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In Silico Docking to Explore the Coronavirus-2 ACE2 Inhibitor Potential in Brown Seaweed *Padina* sp. from Morotai Island, North Maluku, Indonesia

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Abstract*— Efforts to explore new sources of antivirals for coronavirus-2 from abundant marine natural materials are highly encouraged. The study aimed to explore the potential compounds of brown seaweed *Padina* sp. from Morotai Island extracted using three solvents, i.e., n-hexane, ethyl acetate, and acetone, as an antiviral against coronavirus-2 through an entry inhibitor mechanism using bioinformatics tools. The target protein was Angiotensin-Converting Enzyme-related carboxypeptidase (ACE2) receptor. Protein structure was downloaded from PDB and prepared using Chimera. The interaction of compounds to ACE2 was predicted using AutoDock4 and AutoDockTools. MLN-4760 was used as a standard compound. Results showed that 15 selected compounds were potential as ACE2 inhibitors, resulting in negative binding energies, low inhibition constant, and varying binding modes. The conformation structure of all compounds was occupied on the ACE-2 active site. Four compounds were highly potential as ACE2 inhibitors with binding energy lower than a standard compound, comprised of Neophytadiene (diterpene); 6,9,12,15-Docosatetraenoic acid, methyl ester (fatty acid); N-Dimethylaminomethyl-tert-butyl-isopropylphosphine (alkaloid) and 8,11-Octadecadienoic acid, methyl ester (fatty acid). Ethyl acetate and acetone are suggested to be used as solvents for the extraction to produce compounds as ACE2 inhibitors, but ethyl acetate was found to be the most effective. Brown seaweed of *Padina* sp. is recommended to be developed as a pharmaceutical and nutraceutical preparation for COVID-19. Further in vivo and in vitro studies are suggested to confirm this study's results and provide stronger evidence.

***Keywords*— Molecular docking; antiviral; macroalgae; *Padina*; ACE-2; COVID-19.**

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I. INTRODUCTION

The coronavirus-2 outbreak that causes severe acute respiratory syndrome of COVID-19 disease has been declared a global pandemic and public health emergency that received international concern during 2019-2022. The COVID-19 disease causes a variety of symptoms, ranging from mild to severe respiratory distress associated with sepsis, multi-organ dysfunction, and death [1]. As of 31 May 2023, confirmed cases of COVID-19 reported to the World Health Organization (WHO) have reached 766 million worldwide, including 6.9 million deaths. Even recently, on 11 May 2023, WHO declared the end of Covid-19 as a global health emergency. Covid-19 continues to spread, the virus continues to evolve and remains a global health threat, but to a lesser extent [2]. Therefore, it is still necessary and essential to continue efforts to explore new drugs or medicinal ingredients with antiviral potential that can provide immunization against this coronavirus-2 [3].

The coronavirus-2 particle comprises a positive single strand of ribonucleic acid (+RNA) surrounded by a membrane protein (M) and an envelope protein (E). It also has a spike envelope (S) protein capable of interacting with the Angiotensin-Converting Enzyme-related carboxypeptidase (ACE2) receptor on host cells. This spike protein comprises subunits 1 (S1) and 2 (S2), where the S1 spike protein will interact with the host cell membrane protein ACE2. This interaction will change the conformation of the host cell membrane and bring coronavirus-2 particles into the cytoplasm [4], [5], [6]. Several studies have been employed

to understand the virulence mechanism of coronavirus-2. It has been reported that coronavirus-2 can recognize human ACE2 more efficiently than the previous coronavirus-1, increasing the capacity for human-to-human transmission [7], [8]. Therefore, the contagion prevention efforts of coronavirus-2 recommended the search for new pharmaceutical preparations, both from various classes of chemicals and natural ingredients, to focus on their pharmacologically active components as ACE2 inhibitors.

About one-third of marketed drug products are derived from natural ingredients, directly or indirectly [9]. Natural products in secondary metabolites show positive signs for antiviral treatment and immunotherapy through *in silico docking* genomic studies [10]. In particular, seaweed or macroalgae have certain bioactive constituents with pharmacological activity, which are not present in terrestrial organisms [3]. The bioactive components in seaweed, such as phenolic compounds, natural pigments, sulfated polysaccharides, fibers, or halogen compounds, are very broad [11], [12]. Various pharmacological applications have been reported from seaweeds, including antibacterial, antifungal, anti-inflammatory, neuroprotective, anti-tumor, immunomodulator, anti-cancer, anti-allergy, anti-oxidants, etc., [13], [14]. Seaweeds are generally classified into three classes, namely brown (Phaeophyceae), green (Chlorophyceae) and red (Rhodophyceae). Brown seaweeds showed higher anti-oxidant activity than red and green [15], [16].

North Maluku is a group of islands in the eastern part of Indonesia with abundant marine biological resources and high potential to be explored. In particular, the brown seaweed of *Padina* sp. grows well in a range of habitats from the intertidal to subtidal zones in clear waters at a depth of 15 to 20 m. It grows attached to the substrates or as epiphytes and is easily recognized due to its structural resemblance to a peacock's tail [16]. This brown seaweed is widely distributed in the coastal waters from the north (Morotai Island), central (Ternate Island), and south (Kayoa Island) of North Maluku. Differences in locations where seaweed grows greatly affect the content of bioactive compounds [15]. Brown seaweed in tropical countries is reported to produce better secondary metabolites as a protection system against high ultraviolet radiation [17].

Previous study reports on the phytochemical profiling of brown seaweed *Padina* sp. samples from marine waters in Morotai Islands using three solvents comprised of n-hexane, ethyl acetate, and acetone showed the presence groups of alkanes and fatty acids, a small number of terpenoids, steroids, alkaloids, aromatics, and carboxylic acids [18], [19]. Therefore, this research was a follow-up study that aims to explore and screen the potential pharmacological activity of selected compounds of that brown seaweed sample as antiviral against coronavirus-2 through ACE2 inhibitor mechanism using a bioinformatics approach of *in silico docking*. *In silico* molecular docking studies can provide initial results quickly and economically before standard experimental techniques. This method can predict the experimental binding modes and the affinity of small molecules within a specific receptor target binding site [20]. The results of this research are significant in providing essential information for further development and utilization of brown seaweed of *Padina* sp. abundant marine resources in tropical waters as antiviral pharmaceutical and nutraceutical preparations for COVID-19.

II. Materials and Method

A. Preparation of Target Protein and Standard Ligand

The target protein structure used was Angiotensin-Converting Enzyme-related carboxypeptidase (ACE2). The protein's three-dimensional structure was downloaded via the protein data bank (PDB) website https://www.rcsb.org/structure/1R4L with PDB code: 1R4L [21]. Protein structure was downloaded in PDB format and then prepared using the Chimera program [22]. Protein preparation was carried out by removing other residues to obtain a single protein structure, subsequently continued by adding hydrogen atoms and atomic charges. In the structure of this protein, there was a compound that binds directly and is used as a positive standard, namely MLN-4760. The standard compound of MLN-4760 is proven to be a highly potent and selective ACE2 inhibitor, including its interaction with the coronavirus-2 spike receptor binding domain in humans by bioinformatics simulation [23], [24]. This compound was then optimized using the AM1-BCC method in Chimera and saved in PDB format.

B. Preparation of Ligand

The bioactive compounds of *Padina* sp. from Morotai Islands extracted using three solvents (n-hexane, ethyl acetate, and acetone) retrieved from previous reports [18], [19] served as ligands. Five compounds of each solvent extract were selected. Thus, in total, the preparation was carried out on 15 ligands. All compounds were modeled three-dimensionally and saved in PDB format. The standard ligand (AM1-BCC in Chimera) also optimized all compounds using the same method. After optimizing the structure, all ligands were ready for docking to the target protein.

C. Re-docking of Standard Ligand

Before molecular docking, standard ligands were re-docked using the AutoDock4 and AutoDockTools programs [25] to validate the subsequent procedure to be used. Re-docking analysis was performed by re-attaching the standard lig-and compound to the active side of the protein, with a grid box size of 30 x 25 x 30 Å and a spacing of 0.375 Å. The algorithm used was the Lamarckian [26], which set the number of conformations produced at 10. The best conformation (high validity) was the one with an RMSD value of less than 2 Å [27].

D. Molecular Docking Analysis

The docking process was conducted on 15 selected compounds as ligands and the ACE2 target protein as a macromolecule. The *in silico* molecular docking method used was the same as the re-docking, with a grid box size of 30 x 25 x 30 Å and a spacing of 0.375 Å. The algorithm used is Lamarckian, with 10 conformations and a maximum number of evaluations of 2,500,000. The best conformation is chosen based on the binding energy. The lowest binding energy is the best conformation for stability reasons [28]. Visualization of

the interaction of ligands and target proteins was carried out using the Discovery Studio Visualizer program.

III. Results and Discussion

A. Re-docking of MLN-4760 to ACE2

The results of the re-docking analysis of the standard compound (MLN-4760) to target protein ACE2 are shown in Table 1. The conformation number 8 shows the lowest RMSD value of 1.70 Å, indicating that the conformational overlapping before and after molecular docking has a high similarity [26], [27]. Therefore, this re-docking analysis result of number 8 was used as a standard to validate further molecular docking of the target compounds. The visual interaction results of MLN-4760 to ACE2 are shown in Fig. 1. There were two interactions of H-bond from the amino acid residue His345 and other interactions in electron stacking and van der Waals.

TABLE I
RE-DOCKING RESULTS OF MLN-4760 TO ACE2

Conformation	Binding energy (kcal/mol)	RMSD (Å)
1	-2.58	4.67
2	-2.57	5.10
3	-2.92	2.20
4	-3.27	4.92
5	-5.23	1.85
6	-3.85	4.93
7	-1.70	4.66
8*	**-5.07***	**1.70***
9	-3.88	4.92
10	-2.36	2.07

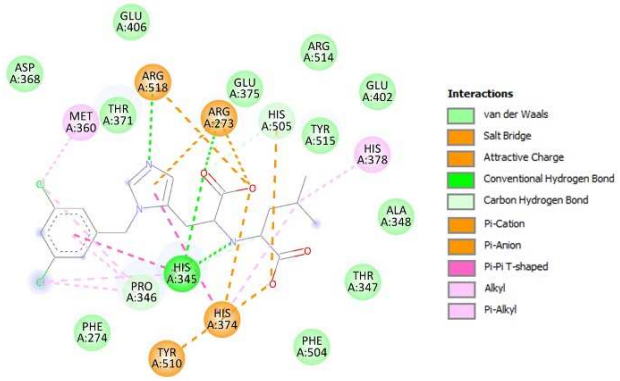

Fig. 1 Visualization 2D interaction of MLN-4760 to ACE2

B. Molecular docking of bioactive compounds of Padina sp. from Morotai Island to ACE2

The results of the molecular docking of 15 bioactive compounds of *Padina* sp. from Morotai Island are shown in Table 2. The selected compounds from the n-hexane extract were fatty acids, ester, and alkane. There was only one compound, namely Diisobutyl cellosolve (3a), that did not show any H-bond interaction with ACE2. The binding energy of cis-Vaccenic acid (2a) was the lowest, although the value was still higher than that of the standard compound (Table 1 & 2). The interaction visualization of the compound Vaccenic acid with ACE2 is shown in Fig. 2A. It can be seen that the carboxylic acid group plays an important role because it can form H-bond interactions, which contributes to binding energy. Further, the conformation of all compounds can bind to the active site of the ACE2 target protein, as shown in Fig. 2B.

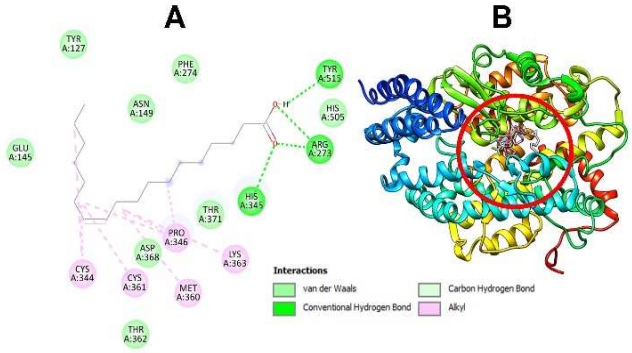

Fig. 2 Visualization 2D interaction of A. Vaccenic acid with ACE2 and B. The conformation structure of compounds 1a-5a (n-hexane extract) on the active site of ACE2

In the ethyl acetate extract, two compounds have lower binding energy than the standard compound, i.e., Neophytadiene (3b) and 6,9,12,15-Docosatetraenoic acid, methyl ester (4b) (Table 2). Visualization of the interaction of these two compounds can be seen in Fig. 3A-B. Specifically, in the compound Neophytadiene, H-bond interaction was not found. However, van der Waals and electron stacking several amino acids contributed to its low binding energy. Whilst, in compound 6,9,12,15-Docosatetraenoic acid, methyl ester, there was one H-bond interaction with the Arg273 residue, also identified some other additional interactions. All compounds in the ethyl acetate extract had negative energy binding values, indicating their ability to bind with ACE2. It can be seen in the conformation structure of the molecular docking, which shows that all compounds were on the active site of the ACE2 (Fig. 3C).

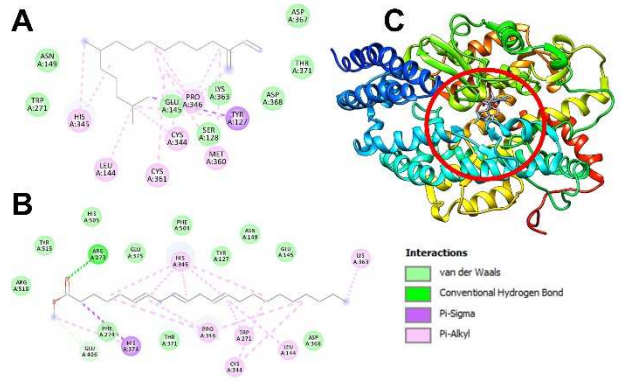

Fig. 3 Visualization 2D interaction of A. Neophytadiene and B. 6,9,12,15-Docosatetraenoic acid, methyl ester with ACE2, and C. The conformation structure of all compounds 1b-5b (Ethyl acetate extract) on the active site of ACE2.

Likewise, the acetone extract showed 2 compounds that had lower binding energy than the standard compound, i.e., N-Dimethylaminomethyl-tert-butyl-isopropylphosphine (1c) and 8,11-Octadecadienoic acid, methyl ester (5c). However, the binding energies of these two compounds were still higher than those of the two compounds (3b and 4b) from ethyl acetate extract (Table 2). Visualization of the interactions

between these two compounds with ACE2 was shown in Fig. 4A-B, respectively. In compound N-Dimethylaminomethyl-tert-butyl-isopropylphosphine, there were pi-sigma and van der Waals interactions instead of H-bond. In compound 8,11-Octadecadienoic acid, methyl ester, there was one H-bond interaction with the His345 amino acid residue. The conformation structure of the molecular docking showed that all compounds were occupied on the active site of the ACE2 (Fig. 4C).

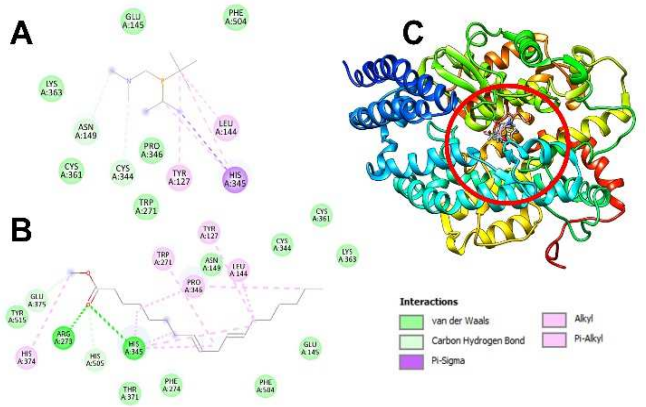

Fig. 4 Visualization 2D interaction of A. N-Dimethylaminomethyl-tert-butyl-isopropylphosphine and B. 8,11-Octadecadienoic acid, methyl ester with ACE2, and C. The conformation of compounds 1f-5f (Acetone extract) on the active site of ACE2.

B. Comparison of Binding Energies to ACE2 of all Compounds with MLN-4760

A comparison of the binding energies of all compounds from different solvent extracts with MLN-4760 as a standard compound is shown in Fig. 5. It can be seen that all compounds produced negative binding energies. However, all compounds from n-hexane extract showed higher binding energies than MLN-4760 (>-5.07 kcal/mol), so it is not recommended. Meanwhile, there were four promising compounds from ethyl acetate and acetone extracts which have lower binding energies than MLN-4760 (<-5.07 kcal/mol) comprised of Neophytadiene (3e); 6,9,12,15-Docosatetraenoic acid, methyl ester (4e); N-Dimethylaminomethyl-tert-butyl-isopropylphosphine (1c) and 8,11-Octadecadienoic acid, methyl ester (5c).

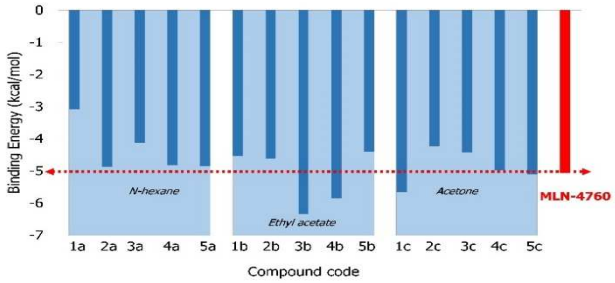

Fig. 5 Comparison of the binding energies to ACE2 of all compounds from different extracts with MLN-4760 (a standard compound)

TABLE II
MOLECULAR DOCKING RESULTS OF BIOACTIVE COMPOUNDS OF BROWN SEAWEED *PADINA* SP. FROM MOROTAI ISLAND

Compound			Binding energy (kcal/mol)	Inhibition constant (μM)	H-bond interaction (Å)
Code	Name	Class			
n-hexane extract					
1a	2-Ethyl-oxetane	Alkane	-3.08	5520	Arg273 (2.218), His345 (1.975)
2a	cis-Vaccenic acid	Fatty acid	-4.87	269.58	Arg273 (2.124 & 1.699), His345 (2.182)
3a	Diisobutyl cellosolve	Ester	-4.13	939.4	Not available
4a	cis-5,8,11,14,17-Eicosapentaenoic acid	Fatty acid	-4.82	293.53	Arg273 (1.957), His345 (2.210)
5a	[1,1'-Bicyclopropyl]-2-octanoic acid, 2'-hexyl-, methyl ester	Fatty acid	-4.86	276.08	His374 (1.960)
Ethyl acetate extract					
1b	Hexadecanoic acid, methyl ester	Fatty acid	-4.54	467.55	Arg273 (2.188), His345 (2.046)
2b	10-Octadecenoic acid, methyl ester	Fatty acid	-4.62	411.21	His345 (1.779)
3b	**Neophytadiene**	**Diterpene**	**-6.35***	**21.98**	**Not available**
4b	**6,9,12,15-Docosatetraenoic acid, methyl ester**	**Fatty acid**	**-5.85***	**51.77**	**Arg273 (1.878)**
5b	17-Octadecynoic acid	Fatty acid	-4.4	559.3	Arg273 (2.158 & 1.983)
			Acetone extract		
1c	**N-Dimethylaminomethyl-tert-butyl-isopropylphosphine**	**Alkaloid**	**-5.66**	**71.24**	**Not available**
2c	2-Pentanone, 4-hydroxy-4-methyl-	Terpenoid	-4.23	787.06	Cys344 (2.054)
3c	Cyclobutanone, 2-methyl-4-hydroxy-	Fatty acid	-4.43	564.90	His345 (2.128), Ser128 (1.779)
4c	1-Nonanol, 4,8-dimethyl-	Alcohol	-4.97	227.67	Lys363 (2.098), Asp368 (1.920)
5c	**8,11-Octadecadienoic acid, methyl ester**	**Fatty acid**	**-5.11**	**180.15**	**His345 (2.177)**

Note: *Binding energy lower than standard compound MLN-4760 (<-5.07 kcal/mol)

C. General Discussions

Interestingly, the molecular docking analysis showed that selected bioactive compounds of brown seaweed *Padina* sp. from Morotai Island indicated positive results as ACE2 inhibitors for coronavirus-2. Of the three different solvents used for extraction, the interaction of 15 compounds to ACE2 resulted in negative binding energies and low inhibition constant, also with some varying number and type of binding modes (Table 1 & Fig. 5). The conformation structure of the molecular docking also showed that all compounds were occupied on the active site of the ACE2 (Fig. 2, Fig. 3, Fig. 4).

Four compounds were highly potential as ACE2 inhibitors for coronavirus-2 with lower binding energy than the standard compound MLN-4760 as shown in Table 2 and Fig. 5. They were extracted using ethyl acetate and acetone solvents, comprised of Neophytadiene (-6.35) and 6,9,12,15-Docosatetraenoic acid, methyl ester (-5.85); N-Dimethylaminomethyl-tert-butyl-isopropylphosphine (-5.66) and 8,11-Octadecadienoic acid, methyl ester (-5.11). The ability to bind (affinity) indicates the drug candidate's strength to bind to the receptor. The lower the binding energy indicates the higher the affinity between the receptor and the ligand and the more stable the interaction between the ligand and the receptor [28]. In molecular docking research, the H-bond generally acts as a facilitator to increase ligand binding affinity by moving water molecules bound to proteins into large volumes of solvent [29].

In terms of bioactive compound class with ACE2 inhibitor potentials in brown seaweed *Padina* sp. from Morotai Island are mostly categorized as fatty acids, i.e., 6,9,12,15-Docosatetraenoic acid, methyl ester, and 8,11-Octadecadienoic acid, methyl ester (Table 2). Many previous studies have reported that naturally occurring lipids have been shown to possess health benefits in several disease states, including as antiviral for COVID-19. Fatty acids, particularly polyunsaturated (PUFA), have a main role in decreasing inflammation, reducing oxidative stress, and mitigating coagulopathy in the cardiovascular system [29], [30]. It is considered adequate to inhibit ACE2-controlled coronavirus-2 binding and cellular entry and stabilize the spike protein in a closed conformation, thus hindering its interaction with ACE2 [30], [31]. Several fatty acids and essential oils from functional foods have also been identified as ACE2 modulators, such as in geranium and lemon [32], black seed [33], olive [34], garlic [35], etc.

Neophytadiene is a compound from the diterpene class with high potential as an ACE2 inhibitor (Table 2). The low binding energy was contributed by van der Waals and electron stacking on several amino acids instead of H-bond (Fig. 3A). Neophytadiene has an essential role as an anti-inflammatory, antimicrobial, and antifungal, also with anti-oxidant properties [36]. This study is the first to report the promising potential of Neophytadiene from brown seaweed *Padina* sp. as an ACE2 inhibitor.

N-Dimethylaminomethyl-tert-butyl-isopropylphosphine was a compound from the alkaloid class with high potential as an ACE2 inhibitor (Table 2). In this compound, there were pi-sigma and van der Waals interactions instead of H-bond (Fig. 4A). Alkaloids have demonstrated potential anti-coronavirus activity through inhibition of pathogenesis-related targets from the Coronaviridae family, which are important for the virus life cycle [37]. It is also associated with anti-inflammatory, immunomodulatory, and antiviral activities by inhibiting the release of coronavirus infectious particles and reducing viral-induced cytopathic effects in the cellular lineage Vero E6 [38].

Ethyl acetate and acetone were suggested to be used as solvents for the extraction to produce bioactive compounds as ACE2 inhibitors in the brown seaweed *Padina* sp. However, ethyl acetate was the most effective (Table 2, Fig. 5). The extraction of a compound by a solvent is highly dependent on the solubility of the compound in the solvent [39]. Ethyl acetate is a semi-polar solvent that can attract both polar and nonpolar compounds. In addition, it has low toxicity and is easy to volatilize [40]. Acetone is a polar solvent that only attracts polar compounds. However, using an acetone solvent gave the best pigment quality in seaweed [41]. Whilst n-hexane is often used as an inert organic solvent due to its non-polarity. It is widely used to extract lipids from seeds such as nuts and flax [42].

This study finding showed that brown seaweed *Padina* sp. from North Maluku has high potential as a coronavirus-2 ACE2 inhibitor mostly due to its fatty acids, as an *in silico* study predicted. Further in vivo and in vitro studies are required to confirm this study's results and provide stronger evidence. Brown seaweed *Padina* sp. is recommended for development as a pharmaceutical and nutraceutical preparation for COVID-19. Nutraceuticals, also known as functional foods, are foods or parts of foods that play an important role in modifying and maintaining normal physiological functions for human health. It is consumed as part of a regular diet that provides high nutrition and is associated with several health benefits, including reducing the risk of chronic diseases [43]. Brown seaweed of *Padin*a sp. can be considered a potential nutraceutical since it is already used as food, has essential fatty acids for the nutrition of mammals, does not cause toxicity, and has anti-oxidant activity [44]. Previous reports showed that countries with high intakes of PUFA, particularly from marine origin, have lower fatality rates of COVID-19 in their diets [31], [45].

IV. Conclusion

This *in silico* study has predicted that brown seaweed *Padina* sp. from the Morotai Islands has the potential as an antiviral for COVID-19. It is recommended to be developed as a pharmaceutical and nutraceutical preparation for COVID-19. Four compounds had high potential as ACE2 inhibitors with binding energies lower than standard MLN-4760, composed of 2 fatty acids, 1 diterpene, and 1 alkaloid. Ethyl acetate and acetone were suggested to be used as solvents for the extraction to produce bioactive compounds as ACE2 inhibitors, but ethyl acetate was found to be the most effective. Further in vitro and in vivo studies are necessary to confirm this study's results and to provide more substantial evidence.

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References

[1] M. Kandeel, J. Kim, M. Fayez, Y. Kitade, and H. Kwon, "Antiviral drug discovery by targeting the SARS-CoV-2 polyprotein processing by inhibition of the main protease," *PeerJ*, vol. 10, no. e12929, pp. 1–20, 2022. doi: 10.7717/peerj.12929.

[2] M. A. Rahman, S. Cronmiller, Y. Shanjana, and M. Bhuiyam, "The WHO announced COVID-19 is no longer a global public health emergency amid the spreading of Arcturus variant: A correspondence evaluating this decision," *Int. J. Surg.*, vol. 25, no. 37222689, pp. 1–7, 2023. doi: 10.1097/JS9.0000000000000522.

[3] A. Rauf, U. Rashid, A. A. Khalil, S. A. Khan, and S. Anwar, "Docking-based virtual screening and identification of potential COVID-19 main protease inhibitors from brown algae ," *South African J. Bot.*, vol. 143, pp. 428–434, 2020. doi: 10.1016/j.sajb.2021.06.033.

[4] M. Drobysh *et al.*, "Biosensors for the determination of SARS-CoV-2 virus and diagnosis of COVID-19 infection," *Int. J. Mol. Sci.*, vol. 23, no. 666, pp. 1–25, 2022. doi: 10.3390/ijms23020666.

[5] R. García *et al.*, "Identification of potential antiviral compounds against SARS-CoV-2 structural and non structural protein targets: A pharmacoinformatics study of the CAS COVID-19 dataset," *Comput. Biol. Med.*, vol. 133, no. 104364, pp. 1–12, 2021. doi: 10.1016/j.compbiomed.2021.104364.

[6] S. Gao, T. Huang, L. Song, and S. Xu, "Medicinal chemistry strategies towards the development of effective SARS-CoV-2 inhibitors," *Acta Pharm. Sin. B*, vol. 12, no. 2, pp. 581–599, 2022. doi: 10.1016/j.apsb.2021.08.027.

[7] A. G. Harrison, T. Lin, and P. Wang, "Mechanisms of SARS-CoV-2 transmission and pathogenesis," *Trends Immunol.*, vol. 41, no. 12, pp. 1100–1115, 2020. doi: 10.1016/j.it.2020.10.004.

[8] B. Hu, H. Guo, P. Zhou, and Z.-L. Shi, "Characteristics of SARS-CoV-2 and COVID-19," *Nat. Rev. Microbiol.*, vol. 19, pp. 141–154, 2019. doi: 10.1038/s41579-020-00459-7.

[9] D. J. Newman and G. M. Cragg, "Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019," *J. Nat. Prod.*, vol. 83, pp. 770–803, 2020. doi: 10.1021/acs.jnatprod.9b01285.

[10] A. Al-Harrasi, T. Behl, T. Upadhyay, S. Chigurupati, and S. Bhatt, "Targeting natural products against SARS-CoV-2," *Environ. Sci. Pollut. Res.*, vol. 29, pp. 42404–42432, 2022. doi: 10.1007/s11356-022-19770-2.

[11] Y. Kumar, A. Tarafdar, and P. C. Badgujar, "Seaweed as a source of natural anti-oxidants : Therapeutic activity and food applications," *J. Food Qual.*, vol. 5753391, pp. 1–17, 2021. doi: 10.1155/2021/5753391.

[12] H. Padmi *et al.*, "Macroalgae bioactive compounds for the potential antiviral of SARS-CoV-2 : An in silico study," *J. Pure Appl. Microbiol.*, vol. 16, no. 2, pp. 1018–1027, 2022. doi: 10.22207/JPAM.16.2.26.

[13] S. Lomartire and A. M. M. Gonçalves, "An overview of potential seaweed-derived bioactive compounds for pharmaceutical applications," vol. 20, no. 141, pp. 1–32, 2022. doi: 10.3390/md20020141.

[14] N. R. Fitri, I. F. Nuryanti, D. Mutamimah, and N. Adharani, "Phytochemicals and anti-oxidant of seaweed tea," *Int. J. Mar. Eng. Innov. Res.*, vol. 6, no. 4, pp. 255–258, 2021. doi: 10.12962/j25481479.v6i4.11636.

[15] J. R. Hidayati, M. S. Bahry, I. Karlina, and E. Yudiati, "Anti-oxidant activity and bioactive compounds of tropical brown algae *Padina* sp. from Bintan Island, Indonesia," *J. Kelaut. Trop.*, vol. 25, no. 3, pp. 309–319, 2022. doi: 10.14710/jkt.v25i3.15562.

[16] A. Kumar *et al.*, "Algal metabolites can be an immune booster against COVID-19 pandemic," *Anti-oxidants*, vol. 11, no. 452, pp. 1–17, 2022. doi: 10.3390/antiox11030452.

[17] H. Achmad, Huldani, A. B. Carmelita, Fauziah, N. Hidayah, and D. Bokov, "Anti-oxidant and antiviral potential of brown algae (Phaeophyceae)," *Int. J. Pharm. Res.*, vol. 12, no. 3, pp. 2117–2125, 2020. doi: 10.31838/ijpr/2020.12.03.292.

[18] Khadijah, N. H. Soekamto, Firdaus, and Y. M. Syah, "Total content of phenol and anti-oxidant activity from crude extract methanol of brown algae (*Padina* sp.) collected from Kayoa Island, North Maluku," *J. Phys. Conf. Ser.*, vol. 1899, no. 012034, pp. 1–10, 2021. doi:10.1088/1742-6596/1899/1/012034.

[19] Sundari, "The potential of *Padina* sp. brown seaweed from Morotai, Ternate and Kayoa waters as an ACE2 inhibitor to prevent the spread of the SARSCoV-2," University of Khairun, Ternate, North Maluku, Indonesia, 2020.

[20] Y. Fu, J. Zhao, and Z. Chen, "Insights into the molecular mechanisms of protein-ligand interactions by molecular docking and molecular dynamics simulation : A case of oligopeptide binding protein," *Comput. Math. Methods Med.*, vol. 3502514, pp. 1–14, 2018. doi: 10.1155/2018/3502514.

[21] A. Khayrani, R. Irdiani, R. Aditama, D. Kartika, and K. Lischer, "Evaluating the potency of Sulawesi propolis compounds as ACE-2 inhibitors through molecular docking for COVID-19 drug discovery preliminary study," *J. King Saud Univ. – Sci.*, vol. 33, no. 101297, pp. 1–13, 2020. doi: 10.1016/j.jksus.2020.101297.

[22] E. F. Pettersen *et al.*, "UCSF Chimera — A visualization system for exploratory research and analysis," *J. Comput. Chem.*, vol. 25, no. 23, pp. 1605–1612, 2004. doi: 10.1002/jcc.20084.

[23] B. Nami *et al.*, "The interaction of the severe acute respiratory syndrome coronavirus 2 spike protein with drug inhibited angiotensin converting enzyme 2 studied by molecular dynamics simulation," *J. Hypertension*, vol. 39, pp. 1705–1716, 2021. doi: 10.1097/HJH.0000000000002829.

[24] L. Wang *et al.*, "Discovery of potential small molecular SARS-CoV-2 entry blockers targeting the spike protein," *Acta Pharmacol. Sin.*, vol. 43, pp. 788–796, 2022. doi: 10.1038/s41401-021-00735-z.

[25] G. M. Morris *et al.*, "Software news and updates AutoDock4 and AutoDockTools4 : Automated docking with selective receptor flexibility," *J. Comput. Chem.*, vol. 30, no. 16, pp. 2785–2791, 2009. doi: 10.1002/jcc.21256.

[26] G. M. Morris *et al.*, "Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function," *J. Comput. Chem.*, vol. 19, no. 14, pp. 1639–1662, 1998. doi: 10.1002/(SICI)1096-987X(19981115)19:14<1639::AID-JCC10>3.0.CO;2-B.

[27] R. Huey, G. M. Morris, A. J. Olson, and D. S. Goodsell, "Software news and update a semiempirical free energy force field with charge-based desolvation," *J. Comput. Chem.*, vol. 28, no. 6, pp. 1145–1152, 2007. doi: 10.1002/jcc.20634.

[28] L. G. Ferreira, R. N. Santos, G. Oliva, and A. D. Andricopulo, "Molecular docking andstructure-based drug design strategies," *Molecules*, vol. 20, pp. 13384–13421, 2015. doi: 10.3390/molecules200713384.

[29] A. M. Darwesh, W. Bassiouni, D. K. Sosnowski, and J. M. Seubert, "Can N-3 polyunsaturated fatty acids be considered a potential adjuvant therapy for COVID-19-associated cardiovascular complications?," *Pharmacol. Ther. J.*, vol. 219, no. 107703, pp. 1–27, 2020. doi: 10.1016/j.pharmthera.2020.107703.

[30] A. Vivar-sierra *et al.*, "In silico study of polyunsaturated fatty acids as potential SARS-CoV-2 spike protein closed conformation stabilizers :," *Molecules*, vol. 26, no. 711, pp. 1–13, 2021. doi: 10.3390/molecules26030711.

[31] A. Goc, A. Niedzwiecki, and M. Rath, "Polyunsaturated ω - 3 fatty acids inhibit ACE2-controlled SARS-CoV-2 binding and cellular entry," *Sci. Rep.*, vol. 11, no. 5207, pp. 1–12, 2021. doi: 10.1038/s41598-021-84850-1.

[32] K. J. S. Kumar *et al.*, "Geranium and lemon essential oils and their active compounds downregulate Angiotensin-Converting Enzyme 2 (ACE2), a SARS-CoV-2 spike receptor-binding domain in epithelial cells," vol. 2, no. 12, 2019. doi: 10.3390/plants9060770.

[33] C. E. Duru, I. A. Duru, and A. E. Adegboyega, "In silico identification of compounds from Nigella sativa seed oil as potential inhibitors of SARS-CoV-2 targets," *Bull. Natl. Res. Cent.*, vol. 45, no. 57, pp. 1–13, 2021. doi: 10.1186/s42269-021-00517-x.

[34] E. G. Geromichalou and G. D. Geromichalos, "In silico approach for the evaluation of the potential antiviral constituents oleuropein and oleocanthal on spike therapeutic drug target of SARS-CoV-2," *Molecules*, vol. 27, no. 7572, pp. 1–55, 2022. doi: 10.3390/molecules27217572.

[35] B. Thuy *et al.*, "Investigation into SARS-CoV-2 resistance of compounds in garlic essential oil," *ACS Omega*, vol. 5, p. 8312−8320, 2020. doi: 10.1021/acsomega.0c00772.

[36] O. A. Pratama, W. Anindito, S. R. I. Tunjung, and B. S. Daryono, "Bioactive compound profile of melon leaf extract (*Cucumis melo* L . 'Hikapel') infected by downy mildew," *Biodiversitas*, vol. 20, no. 11, pp. 3448–3453, 2019. doi: 10.13057/biodiv/d201143.

[37] M. B. Majnooni, S. Fakhri, G. Bahrami, M. Naseri, M. H. Farzaei, and J. Echeverr, "Alkaloids as potential phytochemicals against SARS-CoV-2 : Approaches to the associated pivotal mechanisms," *Evidence-Based Complement. Altern. Med.*, vol. 6632623, pp. 1–21, 2021. doi: 10.1155/2021/6632623.

[38] P. H. de Matos *et al.*, "Bioactive compounds as potential angiotensin-converting enzyme II inhibitors against COVID - 19 : a scoping review," *Inflamm. Res.*, vol. 71, pp. 1489–1500, 2022. doi: 0.1007/s00011-022-01642-7.

[39] H. Nawaz, M. A. Shad, N. Rehman, H. Andaleeb, and N. Ullah, "Effect of solvent polarity on extraction yield and anti-oxidant properties of phytochemicals from bean (*Phaseolus vulgaris*) seeds," *Brazilian J. Pharm. Sci.*, vol. 56, no. e17129, pp. 1–9, 2015. doi: 10.1590/s2175-

97902019000417129.
[40] A. Akbar, N. H. Soekamto, Firdaus, and Bahrun, "Anti-oxidant of n-hexane , ethyl acetate and methanol extracts of Padina sp with DPPH method Anti-oxidant of n-hexane, ethyl acetate and methanol extracts of *Padina* sp. with DPPH method," *IOP Conf. Ser. Earth Environ. Sci.*, vol. 800, no. 012019, pp. 1–6, 2021. doi: 10.1088/1755-1315/800/1/012019.
[41] P. Garcia-perez *et al.*, "Pigment composition of nine brown algae from the Iberian Northwestern coastline : Influence of the extraction solvent," *Mar. Drugs*, vol. 20, no. 113, pp. 1–17, 2022. doi: 10.3390/md20020113.
[42] R. K. Saini, P. Prasad, X. Shang, and Y. Keum, "Advances in lipid extraction methods — A review," *Int. J. Mol.*, vol. 22, no. 13645, pp. 1–19, 2021. doi: 10.3390/ijms222413643.
[43] C. M. Galanakis, "Functionality of food components and emerging technologies," *Foods*, vol. 10, no. 128, pp. 1–26, 2021. doi: 10.3390/foods10010128.
[44] R. B. S. S. Nogueira *et al.*, "Brown algae *Padina sanctae-crucis* Børgesen : A potential nutraceutical," *Mar. Drugs*, vol. 15, no. 251, pp. 1–15, 2017. doi: 10.3390/md15100251.
[45] P. Weill, C. Plissonneau, P. Legrand, and V. Rioux, "May omega-3 fatty acid dietary supplementation help reduce severe complications in Covid-19 patients?," *Biochimie*, vol. 179, pp. 275–280, 2020. doi: 10.1016/j.biochi.2020.09.003.