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The Importance of Natural ACE2 Inhibitor: Potency of Porang (Amorphophallus muelleri) Glucomannan as Anti-SARS-Cov-2

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ABSTRACT

The inhibition of SARS-Cov-2 S binding with hACE2, expressed in most human tissues, may prevent the severity of virus infection. However, commercial ACE2 inhibitor drugs are still limited, while several natural compounds have already been reported to have anti-ACE2 activity. We found the potential of hydrolyzed glucomannan of porang tuber in the inhabitation of binding activity between ACE2 and S1 of SARS-Cov-2.

Keywords: ACE2, SARS-Cov-2, S1, glucomannan, porang

INTRODUCTION

A year after discovery of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) that caused the Coronavirus Disease 2019 (Covid-19) pandemic, most affected countries already carry out their vaccination programs. However, the need for various strategies to treat and prevent infection still open widely. Possible anti-viral activity from natural resources has become more interesting in this condition where viruses emerge in the light of advancing technological resources available [1].

One of the therapeutic strategies by administration of convalescent plasma, which has been applied since previous coronavirus outbreaks as an adaptive immunotherapy method, especially for comorbid individuals [2]. On the other hand, there are particular interests in the direct inhibition of the interaction between the virus with human Angiotensin-Converting Enzyme 2 (hACE2) as it's cell receptors [3]. It is suggested that the virus variants show improved affinity of spike receptor binding domain (S RBD) to hACE2 [4,5]. ACE2 is the novel homologue of ACE and a key component of renin-angiotensin-aldosterone system (RAS) which is regulator of systemic vascular function both in health and disease [6].

Since the first case of human outbreaks of SARS-Cov in 2003, ACE2 was identified as the cellular receptors where the extracellular part of ACE2 interacts with the SARS-Cov spike glycoprotein (S) to mediate the binding and entry of coronavirus into human cells [7,8]. The S1 subunit of SARS-Cov-2 S protein consists of receptor binding domain (RBD) that contains receptor binding motif (RBM) which cleaves the ACE2 receptor, then the S2 subunits facilitates the viral cell membrane fusion [9]. It was reported that the binding affinity of SARS-Cov-2 S protein with ACE2 is 10-20 times higher than S protein of SARS-Cov [10,11]. Because it is possible for S protein to further mutate, blocking its cell receptors may be a more effective strategy.

ACE2 is expressed in most tissues, mostly in the kidney, endothelium, lungs, and heart where those organs became the targets of SARS-Cov-2 infection especially the lung as the virus transmitted through human respiratory system [12,13]. High expression of ACE2 commonly found in diabetic and heart patients which elevated the risk of infection [13]. Commercial drug for ACE2 inhibitors are still lacking than ACE inhibitor which are widely marketed. On the other hand, natural product such as flavonoids and peptides were reported to have potential against Covid-19 through receptor inhibition of ACE2 [10]. However, the similar potential of polysaccharides much less explored. Polysaccharides as active ingredients have several advantages including wide sources, low toxicity, fewer side effects, good biocompatibility, and able to act an immune regulator [14].

Glucomannan (GM) is a water-soluble polysaccharide abundant in nature, commonly isolated from tubers of *Amorphophallus sp.* This polysaccharide composed of β-1,4 linked d-mannose and d-glucose monomers and reportedly have promising biopharmaceutical benefits [15]. Glucomannan also known to have anti-inflammation and immunomodulator activity which can be used as indirect mechanism to treat SARS-Cov-2 infection [16]. Modified GM from *Amorphophallus konjac* reportedly able to interact with glycoprotein of Human Immunodeficiency Virus (HIV) [17] and also shown potential as ACE inhibitor [18], however its activity as ACE2 inhibitor has never been explored before.

Natural ACE2 inhibitors have the ability to interact with hACE2 interface either by disturbing hydrogen bond between ACE2 and S protein [10] or direct molecular binding with ACE2 [19]. In this study, we investigated on the potency of

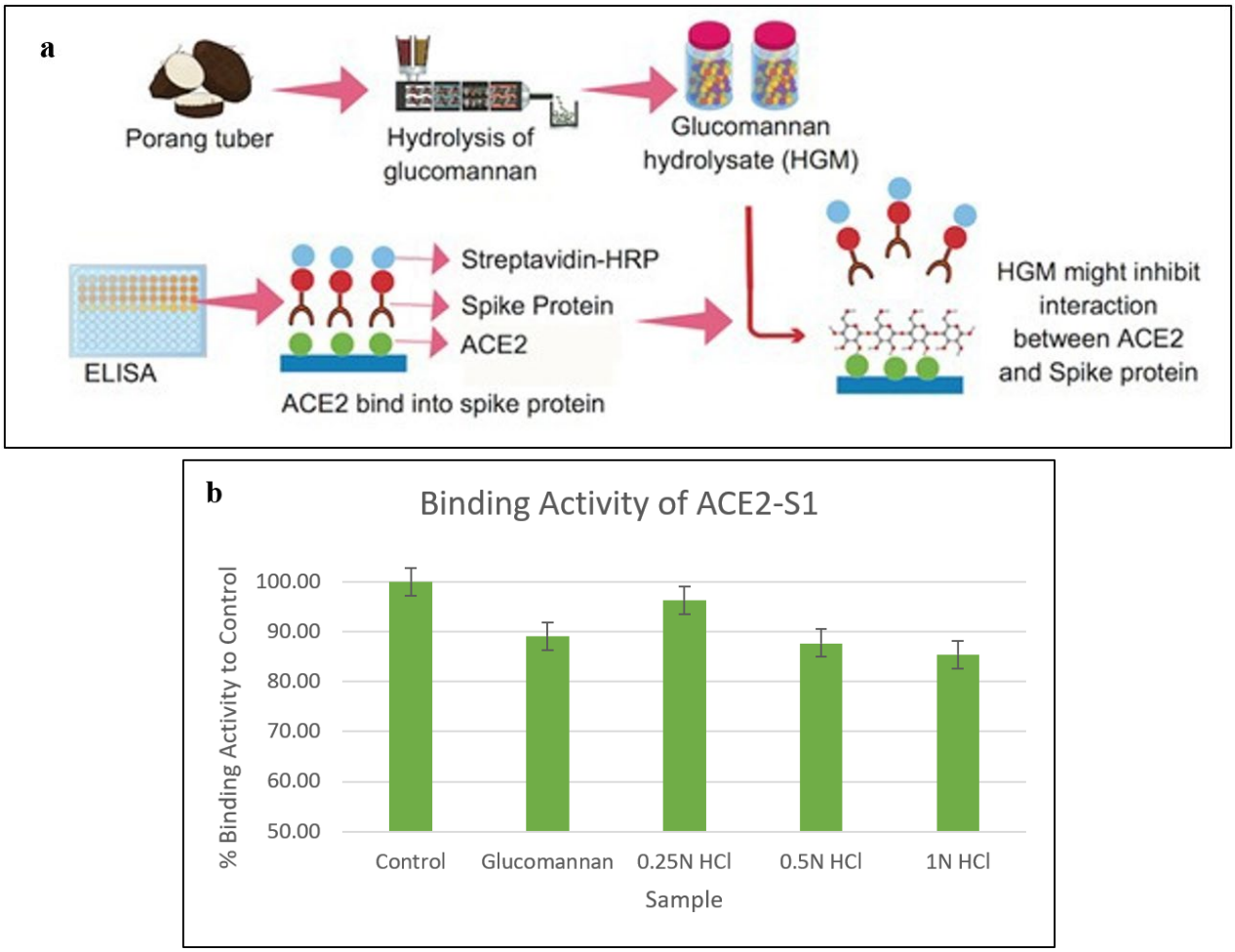

Figure 1. ELISA could be used to examine activity of HGM abrogate interaction between ACE2 and Spike protein (a), and and the inhibitory effect of HGM against ACE2-S1 interaction (b)

glucomannan as inhibitor of ACE2 and SARS-Cov-2 S1 interaction by direct molecular binding. Derived glucomannan from porang tuber (*Amorphophallus muelleri*) which natives in Indonesia.

METHOD AND RESULT

Glucomannan flour was wet extracted from porang tuber, then hydrolysed with HCl in various concentrations (0.25N, 0.5N, and 1.0 N) in order to broke the particles into smaller sizes to improve its bioactivity without changing the chemical structure. Hydrolysis carried for 60 minutes at 75°C, then neutralized with NaOH. Hydrolysed glucomannan (HGM) separated from the solution by precipitation in ethanol, then dried using a fluidised bed dryer at 50°C. The inhibitory activity of HGM on SARS-Cov-2 and ACE2 interaction were tested using enzyme-linked immunosorbent assay (ELISA) kit purchased from BPS Bioscience (San Diego, CA, USA), following the manufacturers' instruction.

The result shows that hydrolysed glucomannan slightly reduce the binding activity between ACE2 and S1 of SARS-Cov-2. The greater inhibitory effect obtained by HGM produced by more significant hydrolysis, which suggested the particle size of glucomannan plays a significant role in its bioactivity. The data indicate the potency of hydrolysis with higher than 1N HCl concentration can be done to produce glucomannan with much smaller particle size to provide a more significant to optimal ACE2 – S1 interaction inhibitory effect.

DISCUSSION

Throughout the pandemic, there are unique situations where people independently learn and look for information on drugs and Covid-19 prevention. Unfortunately, due to poor healthcare-seeking behaviour, most people tend to self-medicate their symptoms [20]. This became prevalent especially in developing countries where there are commonly lack of massive awareness programmes, causing the growth of rumours, stigma, and conspiracy theories around public health emergencies [21,22]. While such medical conspiracy theories can motivate people to refusing vaccines or antibiotics, this situation often accompanied by widespread rumours about natural remedies that seems to be easier to follow by the wider community such as consuming specific mixes of herbs and spices that they believe would strengthen the lungs against virus [22].

Indonesia included as one of the biggest source of rumours, stigma, and conspiracy theories around Covid-19 pandemic, lead to mistrust with governments and health professionals [22]. Self-medication method by consuming supplements and natural product labelled as “Anti Covid-19” without prescription became a common sight [23]. Natural or plant-based health products has been generally more preferred

mostly motivated by people's familiarity with the raw materials, it was more influential than their personal background including nationality, education, employment, or income [24].

Research and development of natural and plant-based medicine such as ACE2 inhibitors became important especially in countries that still strongly hold on local wisdom of traditional treatments. This experiment becomes a gateway for further anti-viral study of porang glucomannan and new approach to produce more natural based medicines.

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REFERENCES

1. Ahmad A, Rehman MU, Alkharfy KM. An alternative approach to minimize the risk of coronavirus (Covid-19) and similar infections. Eur. Rev. Med. Pharmacol. Sci., 2020;24(7):4030-4. https://doi.org/10.26355/EURREV_202004_20873
2. Hachim SK. The convalescent serum for treatment of COVID-19 infection: Review. European J. Med. Ed. Te., 2020;4109;1:5-8. https://doi.org/10.30935/ejmets/8016
3. Williams-noonan BJ, Todorova N, Kulkarni K, Aguilar M, Yarovsky I. An Active Site Inhibitor Induces Conformational Penalties for ACE2 Recognition by the Spike Protein of SARS-CoV-2. 2021. https://doi.org/10.1021/acs.jpcb.0c11321 PMid:33657325 PMCid:PMC7945587
4. van Oosterhout C, Hall N, Ly H, Tyler KM. COVID-19 evolution during the pandemic–Implications of new SARS-CoV-2 variants on disease control and public health policies. Virulence, 2021;12(1):507-8. https://doi.org/10.1080/21505594.2021.1877066 PMid:33494661 PMCid:PMC7849743
5. Nelson G, Buzko O, Patricia S, Niazi K, Rabizadeh S, Soon-Shiong P. Molecular dynamic simulation reveals E484K mutation enhances spike RBD-ACE2 affinity and the 1 combination of E484K, K417N and N501Y mutations (501Y.V2 variant) induces conformational 2 change greater than N501Y mutant alone, potentially resulting in an e. bioRxiv, 2021:2021.01.13.426558. https://doi.org/10.1101/2021.01.13.426558
6. Tikellis C, Thomas MC. Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease. Int. J. Pept., 2012;2012. https://doi.org/10.1155/2012/256294 PMid:22536270 PMCid:PMC3321295
7. Jia HP, et al. ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. J. Virol., 2005;79(23):14614-21. https://doi.org/10.1128/jvi.79.23.14614-14621.2005 PMid:16282461 PMCid:PMC1287568
8. Machhi J, et al. The Natural History, Pathobiology, and Clinical Manifestations of SARS-CoV-2 Infections," J. Neuroimmune Pharmacol., vol. 15, no. 3, pp. 359–386, 2020, https://doi.org/10.1007/s11481-020-09944-5 PMid:32696264 PMCid:PMC7373339
9. Huang Y, Yang C, feng Xu X, Xu W, wen Liu S. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol. Sin., 2020;41(9):1141-9. https://doi.org/10.1038/s41401-020-0485-4 PMid:32747721 PMCid:PMC7396720
10. Muchtaridi M, Fauzi M, Ikram NKK, Gazzali AM, Wahab HA. Natural flavonoids as potential angiotensin-converting enzyme 2 inhibitors for anti-SARS-CoV-2. Molecules, 2020;25(17). https://doi.org/10.3390/molecules25173980 PMid:32882868 PMCid:PMC7504743
11. Ace W, Enzyme A, Receptor M, Davidson AM, Wysocki J, Batlle D. Interaction of SARS-CoV-2 and other coronavirus. 2020:1339-49. https://doi.org/10.1161/HYPERTENSIONAHA.120.15256
12. Pagliaro P, Penna C. ACE/ACE2 ratio: A key also in 2019 coronavirus disease (Covid-19)?. Front. Med., 2020;7(June):17-21. https://doi.org/10.3389/fmed.2020.00335 PMid:32626721 PMCid:PMC7314898
13. Kumar P, et al. Role of ACE2 receptor and the landscape of treatment options from convalescent plasma therapy to the drug repurposing in COVID-19. Mol. Cell. Biochem., 2020;476(2):553-74. https://doi.org/10.1007/s11010-020-03924-2 PMid:33029696 PMCid:PMC7539757
14. Iravani S, Varma RS. Important roles of oligo-and polysaccharides against sars-cov-2: Recent advances. Appl. Sci., 2021;11(8):3512. https://doi.org/10.3390/app11083512
15. Alonso-Sande M, Teijeiro-Osorio D, Remuñán-López C, Alonso MJ. Glucomannan, a promising polysaccharide for biopharmaceutical purposes. Eur. J. Pharm. Biopharm., 2009;72(2):453-62. https://doi.org/10.1016/j.ejpb.2008.02.005 PMid:18511246
16. Huang C, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, 2020;395(10223):497-506. https://doi.org/10.1016/S0140-6736(20)30183-5
17. Bo S, Muschin T, Kanamoto T, Nakashima H, Yoshida T. Sulfation and biological activities of konjac glucomannan. Carbohydr. Polym., 2013;94(2):899-903. https://doi.org/10.1016/j.carbpol.2013.01.049 PMid:23544648
18. Song Q, et al. Preparation, structure analysis and ACE inhibitory activity of konjac oligosaccharide. Ind. Crops Prod., 2018;124(August):812-21. https://doi.org/10.1016/j.indcrop.2018.08.034
19. Cheng L, Zheng W, Li M, Huang J, Bao S. Citrus fruits are rich in flavonoids for immunoregulation and potential targeting ACE2. Preprints, 2020. Available at: https://www.preprints.org/manuscript/202002.0313/v1
20. Mudenda S, et al. Self-medication and its consequences during & after the coronavirus disease 2019 (COVID-19) pandemic: A global health problem. Eur. J. Environ. Public Heal., 2020;5(1):em0066. https://doi.org/10.29333/ejeph/9308
21. Naveed A. COVID-19 in Pakistan: Current scenario and future perspective. J. Clin. Exp. Investig., 2020;11(4):em00753. https://doi.org/10.29333/jcei/8354
22. Islam MS, et al. COVID-19-related infodemic and its impact on public health: A global social media analysis. Am. J. Trop. Med. Hyg., 2020;103(4):1621-9. https://doi.org/10.4269/ajtmh.20-0812 PMid:32783794 PMCid:PMC7543839

23. D'arqom A, Sawitri B, Nasution Z, Lazuardi R. Anti-COVID-19' medications, supplements, and mental health status in Indonesian mothers with school-age children. Int. J. Womens. Health, 2021;13(April):699-709. https://doi.org/10.2147/IJWH.S316417 PMid:34285594 PMCid:PMC8286101

24. Van Andel T, Carvalheiro LG. Why urban citizens in developing countries use traditional medicines: The case of suriname. Evidence-based Complement. Altern. Med., 2013;2013. https://doi.org/10.1155/2013/687197 PMid: 23653663 PMCid:PMC3638607