
16. S. Simoh and A. Zainal, *Asian Pac. J. Trop. Biomed.*, **5**, 412 (2015); https://doi.org/10.1016/S2221-1691(15)30378-6
17. S. Siahaan, R.S. Handayani and N.K. Aryastami, *Health Sci. J. Indones.*, **8**, 95 (2017).
18. J. Batoro and D. Siswanto, *Asian J. Med. Biol. Res.*, **3**, 158 (2017); https://doi.org/10.3329/ajmbr.v3i2.33563
19. R. Widyowati and M. Agil, *Chem. Pharm. Bull. (Tokyo)*, **66**, 506 (2018); https://doi.org/10.1248/cpb.c17-00983
20. M. George, S.J. Britto and T. Arulappan, *World J. Pharm. Res.*, **3**, 1042 (2014).
25. D.U.C. Rahayu, H. Haryono and T. Sugita, *Asian J. Chem.*, **11**, 702 (2018); https://doi.org/10.31788/RJC.2018.1122076
26. T. Kamazeri, O. Samah, M. Taher, D. Susanti and H. Qaralleh, *Asian Pac. J. Trop. Med.*, **5**, 202 (2012); https://doi.org/10.1016/S1995-7645(12)60025-X
27. T.T.A. My, H.T.P. Loan, N.T.T. Hai, L.T. Hieu, T.T. Hoa, B.T.P. Thuy D.T. Quang, N.T. Triet, T.T.V. Anh, N.T.X. Dieu, N.T. Trung, N.V. Hue, P.V. Tat, V.T. Tung and N.T.A. Nhung, *Chem. Select*, **5**, 6312 (2020); https://doi.org/10.1002/slct.202000822
28. C. Colalto, *Drug Dev. Res.*, **81**, 950 (2020); https://doi.org/10.1002/ddr.21716
29. I. Aanouz, A. Belhassan, K. El-Khatabi, T. Lakhlifi, M. El-Ldrissi and M. Bouachrine, *J. Biomol. Struct. Dyn.*, (2020); https://doi.org/10.1080/07391102.2020.1758790
30. J. Wang, X. Zhang, A.B. Omarini and B. Li, *J. Food Biochem.*, **44**, e13481 (2020); https://doi.org/10.1111/jfbc.13481
31. C. Giuliani, G. Pieraccini, C. Santilli, C. Tani, M. Bottoni, S. Schiff, G. Fico, A. Papini and S. Falsini, *Chem. Biodivers.*, **17**, e2000707 (2020); https://doi.org/10.1002/cbdv.202000707
32. R.R. Narkhede, A.V. Pise, R.S. Cheke and S.D. Shinde, *Nat. Prod. Bioprospect.*, **10**, 297 (2020); https://doi.org/10.1007/s13659-020-00253-1
33. N.V. Pandey, *Virus Dis.*, **31**, 1 (2020); https://doi.org/10.1007/s13337-019-00563-0
34. G.S. Dave, K.D. Rakholiya, M.J. Kaneria, B.P. Galvadiya, S.R. Vyas, V.H. Kanbi and M.P. Patel, *Phyther. Res.*, 34, 3400 (2020); https://doi.org/10.1002/ptr.6796
35. A.A. Elfiky, *J. Biomol. Struct. Dyn.*, (2020); https://doi.org/10.1080/07391102.2020.1761881
36. L. Luo, J. Jiang, C. Wang, M. Fitzgerald, W. Hu, Y. Zhou, H. Zhang and S. Chen, *Acta Pharm. Sin. B*, **10**, 1192 (2020); https://doi.org/10.1016/j.apsb.2020.05.007
37. P. Chowdhury, *J. Biomol. Struct. Dyn.*, (2020); https://doi.org/10.1080/07391102.2020.1803968
38. Z. Zhuang, X. Zhong, H. Zhang, H. Chen, B. Huang, D. Lin and J. Wen, *Comb. Chem. High Throughput Screen.*, (2021); https://doi.org/10.2174/1386207323999201029122301
39. A. Sagaama, S.A. Brandan, T. Ben Issa and N. Issaoui, *Heliyon*, **6**, e04640 (2020); https://doi.org/10.1016/j.heliyon.2020.e04640