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An evidence of microalgal peptides to target spike protein of COVID-19: In silico approach

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ABSTRACT

The outbreak of the novel coronavirus (COVID-19) has affected millions of lives and it is one of the deadliest viruses ever known and the effort to find a cure for COVID-19 has been very high. The purpose of the study was to investigate the *anti*-COVID effect from the peptides derived from microalgae. The peptides from microalgae exhibit antimicrobial, anti-allergic, anti-hypersensitive, anti-tumor and immune-modulatory properties. In the *In silico* study, 13 cyanobacterial specific peptides were retrieved based on the extensive literature survey and their structures were predicted using Discovery Studios Visualizer. The spike protein of the novel COVID19 was retrieved from PDB (6LU7) and further molecular docking was done with the peptides through CDOCKER. The five peptides were bound clearly to the spike protein (SP) and their inhibitory effect towards the SP was promising among 13 peptides were investigated. Interestingly, LDAVNR derived from *S.maxima* have excellent binding and interaction energy showed −113.456 kcal/mol and −71.0736 kcal/mol respectively to target SP of COVID. The further investigation required for the *in vitro* confirmation of *anti*-COVID from indigenous microalgal species for the possible remedy in the pandemic.

Author statement

Davoodbasha MubarakAli design the experiment, guidance, drafting and proof reading; Jaulikar Mohamed Saalis, data acquisition, process; Raghunathan Sathya, data processing and discussion; Navabshan Irfan, data interpretation and discussion and Jung-Wan Kim, reviewing and proofreading.

All the authors are solely understand the submission.

1. Introduction

Spirulina is a prokaryotic, filamentous, blue green algae that grow in mineral rich alkaline water which acts as a nutritive agent. *Spirulina* is a highly nutritional food known to mankind and it is considered to be a superfood because of its phenomenal therapeutic and medicinal properties. *Spirulina* is well recognized because of its abundance in nutrients as there is a high content of protein and other nutrients such as carotenoids, omega-3 and 6 PUFA, γ-Linolenic acid, sulfolipids, glycolipids, polysaccharides, provitamins vitamin and minerals. *S. platensis* and *S. maxima* are the two most common species of *Spirulina* that have been used in nutritional supplements. *Spirulina* has been used as food for human consumption, feed for cattle and it is also used in poultry and aquaculture. One of the exceptional features of *Spirulina* is that it can be easily consumed. Studies have proven that *Spirulina* has the potential to be the remedy for numerous diseases [1].

Spirulina has been identified as a good source of algal peptides. Usually, these biologically active peptides have 2–20 amino acid residues per molecule but sometimes they have more than 20 residues of amino acids which have different mode of actions depending on the amino acid sequences [2]. A short peptide with a molecular weight of <6000 Da and thus increases the chances of passing the intestinal barrier and show powerful biological activities. *Spirulina* derived nutraceutical's have therapeutic role in enhancing adaptive and innate immunity against coronavirus and other viral illnesses [3]. Algal

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Table 1
Peptides derived from *Spirulina* sp. for biomedical applications chronologically.

Peptides	Species	Enzyme Extraction	Application	Reference
LDAVNR MMLDF	*S.maxima*	pepsin, trypsin and α-chymotrypsin	Anti-inflammatory	[3]
KLVDASHRLATGDVAVRA	*S.platensis*	Papain hydrolysate and Alkaline protease	Antibacterial	[4]
YGFVMPRSGLWFR	*S.platensis*	Proteases (trypsin, alcalase and papain)	Anti-tumor	[5]
FSESSAPEQHY	*S.platensis*	Proteolytic digestion	Antioxidant	[6]
NALKCCHSCPA LNNPSVCDCDCMMKAAR NPVWKRK CANPHELPNK	*S.platensis*	Trypsin, alcalase, pepsin, papain and protamex	Anti-obesity	[7]
GVPMPNK RNPFVFAPTLLTVAAR LRSELAAWSR	*S.platensis*	Enzymatic hydrolysate	Anti-diabetes	[8]
IGP	*S.platensis*	Alcalase	Functional food	[9]

peptides exhibit antimicrobial, anti-allergic, anti-hypersensitive, anti-tumor and immunomodulatory properties. These algal peptides can be obtained by various methods such as enzymatic hydrolysis, cell lysis, protein extraction and purification. Table 1 describing the potential applications of algal peptides reported chronologically [2–9]. In vivo and In vitro studies of Spirulina have been done to see its efficacy in the treatment of numerous diseases such as hepatotoxicity, hyperglycemia, hyperlipidemia, immune-compromization and immune resistance enhancement in some types of cancer. Presently, there is a sharp increase in the number of diseases and disorders like diabetes, oxidative stress, cancer, cardiovascular diseases and this can be a result of excess usage of food additives, improper diet and potent viruses such as the COVID-19. Naturally occurring algal peptides are more suitable to overcome such diseases and disorders [10].

Recent outbreak of COVID-19 has majorly affected millions of lives and it is one of the deadliest viruses ever known. The death rate was found 2.2 million from 100 million reported cases around the world [11]. Since then, the effort to find a cure for COVID-19 has been very high. Algal peptides have a good biological activity and remarkable advantages for discovering a new drug against the novel coronavirus. The aim of this study was to investigate *anti*-COVID effect from the peptides which were derived from *Spirulina* through in silico to proceed for the in vitro and in vivo confirmation.

2. Materials and methods

2.1. Retrieval of algal peptides sequence

Peptides of *Spirulina* sp. which were found over the last few years were taken and their structure was drawn with the aid of Discovery Studio Visualizer (Ver 1.7) https://discover.3ds.com/discovery-studio-visualizer. A total of 13 peptides were derived for the docking studies (S.Fig. 1).

2.2. Retrieval of COVID19 spike protein

Data of spike protein of the coronavirus was retrieved from the Protein Data Bank which was registered with the PDB ID: 6LU7. The spike protein obtained has a resolution of 2.16 Å which was suitable for the docking studies. The structure of the spike protein was obtained as shown in S.Fig. 2.

2.3. Preparation of protein

In the simulation of molecular mechanics, an important step is to allocate a forcefield to the input molecule. The forcefield applied here is the CHARMm forcefield. The match is carried out by comparing the input structures' residue names and atom names to the RTF file's residue template. Other forms of molecules, such as carbohydrates, lipids, and small molecule ligands, have even more variable residue and atom names. Additionally some residue patches may be included in each of the supported forcefields to allow for differences in the residues [12].

$$E_{pot} = E_{bond} + E_{angle} + E_{torsion} + E_{oop} + \quad E_{elec} + E_{vdW} + E_{contraint} + E_{user}$$

where, the OOP (out-of-plane) is explained as improper torsion.

2.3.1. Minimization

The minimization protocol involves reducing a structure's energy through geometrical optimization. For example, preparation of crystallographic protein structure can be done using the minimization protocol with various parameters (S.Table 1).

2.3.2. Define binding site

The binding site tools will identify, edit, and visualize a receptor's binding sites for the docking purpose. The first visible molecule will be used as the receptor if no receptor has been identified. By clicking this while the receptor molecule is accessible and selected, you may adjust the current receptor. Using these techniques, you can identify locations inside the receptor using a variety of methods such as from receptor cavities, PDB site records and current selection. The XYZ coordinates of the SP was −10.749951 12.462226 68.919085 respectively.

2.4. Preparation of peptides and molecular docking

Prior to dynamics, structures are subjected to energy minimization in order to facilitate conformation and remove steric overlap, which causes poor interactions [11]. The parameters for minimization of peptides listed in Table 4. The implementation of CHARMm based docking tool using a rigid receptor is CDOCKER [13,14]. The parameters for the docking are listed in the S.Table 3.

3. Results and discussion

The biotechnological applications of *Spirulina* have been well studied to explore the possible utilization as food and medicine. *Spirulina* has been used as a protein source in Nile Tilapia grow-out diets, as an antifungal to hinder the production of fumonisin and it lowered the infection by the species of *Fusarium* and the fumonisin contamination [15]. *S. platensis*, *S. maxima* and *S. fusiformis* have the majority of applications such as anticancer, anti-inflammatory, anti-hypersensitive, anti-hyperglycemia. It has been found that *S. platensis* prevents hyperglycemia in rats by regulating gluconeogenesis and apoptosis and used as a biodiesel [16–18]. Notably, *S. platensis* is the ability to boost the immune response used for dye degradation obtained high product yield during solar catalytic pyrolysis [19]. An application of the *S. maxima* is that it helps in the suppression of LPS-induced pro-inflammatory cytokines [20]. Some of the applications of *S. fusiformis* include having a neuro-protective effect in wistar albino rats used in diets [21,22]. With all these applications in consideration, hence *Spirulina* proves to have a

Table 2
Depict the outcome of the minimization of protein.

Name	Forcefield	Initial Potential Energy (kcal/mol)	Potential Energy (kcal/mol)	Van der Waals Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	Initial RMS Gradient (kcal/(mol x A)	Final RMS Gradient (kcal/(mol x A)	Minimization Criteria
6LU7	CHARMm	−6089.4811	−21828.1094	−2254.9722	−22201.1649	165.7776	0.9412	CONJUG > Minimization exiting with number of steps limit (200) exceeded.

Table 3
Outcome of minimization of peptides.

S.No	Name	Initial Potential Energy	Initial RMS Gradient	Potential Energy	Van der Waals Energy	RMS Gradient
1.	LDAVNR	150.481	120.501	−397.492	−10.5394	0.00967
2.	MMLDF	356.197	179.237	−179.38	−15.41	0.05258
3.	KLVDASHRLATGDVAVRA	92,181.1	59763.9	−812.044	−47.5627	0.08777
4.	YGFVMPRSGLWFR	1567.76	613.183	−463.469	−34.0934	0.03712
5.	FSESSAPEQHY	91853.6	76968.5	−419.935	−28.0077	0.10435
6.	NALKCCHSCPA	2.8296	2.97048	−379.796	−28.433	0.09881
7.	LNNPSVCDCDCMMKAAR	927.677	361.57	−756.768	−45.6692	0.08816
8.	NPVWKRK	831.568	477.17	−318.331	−22.9265	0.08771
9.	CANPHELPNK	92758.2	79688.6	−513.889	−28.0194	0.45331
10.	GVPMPNK	4.95266	1.0006	−288.691	−17.3199	0.00976
11.	RNPFVFAPTLLTVAAR	2324.89	534.331	−453.94	−54.4466	0.08229
12.	LRSELAAWSR	139.057	124.129	−472.394	−26.2876	0.15233
13.	IGP	−33.4733	18.3465	−151.144	−2.82809	0.00887

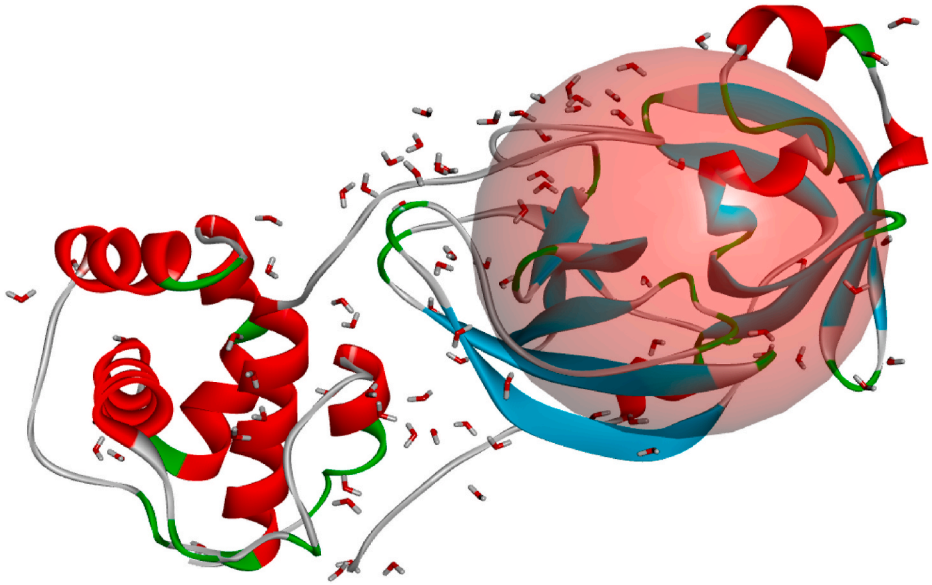


Fig. 1. Secondary structure of the COVID-19 spike protein (PDB ID: 6LU7) with the binding site.

great potential for a large number of applications.

Algal peptides have been derived from different species of *Spirulina* such as *S. platensis*, *S. maxima* and these peptides have been majorly derived from *S. platensis*. These algal peptides were obtained over the years of work and research with different methods of extraction and they were found to have a specific mode of action. Peptide sequences, LDAVNR, MMLDF obtained from *S. maxima* had an anti-inflammatory mode of action and they were purified from the enzymatic hydrolysate of *S. maxima* with the use of gastrointestinal endopeptidases such as trypsin, α-chymotrypsin and pepsin [2]. To assess the impact of algal peptides on COVID-19 marker through *in silico* studies.

Minimization is the process of bringing a molecule to the lowest energy level. The results of minimization of protein showed that the initial potential energy reduced from −6089.48111 kcal/mol to −21828.10946 kcal/mol. The initial RMS gradient value was 165.77769 kcal/(mol x A) and it reduced to 0.94123 (kcal/(mol x A) which is the final RMS gradient value. Additionally, the Van der Waals energy was −2254.97222 kcal/mol and the electrostatic energy was found to be −22201.16498 kcal/mol (Table 2) (see Fig. 1).

Minimization of 13 peptides were done and the results are shown in the table above. The initial potential energy for these 13 peptides ranged from −33.4733 kcal/mol to 92758.2 kcal/mol and the final potential energy range was from −812.044 kcal/mol to −151.144 kcal/mol. The values of Initial RMS gradient ranged from 1.0006 kcal/mol to 79688.6 kcal/mol and that of final RMS gradient ranged from 0.00887 kcal/mol to 0.45331 kcal/mol. Additionally, Van der Waals energy range was from −54.4466 kcal/mol to −2.82809 kcal/mol (Table 3). Molecular docking of 13 different peptides was done out of five peptides bound perfectly inside the COVID-19 spike protein (PDB ID: 6LU7) binding pocket. The docking of peptides inside the binding pocket was observed

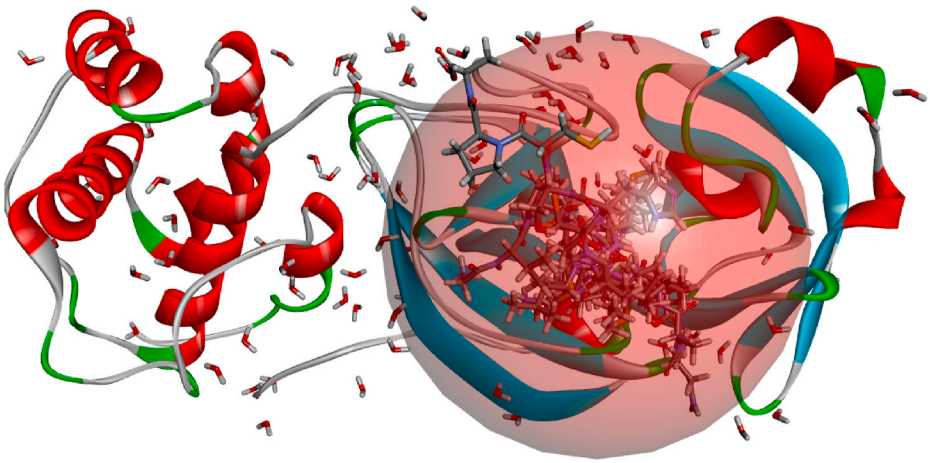


Fig. 2. Peptides docked inside the COVID-19 Spike protein's binding pocket.

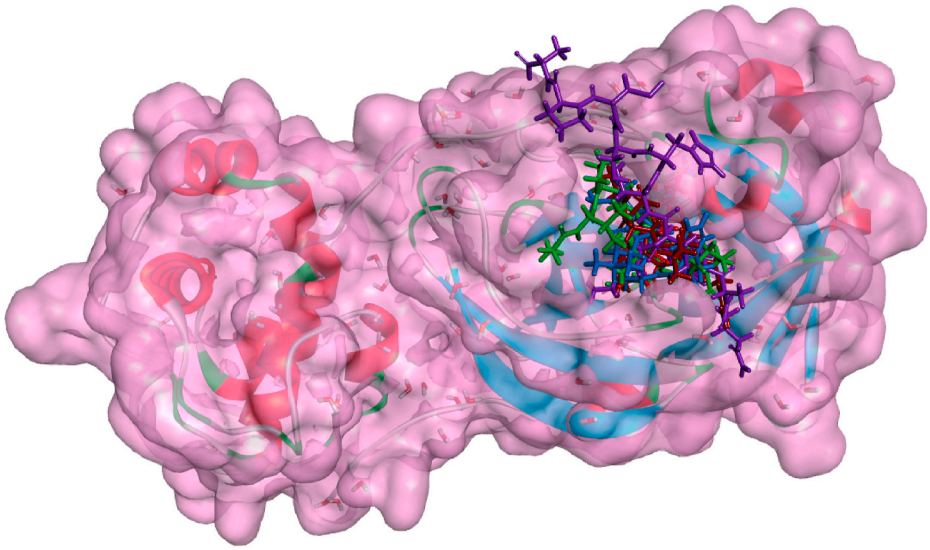


Fig. 3. Surface view of peptides on the COVID-19 spike protein's binding location.

(Fig. 2).

Fig. 3 the surface view that 5 out of 13 peptides bound perfectly to the COVID-19 spike protein (6LU7). They demonstrated the lock and key model precisely by forming a proper conformation. The five peptides which bound perfectly were LDAVNR, MMLDF, NALKCCHSCPA, GVPMPNK and IGP. Peptide, LDAVNR formed a conventional hydrogen bond with GLN A:189, THR A: 26, SER A,: 144, HIS A: 164 and GLU A:166 and a carbon hydrogen bond with GLU A:166. An alkyl bond was formed with MET A:49. Also, a sulfur bond was formed with MET A:165. A peptide, MMLDF formed a conventional hydrogen bond with GLU A:166, ASN A:142, CYS A:145 and HIS A:164. Carbon hydrogen bonds were formed with GLN A:189 and MET A:165. With MET A:49, a pi-sulfur bond was created. PRO A: 168 and HIS A:41 produced the Pi alkyl bond and the alkyl bond, respectively (see Fig. 4).

Peptide, NALKCCHSCPA formed conventional hydrogen bonds with GLN A:189, ASN A:119, THR A:26 and PHE A:40. Carbon hydrogen bond was formed with LEU A:141. Water hydrogen bonds were formed with HOH A:416 and HOH A:433. A salt bridge was formed with GLU A:166. Pi-Alkyl bonds and alkyl bonds were formed with ALA A:191, CYS A:145 and LEU A:50. The peptide, GVPMPNK formed conventional hydrogen bonds with LEU A:167, HIS A:164, GLY A:143, CYS A:145 and HIS A:163. Carbon hydrogen bonds were formed with PRO A:168, GLN A:189 and MET A:165. Here, GLY A:170 was the unfavorable donor. GLU A:166 was the only attractive charge seen. Alkyl and Pi-Alkyl bonds were formed with HIS A:41. HIS A:164, CYS A:145, HIS A:41, GLY A:143 and SER A:144 established conventional hydrogen bonds with peptide 13 (IGP). With MET A:165, GLN A:189, and ASN A:142, carbon hydrogen bonds were produced. LEU A:141 was the unfavorable acceptor in this case. HIS A:163 and MET A:49 were used to create Pi-alkyl and alkyl linkages.

The five peptides showed refined poses and eight peptides failed to bind inside the COVID19 SP bind pocket. The peptides which showed refined poses are the peptide, LDAVNR, MMLDF, NALKCCHSCPA, GVPMPNK and IGP. The values of CDOCKER energy and interaction energy for these peptides are shown (Table 4). With a binding energy of −113.456 kcal/mol and interaction energy of −71.0736 kcal/mol, LDAVNR was found to have the best binding energy. With an interaction value of −82.2964 kcal/mol, peptide 6 had the second best binding energy of −103.469 kcal/mol. A peptide, IGP had the lowest binding energy (−48.8787 kcal/mol) and the lowest interaction energy (−48.8946 kcal/mol). Recent docking study was done with novel azo imidazole derivatives with the coronavirus SP, 6LU7 and the results showed that out of six ligands, ligand 5 had the best affinity towards the spike protein with the binding energy of −8.1 kcal/mol [23]. In comparison with ligand 5, LDAVNR showed good value of binding energy with the SP. It was reported that SARS – CoV as the capacity to bind with

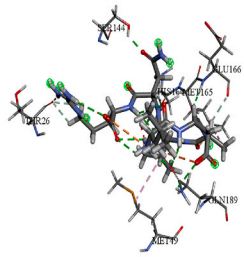
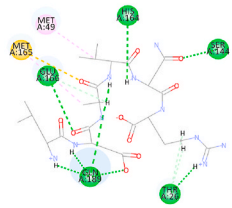
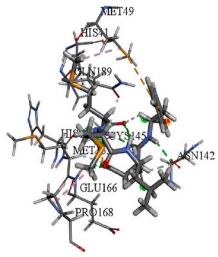
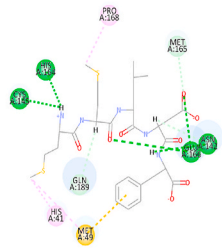
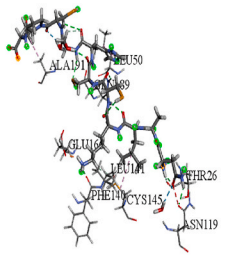
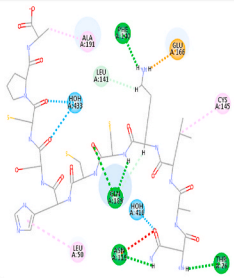
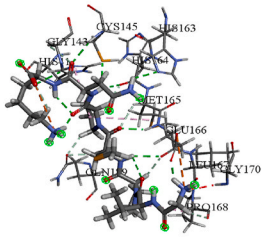
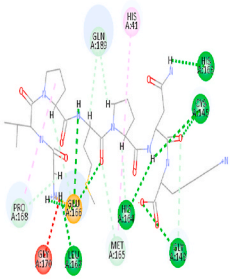
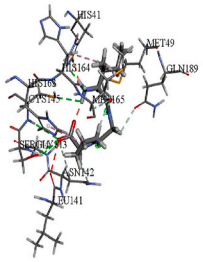
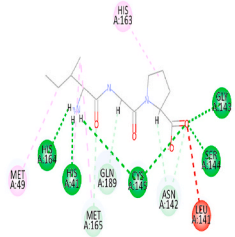
Microalgal peptides	Interaction of active amino acids in 3D view	Interaction of active amino acids in 2D view
LDAVNR		
MMLDF		
NALKCCH SCPA		
GVPMPNK		
IGP		

Fig. 4. 2D and 3D view of the interaction of active amino acids with algal peptide, LDAVNR, MMLDF, NALKCCHSCPA, GVPMPNK and IGP.

the host cell of human ACE2 through receptor binding domain [24]. In addition, it has been proved that human ACE2 as a major receptor of Corona virus and act as an extracellular domain which makes binding with SARS- CoV [25,26]. The glycoprotein S of SARS-CoV-2 has the ability to activate the most powerful and long lasting neutralizing host cells against COVID-19 [27,28]. Due to highly frequent recurrent genetic recombination SARS- CoV-2 as emerged notably in the spike glycoprotein's RBD [29]. Marine-derived compounds such as oleic acid, saringosterol, Sitosterol, Caulerpin, Glycoglycerolipids, Kjellmanianone, and Loliolide extracted from red, green, and brown macroalgae were recently reported as candidate inhibitors against $3CL^{pro}$, the SP, and the ACE-2 receptor of SARS-CoV-2 in a molecular docking-based study [30].

4. Conclusion

There is endless effort have been made to treat COVID-19 world-

Table 4
Docking score of successfully bound peptides.

Name	Energy_CDOCKER (kcal/mol)	Interaction_Energy_CDOCKER (kcal/mol)
LDAVNR	−113.456	−71.0736
MMLDF	−93.0963	−58.6137
NALKCCHSCPA	−103.469	−82.2964
GVPMPNK	−82.949	−87.0422
IGP	−48.8787	−48.8946

wide. The present study could help to finding a way to treat and or develop a therapeutic effect against COVID-19. Despite the fact that there has been a handful studies found on the *Spirulina* health benefits, the evidence for its potential therapeutic use is compelling. Potential microalgal peptides with special reference to *Spirulina* species have been retrieved and docking studies along with the COVID-19 spike protein (PDB ID: 6LU7). The five peptides were derived are bound successfully inside the binding pocket of the spike protein satisfying the lock and key model out of 13 peptides studied. In particular, a peptide LDAVNR showed the best binding energy −113.456 kcal/mol and interaction energy of −71.0736 kcal/mol among peptides were investigated. This study pave a way to understand the effectiveness of algae could be used for the immunity enhancement and to overcome the pre and post COVID treatment complications. The further investigation with In vito and In vivo are to be directed to confirm the efficacy.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.micpath.2021.105189.

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