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Original Article

Green alga *Caulerpa racemosa* components as antiviral candidates for SARS-COV-2

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Abstract

Coronavirus disease 2019 (COVID-19) is a viral disease caused by the highly transmittable severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which accounts for the recent pandemic. Meanwhile, green algae in the genus *Caulerpa* are known to contain bioactive compounds which are hypothesized to have anti-SARS-CoV-2 activity. Therefore, the aim of this study was to analyze the anti-SARS-CoV-2 potential of compounds extracted from the green alga *Caulerpa racemose* extract was obtained through maceration with 96% ethanol. The compounds present in the extract were identified through Gas Chromatography-Mass Spectroscopy (GC-MS) and their binding affinities were analyzed *in silico* using the PyRx application, then visualized in the PyMOL application. GC-MS analysis of *Caulerpa racemosa* extract showed 92 spectral, each of which was assigned to a bioactive compound. Of the six compounds with a strong binding affinity, n-[1-(1-Adamantan-1-yl-propyl)-2,5-dioxo-4-trifluoromethyl-imidazolidin-4-yl]4-methoxy-benzamide had the lowest score (-8.1 kcal/mol). An active compound found in *Caulerpa racemose* extract had a competitive binding affinity score and could interact with the SARS-CoV-2 3C-like protease binding site. The molecular dynamics calculations demonstrated that RMSD values of the selected inhibitors remained stable throughout a 15 ns simulation. Additionally, the simulation provided valuable insights into the binding site by identifying crucial residues and assessing the protein's compactness through RMSF and Rg measurements. Compound selection was reinforced by multiple measurements, including pharmacokinetics, and absorption, distribution, metabolism, and excretion toxicity (ADMET) tests. The *in silico* analysis suggests that *Caulerpa racemosa* seaweed extract is a potential antiviral candidate against SARS-CoV-2.

Keywords: *Antiviral activity, binding affinity, Caulerpa racemosa, SARS-CoV-2*

Introduction

Coronaviruses cause immune system dysregulation, leading to respiratory diseases such as severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS). Caused by the novel coronavirus SARS-CoV-2, coronavirus disease 2019 (COVID-19) is a disease that can be transmitted through fluid droplets which are expelled when breathing, sneezing, coughing, and speaking, making it highly contagious and easily spread from person to person through

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everyday human interaction [1]. On 3 May 2023, the World health Organization (WHO) reported 765,222,932 confirmed cases of COVID-19 with 6,921,614 fatalities [2].Researchers responded this phenomenon by studying the therapeutical agents which could attenuate the disease, in particular through looking at the potential of herbal remedies [3–5]. These include oils extracted from some plants, such as ginger, guava, and eucalyptus, that are known to contain phytochemical compounds with potential as immunomodulators in the human body [6].

As an archipelagic nation, Indonesia is blessed with abundant marine resources. Among these, marine algae or seaweeds found in Indonesian waters are still underutilized. Seaweeds can produce primary and secondary metabolites with a wide range of uses, including applications in the pharmaceutical industry [7]. Previously, seaweed metabolites have been reported to possess antihypertension, antibacterial, antitumor, antioxidant, antifungal, antihypercholesterolemia, and antiviral properties, and some seaweeds have been specifically report as being capable of boosting the immune system [7–9].Several studies have been published on the use of macroalgae in the prevention and treatment of COVID-19, including *Porphyra umbilicalis*, *Caulerpa racemosa*, and *Gelidium* sp. [10]. Of these, the green seaweed *Caulerpa racemosa* is native to South Sulawesi where it is called *lawi-lawi* and tends to be abundant in shallow coastal waters around the province [11]. Despite several studies on the use of macroalgae in the prevention and treatment of COVID-19, the specific therapeutic potential of *Caulerpa racemosa* extract, particularly from the South Sulawesi region, against SARS-CoV-2 remains largely unexplored. Therefore, the aim of this study was to examine the antiviral potential of *Caulerpa racemosa* extract through a novel approach by employing *in-silico* methods.

The main principle of molecular docking is the scoring function that can be used to determine the binding mode and position of a ligand, predict binding affinity, and identify potential drugs for a given target protein. The purpose of molecular docking analysis is to quantitatively predict the strength of molecular binding and provide data based on the level of ligand binding affinity to the protein [12]. Several studies have used the docking process in the search for COVID-19 antiviral drugs [13–15]. This study followed the approach used in a previous study [10], analyzing molecular docking using the PyRx application and visualizing it using PyMOL.

Methods

Seaweed sample collection and processing

The seaweed samples used in this study were *Caulerpa racemosa* obtained from the waters around Kayangan Island, Makassar City, in South Sulawesi Province, Indonesia (119°20.52'E, 5°7.38'N). After collection, the freshly harvested samples were placed in containers for transport and further processing. The samples were identified using morphometric techniques and voucher specimens from the samples were stored at the Faculty of Marine Science and Fisheries, Hasanuddin University. Before extraction, 11 kg of freshly harvested seaweed was prepared by washing under deionized water several times until it was free from saltwater precipitate. The seaweed samples were sorted and cleaned while still wet to remove epiphytes and other impurities that may have been collected during the sampling process. The seaweed was then sun-dried for approximately 8 hours per day until completely dry. To further prepare the samples for extraction, they were cleaned with distilled water to remove any remaining particles. The cleaned samples (90.8 g) were dried in a herb drier.

Extraction and GC-MS analysis of active compounds in *Caulerpa racemosa*

The dry *C. racemosa* samples macerated for a period of 3-4 days in 700 ml of 96% ethanol solution, with an ethanol to sample volume ratio of 2:. The macerated mixture was then filtered through filter paper to obtain a filtrate. The mixture was filtered using a rotary evaporator to obtain the *C. racemose* xtract. Gas Chromatography-Mass Spectroscopy (GC-MS) was performed to identify the active compounds present in the *C. racemosa* extract. An 0.5 mL aliquot of the extract was injected into the GC-MS spectroscope (QP 2010 Shimadzu Ultra) with a column length of 30 m and a diameter of 0.25 mm. The ion source temperature was set at 200°C, and the interface temperature was set at 280°C. The initial column temperature was set at 70°C for 2

minutes, followed by a ramp-up to 200°C and finally to 280°C. The compound present in the *C. racemosa* extract were identified utilizing a comprehensive approach involving GC-MS analysis, and referring to a compound library and standards to ensure accurate and reliable identification of the active compounds present in the *C. racemosa* extract. The active compounds in the extract were identified by comparing the mass spectra and retention times of the observed GC-MS peaks with those of known compounds in the library. The retention times of the observed peaks were compared with those of authenticated standards, allowing for further confirmation of the compound identities.

Analysis of ligand-receptor interactions of anti-COVID-19 candidate compounds with molecular docking

The 3CL-protease with protein code 6LU7 was obtained in PDB format from the official protein data bank site (www.uniprot.org) and the necessary docking requirements such as the ligand and protein structure were then prepared. The ligands used in this study were natural active compounds from the *Caulerpa racemosa* seaweed extract identified through GC-MS. The 3D structures of these compounds and of the control inhibitor remdesivir were obtained by downloading the SDF file format from the website https://pubchem.ncbi.nlm.nih.gov/. Remdesivir was selected as the control inhibitor suggested by the findings from a previous study [16]. After downloading the SDF files, the active compounds from *C. racemosa* and the control inhibitor were visualized using PyMOL (Version 1.2r3pre, Schrödinger, LLC) by adding hydrogen atoms. The PyMOL visualization results were saved in mol2 format to prepare the docking requirements for the ligand and target protein. The *in silico* docking process was implemented by inputting the ligand preparation, SARS-CoV-2 protein preparation, and remdesivir control inhibitor preparation into PyRx 0.8 software [17]. The grid of the box is (11.5, 11.7, 69.2, x,y,z) and size of the box is 30 x 30 x 30. Molecular docking and docking analysis data were used to determine the binding affinity. Ligand and protein interaction data were displayed in PyMOL to visualize the attachment location and model/pose on the target protein.

Molecular Dynamics Simulation

Gromacs ver2023.1 (https://www.gromacs.org/) as used to conduct molecular dynamics (MD) simulations on 3CLpro and N- [1-(1-Adamantan-1-YL-Propyl)-2,5-Dioxo-4-Trifluoromethyl-Imidazolidin-4-YL]4-Methoxy-Benzamide. The CHARMM36 force field was chosen for the MD simulation, and the TIP3 water model was employed in the MD system. The system's charge was balanced by introducing ions. Before running the MD simulation, the system underwent energy minimization using the steepest descent integrator for 50000 steps, with a force convergence criterion set at 1000 kcal/mol/nm. Subsequently, each protein-ligand combination was equilibrated using NVT and NPT ensembles within a time frame of 100 ps. Temperature and pressure controllers, specifically the Berendsen and Parrinello-Rahman methods, were used to maintain a temperature of 300 K and a pressure of 1 bar throughout the equilibration process. The MD simulations were run for a total of 50 ns, and the system's coordinates were saved every 2 fs. This 50 ns duration was considered sufficient for achieving a balance between computational time and information. The data obtained from the fluctuation graph indicated a stable equilibration. Various analytical modules included in the GROMACS package were employed to perform structural and conformational analysis on all systems.

ADMET and SARS-CoV-2 Drug Properties

The absorption of a drug is influenced by important molecular properties such as lipophilicity and solubility. The prediction of a drug's oral availability is based on several characteristics defined in Lipinski's rule of five. This prediction was carried out using the SwissAdme tool available on the Swiss Bioinformatics website (http://www.swissadme.ch/). The characteristics considered include logP (lipophilicity ≤ 5), molecular weight (MW ≤ 500 g/mol), number of hydrogen bond acceptors (HBA ≤ 10), number of hydrogen bond donors (HBD ≤ 5), rotatable bonds (nRotb ≤ 10), and polar surface area (PSA ≤ 140 Å^2). Further, the compounds were evaluated for the ADME-Tox (Absorption, Distribution, Metabolism, Excretion - Toxicity). In this study, the ADME-TLab 2.0 tool (https://admetmesh.scbdd.com/), developed by the CBDD Team

of the School of Medicine at Zhejiang University, was utilized. This method enabled the analysis of the drug's solubility, absorption, permeability, and metabolites. Moreover, to assess the ability of compound as SARS-CoV-2 drugs, this study employed https://drugcentral.org/Redial as additional information of the candidate compounds.

Results

The compounds present in the ethanolic extract of *Caulerpa racemosa* were identified using the GC-MS method *Caulerpa racemosa* extract consisted of around 92 spectrum peaks which are presented in Figure 1. Details of the compounds and their respective relative abundance are presented in Table 1. Out of the 92 active compounds identified, the three *C. racemosa* extract compounds with the highest peak areas (%) were 9,12-octadecadienoic acid(z,z), methyl ester (21.31%), hexadecanoic acid, methyl ester (9.83%), and 1,2-benzenedicarboxylic acid (6.83%). Compounds identified from the GC-MS analysis were then used in the docking analysis to observe the interaction between active compounds from *C. racemosa* and the SARS-CoV-2 target protein.

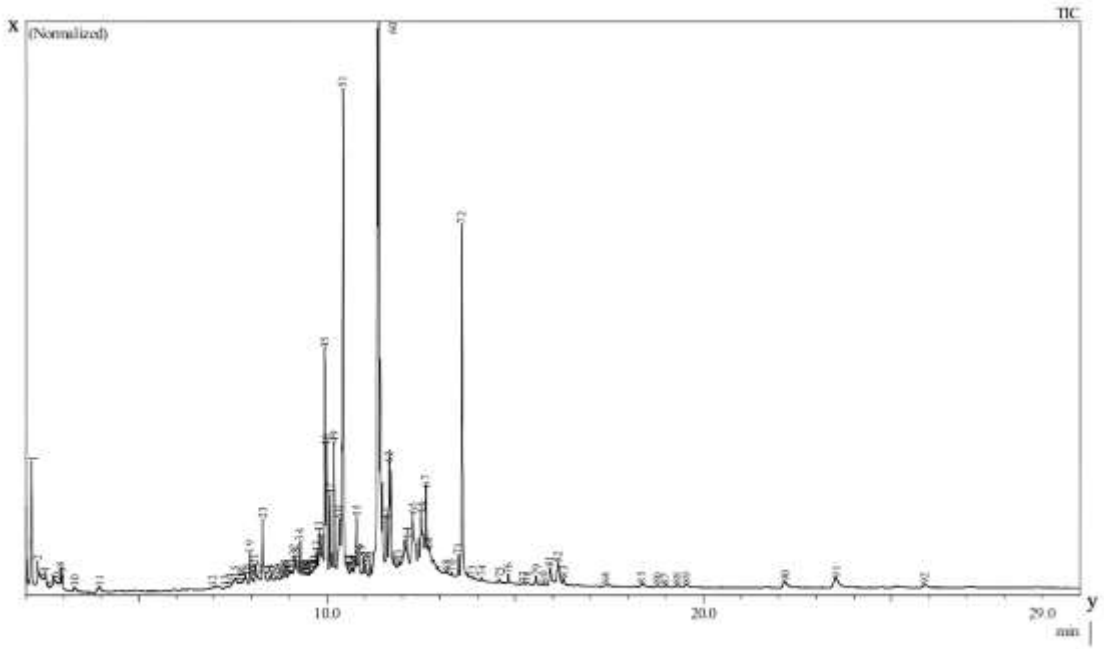

Figure 1. GC-MS plot for the *Caulerpa racemosa* (green seaweed) ethanol extract

The 3-chymotrypsin-like main protease (3CLpro) in SARS-CoV-2 with the protein code 6LU7 PDB (downloaded from the official protein data bank site (www.rcsb.org) in PDB format) was used as the target protein in the docking process and visualized using the PyMol application. To compare binding affinity, Remdesivir as the control inhibitor for the molecular docking process was also visualized in PyMol.

The molecular docking process using the Autodock Vina module in PyRx showed that several active compounds from *C. racemosa* had binding affinity scores that were competitive with the control inhibitor Remdesivir (Supplementary **Table 1**). Based on the docking analysis, the six active compounds showing the highest binding affinity scores with the SARS-COV 2 target protein are compared with Remdesivir in **Table 1**.

The molecular docking analysis results in **Table 1** show that 6 active compounds contained in *Caulerpa racemosa* ethanol extract have binding affinity scores approaching that of Remdesivir (-8.1 kcal/mol). These compounds were then visualized in PyMOL to see the ligand pose against the target SARS-CoV-2 protein, and compare it with that of Remdesivir.

Table 1. Active compounds contained in the ethanolic extract from *Caulerpa racemosa* and their respective *in silico* activity against the SARS-CoV-2 target protein 3CLpro

Compound	Binding affinity (kcal/mol)	Area%
N-[1-(1-Adamantan-1-Yl-Propyl)-2,5-Dioxo-4-Trifluoromethyl-Imidazolidin -4-Yl]4-Methoxy-Benzamide	-8.1	0.04
Cholesta-4,6-Dien-4-Ol, Benzoate, (3.Beta.)-	-7.7	0.07
Lupeol	-7.2	0.15
Stigmasta-5,23-Dien-3-Ol, (3.Beta.)-	-6.8	0.1
Alpha.-Tocopherol-.Beta.-D-Mannoside	-6.7	0.12
Beta.-Tocopherol	-6.1	0.15
Remdesivir (Control)	-8.1	-

Another goal of the study was to employ molecular dynamics simulations to assess the adaptability of the 3CLpro-Ligand complex and the apo system. Gromacs version 2023.1 was used for the *in-silico* experiment, and a number of factors, including temperature, pressure, and potential/kinetic energy, were tracked to assure the simulations' correctness. To evaluate the rigidity of the complexes, the root mean square deviations (RMSD) of the backbone atoms were determined (see **Figure 2a**). Both the Apo 3CLpro and the 3CLpro complex attained a stable state after 15 ns. After 45 ns, both systems showed modest changes, but the RMSD values remained largely stable for the rest of the run. Additionally, **Figure 2b** also showed that, after about 10 ns, the ligand reached equilibrium at a distance of around 1 nm.

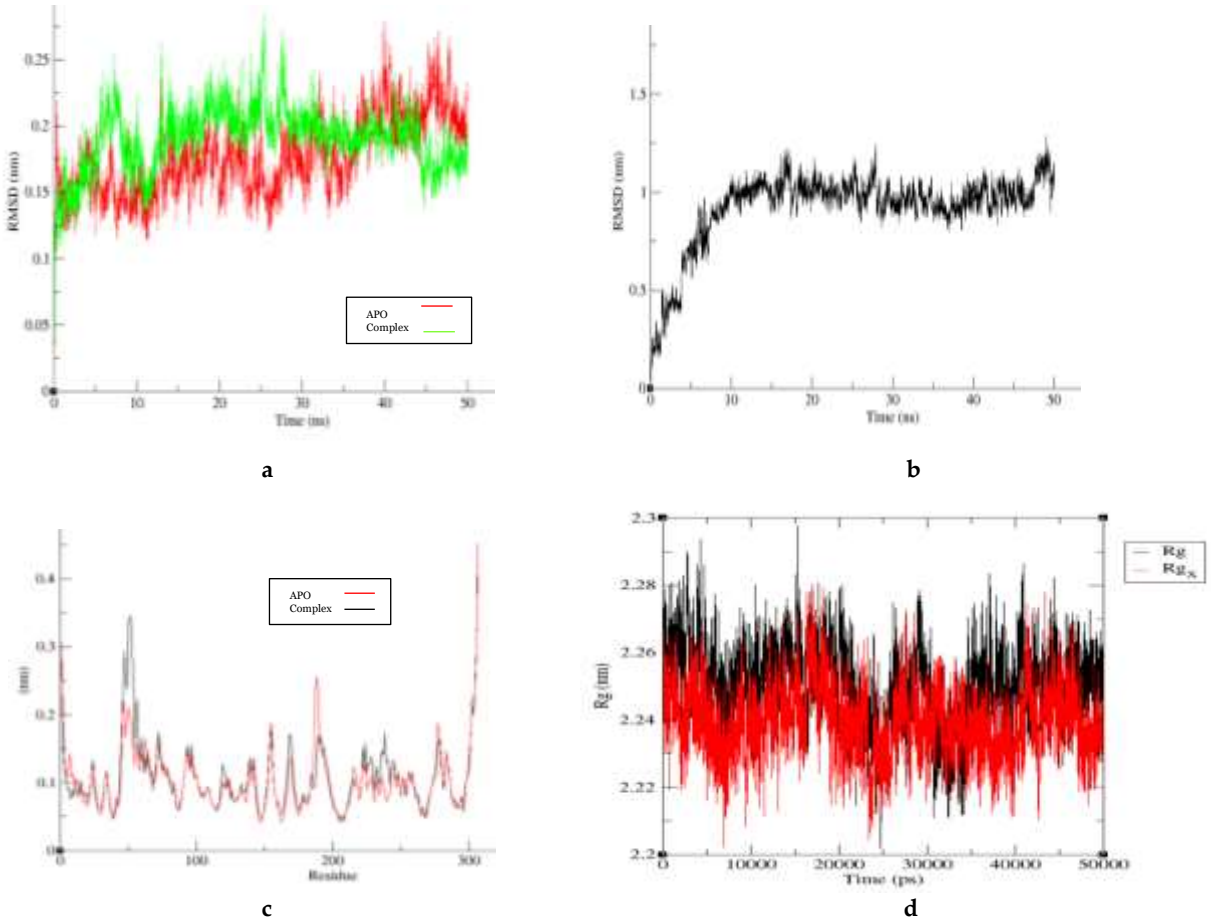

Figure 2. (a)RMSD of 3CLpro apo (red), and 3CLpro-ligand complex (green), and **(b)** RMSD of ligand towards protein during simulation (black). (c)RMSF of 3CLpro apo (red), and 3CLpro-ligand complex (black) and (d) RoG of 3CLpro apo (red), and 3CLpro-ligand complex (black)

To evaluate the flexibility of individual amino acid residues in the targeted protein, the RMSF (Root Mean Square Fluctuations) values of the backbone atoms were computed for both the Apo form and the complex form of 3CLpro. The results are depicted in **Figure 3c.** Notably, the highest peaks in both systems correspond to specific residues, namely Gln306, Asn51, Pro52, and Asp187, as indicated in **Figure 2.**

The gyrating radius, which is determined by calculating the mass-weighted RMSD of a group of atoms with respect to their shared center of mass, provides insight into the level of protein compaction. By analyzing the trajectory of the radius of gyration (Rg), changes in the overall size of the protein during dynamics can be observed. The comparison of the Rg values for the apo 3CLpro and the 3CLpro-ligand complex (3CLpro-average) is presented in **Figure 2d**. The average Rg for both systems was approximately 2.24 nm, indicating a similar level of compaction. Furthermore, the simulation patterns of both systems reached an equilibrium state, as demonstrated by the consistent Rg values throughout the simulation duration.

Table 2. Lipsinki's rule properties

Compound	Mass (Da)	Rbond	HBA	HBD	PSA (Å²)	LOGP	Acute Toxicity	Carcinogenicity
N-[1-(1-Adamantan-1-Yl-Propyl)-2,5-Dioxo-4-Trifluoromethyl-Imidazolidin -4-Yl]4-Methoxy-Benzamide	493	8	7	2	87.74	4.03	-	-
Cholesta-4,6-Dien-4-Ol, Benzoate, (3.Beta.)-	488	8	2	0	26.30	8.08	-	---
Lupeol	462	1	1	1	20.23	7.26	-	---
Stigmasta-5,23-Dien-3-Ol, (3.Beta.)-	412	6	1	1	20.23	7.05	-	---
Alpha.-Tocopherol-.Beta.-D-Mannoside	592	16	2	1	108.61	6.59	-	---
Beta.-Tocopherol	416	12	2	1	29.45	7.79	-	---
Remdesivir (Control Inhibitor)	602	14	12	4	213.36	1.50	-	-

Table 3. Pharmacokinetics properties

Compound	GI absorption	BBB	P-glycoprotein substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
N-[1-(1-Adamantan-1-Yl-Propyl)-2,5-Dioxo-4-Trifluoromethyl-Imidazolidin-4-Yl]4-Methoxy-Benzamide	High	No	Yes	No	Yes	Yes	Yes	Yes
Cholesta-4,6-Dien-4-Ol, Benzoate, (3.Beta.)-	Low	No	No	No	No	No	No	No
Lupeol	Low	No	No	No	No	No	No	No

Stigmasta-5,23-Dien-3-Ol, (3.Beta.)-	Lo	No	No	No	No	No	No	No
Alpha.-Tocopherol-.Beta.-D-Mannoside	Low	No	No	No	No	No	No	Yes
Beta.-Tocopherol	Low	No	Yes	No	No	No	No	No
Remdesivir (Control Inhibitor)	Low	No	Yes	No	No	No	No	Yes

Abbreviations: GI absorption, Gastrointestinal absorption; BBB, Blood Brain Barrier.

Table 4. Predicted anti SARS-CoV-2 activity of compounds extracted from *C. racemosa*

Compound	Live Virus Infectivity		Viral Entry			Viral Replication	In vitro infectivity				Human cell toxicity	Host Protein
	CPE	CPE-C	α-LISA	TruHit-C	EA	3CL-EA	CoV-PPE	CoV-PPE-CS	MERS-PPE	MERS-PPE-CS	hCYTOX	Sigma1R
N-[1-(1-Adamantan-1-Yl-Propyl)-2,5-Dioxo-4-Trifluoromethyl-Imidazolidin -4-Yl]4-Methoxy-Benzamide	Inactive (0.56)	Inactive (0.47)	Active (0.62)	Inactive (0.61)	Inactive (0.69)	Active (0.46)	Active (0.5)	Inactive (0.66)	Inactive (0.53)	Inactive (0.65)	Active (0.58)	Inactive (0.81)
Cholesta-4,6-Dien-4-Ol, Benzoate, (3.Beta.)-	Inactive (0.52)	Inactive (0.62)	Active (0.85)	Inactive (0.42)	Inactive (0.82)	Active (0.74)	Inactive (0.52)	Inactive (0.78)	Active (0.73)	Inactive (0.67)	Inactive (0.47)	Inactive (0.76)
Lupeol	Inactive (1.0)	Inactive (1.0)	Active (0.84)	Active (0.8)	Inactive (0.96)	Inactive (1.0)	Inactive (0.55)	Inactive (0.73)	Active (0.66)	Inactive (0.65)	Inactive (1.0)	Inactive (0.85)
Stigmasta-5,23-Dien-3-Ol, (3.Beta.)-	Inactive (0.55)	Inactive (0.9)	Active (0.87)	Active (0.94)	Inactive (0.970	Active (0.7)	Inactive (0.57)	Inactive (0.76)	Active (0.63)	Inactive (0.67)	Inactive (0.86)	Inactive (0.82)
Alpha.-Tocopherol-.Beta.-D-Mannoside	Inactive (0.88)	Inactive (0.66)	Active (0.78)	Active (0.76)	Inactive (0.67)	Inactive (0.55)	Active (0.7)	Active (0.6)	Active (0.66)	Inactive (0.56)	Active (0.4)	Inactive (0.91)
Beta.-Tocopherol	Active (0.56)	Active (0.58)	Active (0	Active (0	Inactive	Active (0.71)	Active (0.58)	Inactive (0.73)	Active (0.55)	Active (0.54)	Active (0.52)	Inactive (0.74)

			.96)	.99)	(0.77)							
Remdesivir (Contro)	Active (1.0)	Inactive (1.0)	Active (1.0)	Inactive (1.0)	Inactive (1.0)	Inactive (1.0)	Active (0.69)	Inactive (0.68)	Active (0.34)	Inactive (0.5)	Active (0.58)	Inactive (0.96)

Abbreviations: CPE, Cytopathic Effect; CPE-C, Cytopathic Effect (Host Tox Counter) / Cytotoxicity; α-LISA, Alphalisa Protein-Protein Interaction; Truhit-C, Truhit Counter Protein-Protein Interaction; EA, Enzymatics Activity; 3CL-EA; 3c-Like Enzymatics Activity; Cov-PPE, SARS-CoV Pseudotyped Particle Entry; CoV-PPE-CS, SARS-CoV Pseudotyped Particle Entry Counter Screen, MERS-PPE, MERS-CoV Pseudotyped Particle Entry; MERS-PPE-CS, MERS Pseudotyped Particle Entry Counter Screen; hCYTOX , Human Fibroblast Toxicity; Sigma1, Sigma1 Receptor.

Based on ADMET and Pharmacokinetic study, some compounds have not fulfilled the Lipinski's rule of five **(Table 2**), while in the pharmacokinetics identification **(Table 3)**, most compounds are acceptable for absorption in digestion tract. Furthermore, the predicted values of compounds extracted from the green seaweed *C. racemosa* as an anti-SARS-CoV-2 **(Table 4)** show promise for drug development. The promising drugs are those that are active in CPE and are inactive in cytotox, inactive in active in 3CL, and/or active in at least one of the following: AlphaLISA, Cov-PPE, MERS-PPE. They are also inactive in the counter screen (TruHit, Cov-PPE_cs, MERS-PPE_cs) and inactive in hCYTOX.

Discussion

The GC-MS analysis of the *C. racemosa* extract identified a total of 92 active compounds, most of which were fatty acids and alkanes, typically the most prominent phytochemicals in this seaweed (**Table S1**). The profile of bioactive compounds obtained in this present study are similar to identified previously in the red alga *Halymenia durvillei*, where 37 compounds where identified, most of which were fatty acids [10].Lipids may act antagonistically to viral infection by direct inhibition or by regulating adaptive and inflammatory responses [18].

The *in-silico* simulation found that free fatty acids could strongly bind with the spike protein of SARS-CoV-2. The results show that the compounds extracted from the green seaweed *C. racemosa* have molecular docking scores compared to remdesivir. The majority of the natural compounds exhibited slightly lower molecular docking scores than remdesivir, indicating that their binding affinity to the target molecule may be slightly weaker. However, although most of the natural compounds showed slightly lower scores than remdesivir, one compound exhibited a similar level of binding affinity, i.e., N-[1-(1-Adamantan-1-YL-propyl)-2,5-dioxo-4-trifluoromethyl-imidazolidin-4-YL]4-methoxy-benzamide. This binding consequently stabilizes the viral spike (S) protein in a locked conformation and reduces its interaction with the ACE2 receptor. Similar fatty acid binding mechanisms have been observed in both SARS-CoV-2 and Middle East respiratory syndrome-related coronavirus (MERS-CoV) [19]. The existence of a competitive bond affinity score for *C. racemosa* extract and its ability to interact *in silico* at the binding site of 3CLMpro from SARS-CoV-2 makes *C. racemosa* extract a potential candidate as a SARS-CoV-2 antiviral agent.

Our hypothesis was supported numerically by the *in-silico* simulation. However, there may be further compounds of other types present in the green alga *C. racemosa* which still need to be identified and analyzed, in particular through more advanced molecular approaches. Moreover, following these promising results, some studies under *in vitro* and *in vivo* conditions are now needed to further investigate the effectiveness of active compounds from *C. racemosa* in the treatment of COVID-19. Previous studies highlight the use of algae in inhibiting the replication of the SARS-CoV-2 virus [10, 20], and algae have also been found to be effective against other viruses [21-22]. Importantly, the molecular dynamics studies and MMGBSA or MMPBSA calculations should be performed for further advanced investigation using *in silico* study methods.

Conclusion

In summary, this study investigated the potential of natural compounds derived from *Caulerpa racemosa* as antiviral agents against SARS-CoV-2. The results indicate that these compounds have demonstrated promising inhibitory effects on the 3CLpro enzyme of SARS-CoV-2, with a specific compound, n-[1-(1-Adamantan-1-YL-propyl)-2,5-dioxo-4-trifluoromethyl-imidazolidin-4-YL]4-methoxy benzamide, showing the strongest binding affinity. While the therapeutic and nutritional benefits of *C. racemosa* have been recognized, it is important to promote its consumption among the general population. As further research uncovers the potential of *C. racemosa* in preventing SARS-CoV-2, the development of seaweed-based medications could contribute to the expanding array of anti-SARS-CoV-2 treatments. Thus, the findings suggest that the extract from *C. racemosa* holds promise as a candidate for the development of anti-SARS-CoV-2 interventions. Additional pre-clinical studies, including toxicity testing and *in vitro* and *in vivo* investigations e.g., with a mouse model, are required to fully assess the antiviral potential of *C. racemosa* against SARS-CoV-2. These studies will provide valuable insights to advance the development of interventions based on *C. racem*osa for combating SARS-CoV-2.

Ethics approval

Not applicable.

Acknowledgments

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Competing interests

The authors declare that there is no conflict of interest.

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Underlying data

The supplementary table can be accessed in https://figshare.com/s/f79472e477ab6d85e318

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