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Macroalgae Bioactive Compounds for the Potential Antiviral of SARS-CoV-2: An *In Silico* Study

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Abstract

Coronavirus disease (COVID-19), which was due to novel coronavirus was detected in December 2019 in Wuhan, China for the first time and spread rapidly became a global pandemic. This study aimed to predict the potential of macroalgae compounds as SARS-CoV-2 antiviral by inhibiting of ACE2 receptor through *in silico* approach. Twenty-seven macroalgae compounds were obtained from PubChem (NCBI, USA), while target protein ACE2 receptor was collected from Protein Data Bank (PDB). Then the initial screening study drug-likeness conducted by Lipinski rule of five web server and prediction of bioactive probability carried out by PASS (Prediction of activity spectra for biologically active substances) Online web server. After those compounds were approved by Lipinski's rule of five and PASS online prediction web server, the blind docking simulation was performed using PyRx 0.8 software to show binding energy value. Molecular interaction analysis was done using BIOVIA Discovery Studio 2016 v16.1.0 and PyMOL v2.4.1 software. There are six macroalgae compounds approved by Lipinski's rule of five and PASS Online Analysis. The result is that macroalgae compound siphonaxanthin among 27 macroalgae compound showed strong binding energy to bind ACE2 receptor with -8.8 kcal/mol. This study also used the SARS-CoV-2 drugs as positive control: remdesivir, molnupiravir, baricitinib, lopinavir, oseltamivir, and favipiravir. The result shows that siphonaxanthin has lowest binding energy than the common SARS-CoV-2 drug. Macroalgae compounds are predicted to have potential as SARS-CoV-2 antiviral. Thus, extension studies need to investigate by *in vitro* and *in vivo* analysis for confirmation the siphonaxanthin's inhibitory activity in combat SARS-CoV-2.

Keywords: Antiviral, COVID-19, Macroalgae, Medicine, SARS-CoV-2

INTRODUCTION

Coronavirus disease (COVID-19) was detected in late December 2019 in Wuhan City, Hubei Province, China for the first time and spread rapidly became a global pandemic less than six months.¹ Currently in 2022, globally the number of new COVID-19 deaths cases were reported over 370 million.² COVID-19 was due to novel coronavirus, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) that is categorized pathogenic viral infection and high transmittable.³ SARS-CoV-2 require an ACE2 (angiotensin converting enzyme 2) human receptor for binding. SARS-CoV-2 infect human host cells by an exopeptidase. The virus surface spike protein cleaves by an exopeptidase. Another SARS-CoV-2 structure glycoprotein spike facilitate to bind host cells.⁴

Currently, the therapeutic strategies of antiviral drugs against SARS-CoV-2 were reported, such as baricitinib, lopinavir, remdesivir, and favipiravir.⁵ Besides that, the application of nanotechnology as SARS-CoV-2 antiviral has emerged promising technologies today.^{4,6,7} Marine sulphated polysaccharides as one of the most source developed as nanomaterial.⁸ There are 6 derivative compounds of macroalgae sulfated polysaccharides such as agarans, fucoidans, carrageenans, fucans, galactans, and ulvans

(Fig. 1). Carrageenans one of sulphated polysaccharides derivate which isolated from red macroalgae. Carrageenans have wide spectrum as antiviral, the mechanism by prevent the viral particles when it physical binding happens. Carrageenans were reported combating 12 viruses (SARS-CoV-2, HSV, InfV, hRV, HIV, hCV, hCoV-OC43, HPV, TMV, DENV, JEV, and RVFV).⁹ Marine algae also produce marine carotenoids such as fucoxanthin and siphonaxanthin compound are rich antioxidants. One of the target compound is needed to combat SARS-CoV-2 is antioxidant.¹⁰ It is well known that macroalgae are groups of intertidal organisms that will always be exposed by UV light and extreme conditions. Therefore macroalgae secrete secondary metabolism antioxidants compounds as their self-defense. *Sargassum cristaefolium* species from brown macroalgae has antioxidant activity, that was total phenolic content 44.95 ± 2.62 mg gallic acid/g extract and 70.27 ± 3.59 g quercetin/g extract was total flavonoid content.¹¹ Siphonaxanthin compounds from *Codium fragiles* have potential as antiviral with an activity $IC_{50} = 87.4$ μ M.¹²

The recent *in silico* study related have screened 12 algae compounds by inhibit ACE2 receptor, the result showing that 4 compounds have good score.¹³ This study is important for

more exploring and focusing on macroalgae derivative compounds such as carotenoids and sulfated polysaccharides as SARS-CoV-2 antiviral by molecular mechanism reasoning. This study aimed to predict the potential of macroalgae compounds as SARS-CoV-2 antiviral by inhibit ACE2 receptor with *in silico* study approach, that are capable to predict the cellular pathways, molecular interactions type, and binding energy of candidate compound.¹⁴ Besides that, the important of an *in silico* approach as primarily prediction before doing *in vitro* or *in vivo* study. *In silico* research can assist identify promising compounds for

medication creation and widespread exploitation of secondary metabolites from natural resources.

MATERIALS AND METHODS

Materials

The materials in this study were done by hp computer hardware, the specifications are processor Intel® CORE™ i5-DDR4-3200 MHz RAM. While, the software be used to molecular carried out by PyRx v.0.8 (Scripps Research, USA),¹⁵ PyMOL v.2.4.¹⁶ (Schrodinger Inc, USA) for protein sterilization and visualization of the interaction of ligand-target protein, and DS BIOVIA Discovery

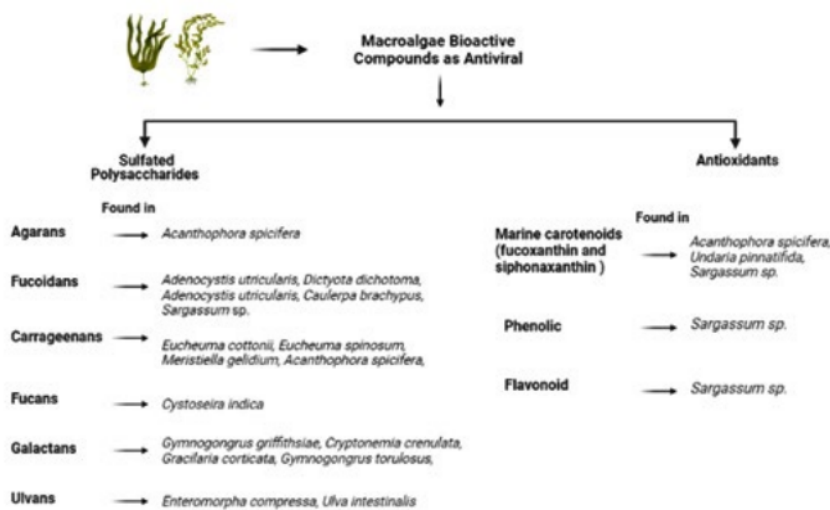


Fig. 1. Macroalgae bioactive compounds as antiviral.

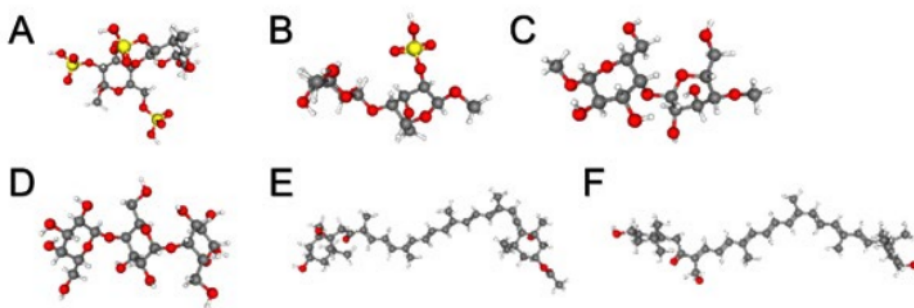


Fig. 2. 3D structure of macroalgae chemical compound from the PubChem database. Lambda carrageenan (CID: 101231953) (A), alpha carrageenan (CID: 102199625) (B), galactan (CID: 53477780) (C), (1->4)-beta-galactan (CID: 53356679) (D), fucoxanthin (CID: 5281239) (E), and siphonaxanthin (CID: 11204185) (F).

Studio 16 v16.1.0 x64 (Dassault Systèmes, France) for analysis of the docking simulation.¹⁷ This study also used the Lipinski rule of five (<http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp>) and PASS Online web server (<http://way2drug.com/passonline/>) for primary study.

Ligand and Target Protein Preparation

The carotenoids derivative macroalgae and sulfated polysaccharides was collected from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>), ligand compounds were collected (Table 1). Protein Data Bank (<https://www.rcsb.org/>) as source for ACE2 target protein collected, then prepared by PyMOL v.2.4.1 (Schrödinger Inc, USA).

Table 1. The ligand compounds were collected

No.	Compound	PubChem CID
1.	An Agarar	405237310
2.	Carrageenan	71597331
3.	kappa-Carrageenan	11966249
4.	lambda-Carrageenan	101231953
5.	lambda-Carrageenan (High-viscosity)	146680192
6.	kappa-Carrageenan; 11114-20-8	73155740
7.	Carrageenan; 9000-07-1	78126884
8.	lambda-Carrageenan	91972149
9.	beta-Carrageenan	102199626
10.	alpha-Carrageenan	102199625
11.	ZINC acetate	11192
12.	Fucoidan; 9072-19-9	402346915
13.	Fucoidan; C08253; 9072-19-9	10452
14.	Fucoidan; W-204037	255374929
15.	A fucan with alpha-(1->3) bonds	405236660
16.	Fucoidan; sulfated Fucose; Sulfated Alga Polysaccharide; NSC631568;	596143
17.	Fucoidan; SC-16162; 9072-19-9	335958879
18.	A fucan with alpha-(1->4) bonds	405234669
19.	Fucoidan; 9072-19-9	406854333
20.	Galactan	53477780
21.	Quinidine Arabino Galactan Sulfate	76519688
22.	(1->4)-beta-galactan	53356679
23.	ulvan	405234592
24.	a fucan with alternating alpha-(1->3) and alpha-(1->4) bonds	405234857
25.	a fucan with alternating alpha-(1->4) bonds	405234669
26.	fucoxanthin	5281239
27.	siphonaxanthin	11204185

Initial Screening Study

Lipinski's rule of five and PASS online prediction web server conducted in this step. There are five rules of Lipinski's rules as like nether than 500 dalton of molecular weight, nether than 5 the number of donor hydrogen bonds, nether than 10 the number of acceptor hydrogen bonds, and nether than 5 of high lipophilicity, two rules from five rules are littlest requirements.¹⁸ This step aims for analyzing the drug-likeness from macroalgae compounds. While for prediction the candidate compound potential of activation (Pa) and inhibition (Pi) was done by PASS online prediction. Ideally, Pi value must be lower than Pa value.

Molecular Docking Study

After 27 ligand compounds were done by initial screening study, then molecular docking study by PyRx 0.8 version¹⁵ for estimating binding energy value of ligand and ACE2 receptor interaction. Blind docking was used to predict ligand bind the target protein ACE2 receptor. Visualization of Protein-Ligand Interaction

To analysis the protein and ligand interaction was conducted by DS BIOVIA Discovery Studio 2016 v16.1.0 x64 (Dassault Systèmes, France) and PyMOL v.2.4.1 (Schrödinger Inc, USA) software. This analysis for prediction the type of chemical bond and interaction position when macroalgae compounds bind ACE2 receptor.

RESULTS AND DISCUSSION

In this *in silico* study aimed for screening macroalgae compounds potential as ACE2 inhibitor. The Macroalgae derivative compounds such as carotenoids and sulfated polysaccharides. Macroalgae compounds were collected from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>). There were 27 compounds collected (Table 1), then an initial screening study was conducted by Lipinski rule of five web server (<http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp>), the result is 25 compounds was approved by Lipinski rule of five and then 25 compounds carried out by PASS online prediction (<http://www.way2drug.com/passonline/>) web server. The result showed that 6 compounds were approved that have the potential as antiviral. The 3D structure of 6 compounds was approved shown in Fig. 1.

Table 2 present the results of Lipinski's five rule which generally predicts a compound as a drug like molecule. Druglikeness explained as the complex balance of diverse molecular properties and structural features that determine whether a particular molecule categorized as a drug or

Table 2. The result of Lipinski rule of five

Lipinski Rule of Five					
Compound	MW (Dalton)	HBD	HBA	LOGP	MR (g/mol)
Lambda-Carrageenan	594.000	3	19	1.297	109.809
Alpha-Carrageenan	416.000	3	12	1.719	85.746
Galactan	370.000	6	11	1.754	82.579
(1->4)-beta-galactan	504.000	10	16	1.457	106.314
Fucoxanthin	312.000	5	6	-0.053	77.145
Siphonaxanthin	312.000	5	6	-0.053	77.145

Note: MW: Molecular Weight, HBD; Hydrogen Bond Donors, HBA; Hydrogen Bond Acceptors, LOGP; High Lipophilicity, MR; Molar Refractivity.

Table 3. The result of PASS online prediction

Compound	Activity	Pa	Pi
Lambda-Carrageenan	Antiviral	0.654	0.004
Alpha-Carrageenan	Antiviral	0.656	0.004
Galactan	Antiviral	0.735	0.004
(1->4)-beta-galactan	Antiviral	0.684	0.007
Fucoxanthin	Antiviral	0.244	0.135
Siphonaxanthin	Antiviral	0.393	0.099

not. That properties include molecular weight, characteristics of hydrogen bonding lipophilicity, and existence of various pharmacophoric features in that compounds.¹⁹ The result is molecular weight value of alpha-carrageenan, galactan, fucoxanthin, and siphonaxanthin under 500.000 dalton, it is predicted that alpha-carrageenan, galactan, fucoxanthin, and siphonaxanthin can enter the cell membrane. While the molecular

Table 4. The result of molecular docking simulation

Compound	PubChem CID	Target Protein	Binding Energy (kcal/mol)
Siphonaxanthin	11204185	ACE2	-8.8
Fucoxanthin	5281239	ACE2	-8.7
(1->4)-beta-galactan	53356679	ACE2	-8.3
Alpha-Carrageenan	102199625	ACE2	-7.5
Lambda-Carrageenan	101231953	ACE2	-7.4
Galactan	53477780	ACE2	-7.0

Table 5. The result of molecular docking simulation from drugs as control

Drug as Control	PubChem CID	Target Protein	Binding Energy (kcal/mol)
Remdesivir	121304016	ACE2	-7.7
Molnupiravir	145996610	ACE2	-7.5
Baricitinib	44205240	ACE2	-7.1
Lopinavir	92727	ACE2	-6.8
Oseltamivir	65028	ACE2	-6.2
Favipiravir (Avigan)	492405	ACE2	-5.7

weight of lambda-carrageenan and (1->4)-beta-galactan have a molecular weight more than 500.000 dalton, so that both of the compound estimated unable to pass membrane cells. Advanced study be required for making molecular weight smaller under 500.000 dalton. Log P value indicates the coefficient of solvability in water or fat, the coefficient range is -0.4 to 5. The larger log P number represents that the more hydrophobic molecules characteristics would be. The over hydrophobic molecules cause the increased level

of toxicity effect because of molecules longer disconnected in the lipid bilayer membrane will be spread broadly in the body. Thus, the selective effect of the compound inhibit target protein is reduced. Meanwhile, the more negative the log P number, the more non-permeable the molecule will be.^{20,21}

Table 3 shows the result of PASS online prediction webserver for prediction the ability of the bioactive compound from macroalgae as

antiviral for activation or inhibition by human cells. The principle is that the Pa (potential activation) value must be higher than Pi (potential inhibition) value. In this *in silico* study Pa>0.3. The results showed macroalgae Pa value larger than its Pi value. It indicates when a macroalgae compound penetrate human body, it have potential to inhibit ACE2 protein.

Table 4 shows the result of macroalgae compound molecular docking simulation.

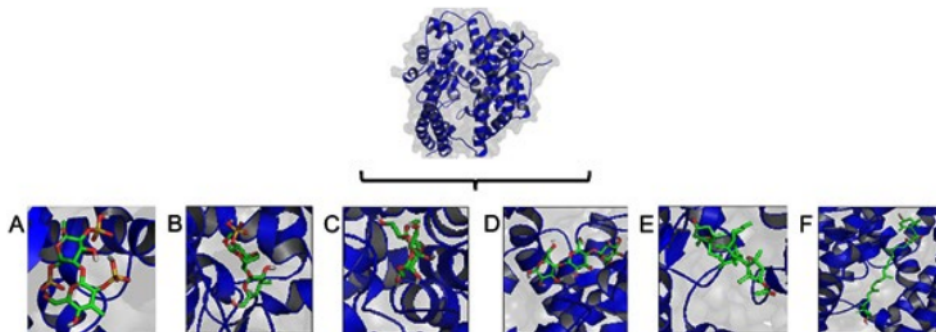


Fig. 3. Molecular visualization of macroalgae bind to ACE2 protein receptor. The ACE2 protein receptor displayed on transparent surface and blue cartoon structure. Lambda carrageenan (CID: 101231953) (A), alpha carrageenan (CID: 102199625) (B), galactan (CID: 53477780) (C), (1->4)-beta-galactan (D) (CID: 53356679), fucoxanthin (CID: 5281239) (E), and siphonaxanthin (CID: 11204185) (F).

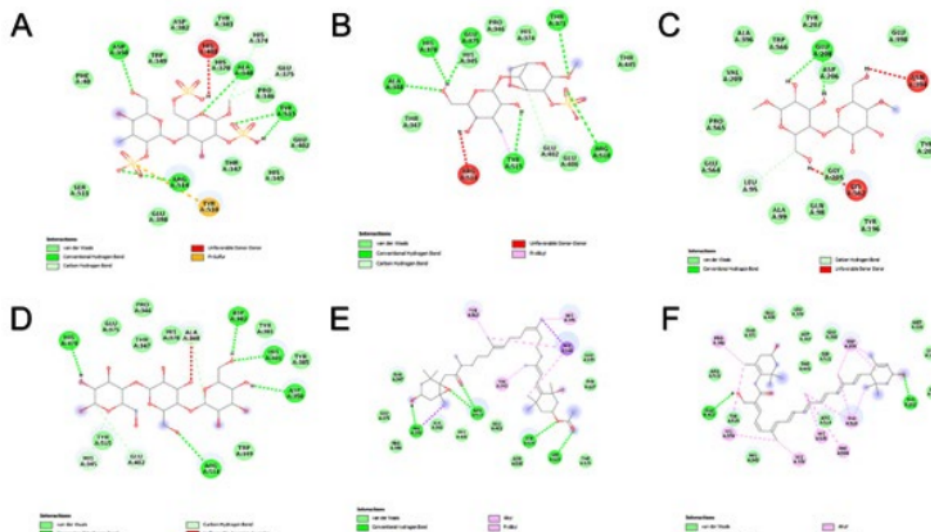


Fig. 4. Chemical interaction between macroalgae compound with target protein ACE2 receptor. Lambda carrageenan (CID: 101231953) (A), alpha carrageenan (CID: 102199625) (B), galactan (CID: 53477780) (C), (1->4)-beta-galactan (D) (CID: 53356679), fucoxanthin (CID: 5281239) (E), and siphonaxanthin (CID: 11204185) (F).

Table 6. The summary of amino acid residues from macroalgae

Compound	Amino Acid Residues	Bond Type
Lambda-Carrageenan	SER A:511, GLU A:398, THR A:347, HIS A:345, GLU A:402, PRO A:346, HIS A:378, TYR A:381, ASP A:382, TRP A:349, PHE A:40, ARG A:514, TYR A:515, ALA A:348, ASP 350, GLU A:375, HIS 374, HIS A:401, TYR A: 510	Van der Waals, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Unfavorable Donor-Donor, Pi-Sulfur
Alpha- Carrageenan	THR A:347, GLU A:406, THR A:445, HIS A:374, PRO A:346, HIS A:345, TYR A:515, ARG A:518, THR A:371, GLU A:375, HIS A:378, ALA 348, GLU A:402, ARG A:514, TYR A:515	Van der Waals, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Unfavorable Donor-Donor, Pi-Alkyl
Galactan	GLU A:398, TYR A:207, TRP A:566, ALA A:396, VAL A:209, PRO A:565, GLU A:564, ALA A:99, GLN A:98, GLY A:205, TYR A:196, TYR A:202, ASP A:206, GLU A:208, LEU A:95, IYS A:562, ASN A:394	Van der Waals, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Unfavorable Donor-Donor
(1->4)-beta-galactan	TYR A:515, TRP A:349, TYR A:385, TYR A:381, HIS A:378, THR A:347, PRO A:346, GLU A:375, HIS A:374, ARG A:514, ASP A:350, HIS A:401, ASP A:382, HIS A:345, GLU A:402, ALA 348, ALA A:348	Van der Waals, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Unfavorable Donor-Donor
Fucoxanthin	THR A:347, GLU A:375, PRO A:346, ALA A:348, HIS A:401, GLU A:402, ASN A:508, THR A:125, TYR A:127, GLU A:145, HIS A:378, ARG A:514, SER A:124, SER 128, PHE A:504, HIS A:378, PHE A:504, HIS A:345, TYR A:510	Van der Waals, Conventional Hydrogen Bond, Pi-Sigma, Alkyl, Pi-Alkyl
Siphonaxanthin	ARG A:518, TYR A:515, HIS A:345, ARG A:514, ASP A:509, IYS A:187, MET A:190, GLU A:398, SER A:511, THR: A:445, ASP A:367, LEU A:370, GLU A:406, THR A:371, GLU A:402, TYR A:202, PRO A:346, HIS A:374, HIS A:378, HIS A:505, PHE A:504, TYR A:510, TRP A:203	Van der Waals, Conventional Hydrogen Bond, Alkyl, Pi-Alkyl

Molecular docking simulation was done by PyRx 0.8 version and the followed grid docking result are center X: 166.4430 Y: 223.6339 Z: 301.4075 and dimensions (Å) X: 67.1115 Y: 74.6594 Z: 67.3432. Due to the target protein functional domain is unknown, so in this study aimed blind docking method.²²

Based on the result of the binding energy value from the macroalgae compound selected, siphonaxanthin has the lowest binding energy to bind ACE2 receptor with binding energy value -8.8 kcal/mol. While, from sulfated polysaccharides derivate compound (1->4)-beta-galactan has the lowest binding energy with -8.3 kcal/mol. Ligands with the lowest binding energy are predicted to have a target protein's biological activity. It refers to the aim of this study the compound is predicted to have the ability to inhibit ACE2 receptor. The lowest binding energy interaction ligand-target protein allows molecular complex formation constant temperature and pressure.²³ This study also using common antiviral drug such as remdesivir, molnupiravir, baricitinib, lopinavir, oseltamivir, and favipiravir (avigan).^{5,24-26} These antiviral common drugs used as positive control for comparing the binding energy value to target protein ACE2 receptor. Based on the binding energy result, siphonaxanthin, fucoxanthin, (1->4)-beta-galactan, and (1->4)-beta-galactan has the lowest binding energy than antiviral common drug.

The docking simulation is finished, then molecular complex visualization was conducted by PyMOL v.2.4.1 showed in Fig. 2. Macroalgae compounds can bind to the ACE2 receptor. Fig. 3 present the complex ligands-protein visualization 2D diagram was carried out by DS BIOVIA Discovery Studio 2016 v16.1.0 x64. There are various bond types of macroalgae compounds with ACE2 receptor. Macroalgae carotenoids such as fucoxanthin and siphonaxanthin showed that Van der Waals, Alkyl, and Pi-Alkyl formed the dominant type bond (Fig. 4 and Table 6). While in Macroalgae sulfated polysaccharides, the dominant type bond formed is Van der Waals and Conventional Hydrogen Bond. The higher hydrogen bonds total between protein-ligand complex, the more stable the interaction of protein-ligand.²¹

There are various types of amino acid residues that form an interaction between ligand

and target protein ACE2 receptor, shown in Table 5. Binding to these amino acid residues could potentially contribute to structural alterations of the ACE2 receptor, resulting in functional changes. Therefore, further research related to *in vitro* and *in vivo* study will be interest to know the mechanism of macroalgae compounds as ACE2 receptor and against SARS-CoV-2.

Nowadays, *in silico* studies is important for drug development against SARS-CoV-2. Recent studies promising macroalgae compounds as SARS-CoV-2 drug candidates such as sulfated polysaccharides can inhibit SARS-CoV-2 by binding RBD spike protein. There are 17 seaweed sulphated polysaccharides that were screened as SARS-CoV-2 antiviral. The docking results lowest binding energy is -8.2 kcal/mol from xylan sulphate with positive control using heparin tetrasaccharide N-sulfated and heparin.²⁷ In comparison, the other *in silico* study used 9 investigated compounds marine sulphated polysaccharides promising antiviral agents and using heparin as positive control.²⁸ In both studies used heparin as the positive control. Meanwhile, other studies recommend remdesivir, molnupiravir, baricitinib, lopinavir, oseltamivir, and favipiravir as drugs against SARS-CoV-2. Hence, it is needed for extensive research to develop SARS-CoV-2 antiviral drugs using another positive drug control. Both of those studies do not explain the drug-likeness analysis Lipinski rule of five and predict the bioactive compounds as antiviral using PASS online prediction webserver. Hence, this research is important to conduct with initial screening studies that were done by Lipinski rule of five and PASS online prediction webserver to screen sulfated polysaccharides as antiviral drugs. Other than that, macroalgae is rich with antioxidant compounds that have the potential as SARS-CoV-2 antiviral. Therefore, this study also conducted molecular docking to screen macroalgae antioxidant compounds as SARS-CoV-2 antiviral.

CONCLUSION

The potential of macroalgae as SARS-CoV-2 antiviral is predicted by the inhibition of ACE2 receptor. By the Lipinski rules of five and PASS online prediction result there are 6 macroalgae compounds were approved from 27 macroalgae collected from PubChem database. Molecular

docking results show compound 5 that has lowest binding energy is siphonaxanthin. Siphonaxanthin has the lowest binding energy than the SARS-CoV-2 common drug. Hence, *in vitro* and *in vivo* study related to confirm the inhibitory activity of siphonaxanthin against SARS-CoV-2.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

HP, VDK, ANMA, MHW, MEU drafted the manuscript, compiled information from the literature, and designed the Figures and tables. MTS, OG, SC, NB, ESP, THS, RZ supervised the study. VDK, ANMA, THS, RZ supervised and reviewed the manuscript. All authors read and approved the final manuscript for publication.

FUNDING

None.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

ETHICS STATEMENT

Not applicable.

REFERENCES

1. Machhi J, Herskovitz J, Senan AM, et al. The natural history, pathobiology, and clinical manifestations of SARS-CoV-2 infections. *J Neuroimmune Pharmacol.* 2020;15(3): 359-386. doi: 10.1007/s11481-020-09944-4
2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis.* 2020;20(5):533-534. doi: 10.1016/S1473-3099(20)30120-1
3. Liu YC, Kuo RL, Shih SR. COVID-19: The first documented coronavirus pandemic in history. *Biomed J.* 2020;43(4):328-333. doi: 10.1016/j.bj.2020.04.007
4. Sarangi MK, Padhi S, Dheeman S, et al. Diagnosis, prevention, and treatment of coronavirus disease: A review. *Expert Rev Anti Infect Ther.* 2022;20(2):243-266. doi: 10.1080/14787210.2021.1944103
5. Frediansyah A, Tiwari R, Sharun K, Dhama K, Hapan H. Antivirals for COVID-19: A critical review. *Clin Epidemiol Glob Health.* 2021;9:90-98. doi: 10.1016/j.cegh.2020.07.006
6. Chakravarty M, Vora A. Nanotechnology-based antiviral therapeutics. *Drug Deliver Trans Res.* 2021;11(3):748-787. doi: 10.1007/s13346-020-00818-0
7. Weiss C, Carriere M, Fusco L, et al. Toward Nanotechnology-Enabled Approaches against the COVID-19 Pandemic. *ACS Nano.* 2020;14(6):6383-6406. doi: 10.1021/acsnano.0c03697
8. Manivasagan P, Oh J. Marine polycarbohydrate-based nanomaterials as a novel source of nanobiotechnological applications. *Int J Biol Macromol.* 2016;82:315-327. doi: 10.1016/j.ijbiomac.2015.10.081
9. Salih AEM, Thissera B, Yaseen M, et al. Marine sulfated polysaccharides as promising antiviral agents: A comprehensive report and modeling study focusing on SARS CoV-2. *Mar Drugs.* 2021;19(8):406. doi: 10.3390/md19080406
10. Choudhary J, Dheeman S, Sharma V, et al. Insights of severe acute respiratory syndrome coronavirus (SARS-CoV-2) pandemic: A current review. *Biol Proced Online.* 2021;23(1):5. doi: 10.1186/s12575-020-00141-5
11. 3sedyas ES, Frediansyah A, Martyasari NWR, et al. Effect of particle size on phytochemical composition and antioxidant properties of *Sargassum cristaeifolium* ethanol extract. *Sci Rep.* 2021;11(1):17876. doi: 10.1038/s41598-021-95769-y
12. Yim SK, Kim I, Warren B, Kim J, Jung K, Ku B. Antiviral activity of two marine carotenoids against SARS-CoV-2 virus entry *in silico* and *in vitro*. *Int J Cell Sci Mol Biol.* 2021;22(12):6481. doi: 10.3390/ijms22126481
13. Rauf A, Rashid U, Khalil AA, et al. Docking-based virtual screening and identification of potential COVID-19 main protease inhibitors from brown algae. *S Afr J Bot.* 2021;143:428-434. doi: 10.1016/j.sajb.2021.06.033
14. Kharisma VD, Widyandana MH, Ansori ANM, Nege AS, Naw SW, Nugraha AP. Tea catechin as antiviral agent via apoptosis agonist and triple inhibitor mechanism against HIV-1 infection: A bioinformatics approach. *J Pharm Pharmacogn Res.* 2021;9(4):435-45. doi: 10.1038/s41598-021-95769-y
15. Kharisma VD, Agatha A, Ansori ANM, et al. Herbal combination from *Moringa oleifera* Lam. and *Curcuma longa* L. as SARS-CoV-2 antiviral via dual inhibitor pathway: A viroinformatics approach. *J Pharm Pharmacogn Res.* 2021;10(1):138-146.
16. Kharisma VD, Ansori ANM, Nugraha AP. Computational study of ginger (*Zingiber officinale*) as E6 inhibitor in human papillomavirus type 16 (HPV-16) infection. *Biochem Cell Arch.* 2020;20(Suppl 1):3155-3159. doi: 10.35124/bca.2020.20.S1.3155
17. Yadav S, Pandey SK, Singh VK, Goel Y, Kumar A, Singh SM. Molecular docking studies of 3-bromopyruvate and its derivatives to metabolic regulatory enzymes: Implication in designing of novel anticancer therapeutic strategies. *PLoS One.* 2017;12(5):e0176403. doi: 10.1371/journal.pone.0176403
18. Lipinski CA, Lombardo F, Dominy BW, Feeney

- PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev.* 2001;40(1-3):3-26. doi: 10.1016/S0169-409X(00)00129-0
19. Ansori ANM, Kharisma VD, Parikesit AA, et al. Bioactive compounds from mangosteen (*Garcinia mangostana* L.) as an antiviral agent via dual inhibitor mechanism against SARS-CoV- 2: An *in silico* approach. *Phcog J.* 2022;14(1):85-90. doi: 10.5530/pj.2022.14.12
20. Shi H, Cui Y, Qin Y. Discovery and characterization of a novel tryptophan hydroxylase 1 inhibitor as a prodrug. *Chem Biol Drug Des.* 2018;91(1):202-212. doi: 10.1111/cbdd.13071
21. de Freitas RF, Schapira M. A systematic analysis of atomic protein-ligand interactions in the PDB. *Med Chem Comm.* 2017;8(10):1970-1981. doi: 10.1039/C7MD00381A
22. Hassan NM, Alhossary AA, Mu Y, Kwok CK. Protein-ligand blind docking using QuickVina-W with inter-process spatio-temporal integration. *Sci Rep.* 2017;7(1):1-13. doi: 10.1038/s41598-017-15571-7
23. Ramirez D, Caballero J. Is it reliable to use common molecular docking methods for comparing the binding affinities of enantiomer pairs for their protein target? *Int J Mol Sci.* 2016;17(4):525. doi: 10.3390/ijms17040525
24. Frediansyah A, Nainu F, Dhama K, Mudatsir M, Harapan H. Remdesivir and its antiviral activity against COVID-19: A systematic review. *Clin Epidemiol Glob Health.* 2021;9:123-127. doi: 10.1016/j.cegh.2020.07.011
25. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med.* 2020;7:1787-1799. doi: 10.1056/NEJMoa2001282
26. Shim SJ, Chan M, Owens L, Jaffe A, Prentice B, Homaira, N. Rate of use and effectiveness of oseltamivir in the treatment of influenza illness in high-risk populations: A systematic review and meta-analysis. *Health Sci Rep.* 2021;4(1):e241. doi: 10.1002/hsr2.241
27. Douma M, Boualy B, Manaut N, et al. Sulphated polysaccharides from seaweeds as potential entry inhibitors and vaccine adjuvants against SARS-CoV-2 RBD spike protein: A computational approach. *J Taibah Univ Sci.* 2021;15(1):649-655. doi: 10.1080/16583655.2021.1999068
28. Hans N, Malik A, Naik S. Antiviral activity of sulfated polysaccharides from marine algae and its application in combating COVID-19: Mini review. *Bioresour Technol Rep.* 2021;13:100623. doi: 10.1016/j.biteb.2020.100623

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