Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Identification of nut protein-derived peptides against SARS-CoV-2 spike protein and main protease

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ABSTRACT

Recently, an outbreak of a novel coronavirus disease (COVID-19) has reached pandemic proportions, and there is an urgent need to develop nutritional supplements to assist with prevention, treatment, and recovery. In this study, SARS-CoV-2 inhibitory peptides were screened from nut proteins *in silico*, and binding affinities of the peptides to the SARS-CoV-2 main protease (M^{pro}) and the spike protein receptor-binding domain (RBD) were evaluated. Peptide NDQF from peanuts and peptide ASGCGDC from almonds were found to have a strong binding affinity for both targets of the coronavirus. The binding sites of the NDQF and ASGCGDC peptides are highly consistent with the M^{pro} inhibitor N3. In addition, NDQF and ASGCGDC exhibited an effective binding affinity for amino acid residues Tyr453 and Gln493 of the spike RBD. Molecular dynamics simulation further confirmed that the NDQF and ASGCGDC peptides could bind stably to the SARS-COV-2 M^{pro} and spike RBD. In summary, nut protein may be helpful as nutritional supplements for COVID-19 patients, and the screened peptides could be considered a potential lead compound for designing entry inhibitors against SARS-CoV-2.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outbreak started in Wuhan, China [1], and COVID-19 was declared a pandemic disease by the World Health Organization (WHO) on March 11, 2020 [2]. To date, the WHO estimates that more than 236.4 million people have been infected with the virus, resulting in more than 4,827, 915 deaths worldwide (https://coronavirus.jhu.edu/map.html). Common symptoms of COVID-19 include a non-productive cough, fever, fatigue, and shortness of breath[3]. SARS-CoV-2 is a new betacoronavirus responsible for COVID-19 [4], with a genome of approximately 30,000 nucleotides [5]. In addition, the SARS-CoV-2 virus is a single-stranded positive-sense RNA virus. The most important structural protein involved in virus entry is the spike protein [6,7]. The spike protein enters host cells by recognizing and binding angiotensin-converting-enzyme 2 (ACE2) receptors [8]. After the coronavirus enters the host cell, the viral messenger RNA is first translated into polyproteins, which are cleaved by two viral proteinases, papain-like protease (PLP) and main protease (M^{pro}) [9,10], to produce non-structural proteins essential for viral replication [11]. Blocking spike protein binding to ACE2 is an effective therapy for SARS-CoV-2 infection [12]. Therefore, the spike protein has emerged as a potential target for antiviral therapy, and the M^{pro} is one of the most promising drug targets in coronaviruses [13]. Inhibitors that suppress the activity of the M^{pro} may inhibit viral replication and provide pathways for the treatment of SARS-CoV-2 [14]. Several studies have demonstrated the 3D structure of the M^{pro}, which can help in the systematic development of drugs to inhibit viral replication, potentially mitigating COVID-19 infection [15].

Currently, there is a rapid development of drugs and antibodies to combat this coronavirus. For example, therapeutic drugs such as chloroquine, monoclonal antibodies, and lumacaftor could block the binding of the SARS-CoV-2 spike protein to the ACE2 receptor, and remdesivir and favipiravir could block the viral RNA synthesis. While the pandemic persists, there is still a need to develop new drugs to combat this virus [16–19]. Drug treatment alone is insufficient, and nutritional supplementation to bolster immune system health should also be considered. Studies have shown that protein deficiency can affect the cardiovascular system and increase the risk of infectious diseases [20]. Proteins are necessary to produce immunoglobulins, anti-inflammatory cytokines, and other components required for disease resistance. Therefore, protein

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supplementation is proven to be a good option. Nuts, rich in protein, have become a widely popular source for protein supplementation in a healthy diet [21]. After protein intake, gastrointestinal enzymes break down the protein macromolecules into amino acids, oligopeptides, or peptides. Previous studies have shown that peptides from different protein resources have multiple functions, including antihypertensive ability, ACE-inhibitory properties, and antibacterial activity [22].

This study aimed to simulate the degradation of nut proteins by gastrointestinal enzymes using *in silico* approach. First, the generated peptides were screened by biological activity, toxicity, and water solubility prediction. Then, the binding capacity and binding stability of selected peptides to the SARS-CoV-2 M^{pro} and spike receptor-binding domain (RBD) were assessed. Peptides with high selectivity and binding affinity were expected to potentially inhibit COVID-19 while being used as supplements.

2. Materials and methods

2.1. In silico digestion of nut proteins

The online ExPASy PeptideCutter program (http://web.expasy.org/peptide_cutter/) was used for *in silico* digestion of the proteins. The NCBI protein sequence database (http://www.ncbi.nlm.nih.gov) was used to retrieve ten protein (Table S1) sequences from peanuts, walnuts, and almonds. Subsequently, the ten proteins sequences were subjected to *in silico* release of peptides by pepsin (pH > 2.0), pepsin (pH 1.3), and trypsin.

2.2. In silico bioactive prediction of peptides

The score calculated in PeptideRanker (http://distilldeep.ucd.ie/PeptideRanker/) was used to predict the potential biological activity of all released peptides. An expected value greater than 0.5 indicated that the peptide might sustain biological activity [23].

2.3. In silico toxicity and solubility prediction of selected peptides

The computational analysis program ToxinPred (http://crdd.osdd.net/raghava//toxinpred/) was used to predict the toxicity of the selected peptides. In this research, the toxicity of all peptides was scored in ToxinPred to differentiate toxic and non-toxic peptides. The peptide property calculator (http://www.innovagen.com/) was used to predict the solubility of the peptides [23]. The peptides sequences were entered into the peptide property calculator, and the predicted results were displayed in a pop-up window [24].

2.4. Molecular docking

The crystal structures of the SARS-CoV-2 M^{pro} (PDB:6LU7) [25] and the RBD of the spike protein (PDB:6M0J) [26] were obtained from the Protein Data Bank (PDB) as targets to screen for their binding peptides. The crystal structures were prepared using the macromolecules module from Discovery Studio (DS) 2017 (Dassault Systèmes, BIOVIA, San Diego, CA, USA) [27]. The amino acid sequences of selected peptides were input into the 'build and edit protein' program of the macromolecules module to draw the peptide structures. The small molecule module was used to optimize the peptide structures with the preparation of ligands and energy minimization. Molecular docking was performed by the CDOCKER protocol of DS 2017 using the default parameters [26]. The structure of the M^{pro} was prepared by removing water and the N3 ligand and adding hydrogen atoms. The binding sites of the M^{pro} were identified based on the current N3 ligand, with coordinates x: −10.8, y: 12.5, and z: 68.9, and a radius of 13.9 Å. The structure of the spike RBD was prepared by removing water and the ACE2 protein, and the binding sites were identified based on the contact residues at the SARS-CoV-2 spike RBD-ACE2 complex (*i.e.*, Lys417, Gly446, Tyr449, Tyr453, Leu455, Phe456, Ala475, Phe486, Asn487, Tyr489, Gln493, Tyr495, Gly496, Gln498, Thr500, Asn501, Gly502G, and Tyr505). Docking was performed with coordinates x: −37.1, y: 29.4, and z: 4.81, and a radius of 21.8 Å.

2.5. Half-life prediction of selected peptides

The online program ProtParam (https://web.expasy.org/protparam/) was used to predict the half-life of the peptides [28]. After entering the sequences of peptides using the single-letter amino-acid code, the "compute parameters" button was selected, and the half-life was estimated from those parameters.

2.6. Molecular dynamic (MD) simulation

MD simulations of the obtained protein-ligand complexes were subjected to 10 ns using the GROMACS 2018 package, and the CHARMM36 force field parameters were used for the protein and water molecules [29]. The protein-ligand complex structure was placed in the center of a cubic box, the remaining volume of the box was filled with TIP3P water molecules, and chlorine/sodium atoms were added to neutralize the system. The system was energy minimized using the steepest descent algorithm. Subsequently, two-step simulations (NVT and NPT) were carried out using a leapfrog algorithm to balance the system. The system's temperature was fixed at 300 K using a V-rescale thermostat, and the pressure of each system was maintained at 1 bar using a Berendsen barostat. The root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), and radius of gyration (Rg) were calculated from the trajectory files obtained during the simulation.

3. Results and discussion

3.1. Digestion and selection of potential peptides

The protein sequences of nut proteins were retrieved from the NCBI protein database, and the walnut, peanut, and almond proteins were selected (Table S1). Through simulation using the PeptideCutter server, the ten proteins were digested by typical enzymes of pepsin (pH1.3), pepsin (pH > 2.0), and trypsin, and a total of 733 peptides were obtained. Previous work has demonstrated that most anti-microbial peptides are composed of 20–50 amino acids and are rich in hydrophobic residues, including leucine, isoleucine, valine, phenylalanine, and tryptophan [30]. However, it has been reported that the relatively small size of the peptide allows for rapid diffusion and secretion of peptides outside the cells, which is a necessary condition for eliciting an immediate defense response against pathogenic microorganisms [26]. Therefore, all peptides were retained for this study.

PeptideRanker is a tool for evaluating the biological activity of peptides. Typically, a value above 0.5 is considered a biologically active peptide. Peptides with potentially high biological activity were selected for further study, and the active score results of the predicted peptides were presented in Table S2. ToxinPred was applied to discriminate between non-toxic and toxic peptides, and the toxicity analysis confirmed that the selected peptides were non-toxic.

Subsequently, the water solubility of the peptides was measured since good water solubility is more conducive to the absorption of biologically active peptides. Overall, nine peptides from the walnut protein, 27 peptides from the peanut protein, and 14 peptides from the almond protein were selected based on the water solubility prediction results (as shown in Table S2). These peptides were non-toxic, had good water solubility and biological activity, and are excellent candidates for further study.

3.2. Prediction of SARS-CoV-2 M^{pro} inhibitory activity of the peptides

Molecular docking is a technique used to predict the interactions of

proteins (receptors) with small molecules (ligands). The DS 2017 CDOCKER program was used for docking analysis to study the binding ability of peptides that met the previous screening requirements with the SARS-CoV-2 M^{pro}. The crystal structure of the SARS-CoV-2 M^{pro} (PDB: 6LU7) was selected as the target to screen for peptides that can effectively inhibit the SARS-CoV-2 virus. Previous research has shown that N3 compounds have functioned as effective inhibitors of the M^{pro} [25]. Therefore, N3 was obtained and kept as a positive control compound, and the N3 binding mode was used to evaluate the binding affinity of 40 peptides to the M^{pro}. All peptides were docked with the M^{pro}, and the results showed that only three peptides could form multiple hydrogen bonds with the M^{pro} at the binding cleft of N3. The CDOCKER ENERGY values of peptides NDQF, CQDCY, and ASGCGDC were −97.986, −104.732, and −108.412 kcal/mol, respectively (shown in Table S2).

Fig. 1b shows the M^{pro} docking postures of the peptide NDQF. NDQF formed eight conventional hydrogen bonds with amino acids His41, Thr190, Gln189, Asp187, His164, Tyr54, Cys145, and Gly143 in the M^{pro}. Gln189, Glu166, Met165, His164, Gly143, and His41 of the M^{pro} formed seven carbon-hydrogen bonds with NDQF, and Cys145 residue forms a pi-sulfur interaction with the NDQF peptide. The interaction between the CQDCY peptide with the M^{pro} was shown in Fig. 1c. CQDCY interacted with the amino acids Asp187 (O), Gln189 (OE1), Asn142 (HD22), Glu166 (OE1), Glu166 (OE2), Cys145 (HN), Ser144 (HN), and Ser144 (HG) via eight conventional hydrogen bonds. Furthermore, Asp187 (HA), His163 (HD2), Glu166 (OE1), and Met165 (HA) formed four carbon-hydrogen bonds with N3. The CQDCY peptide formed pi-alkyl, pi-pi stacked, and attractive charge interactions with Met49, His41, and Glu166 of the M^{pro}, respectively. The CDOCKER ENERGY value of peptide ASGCGDC was −108.412 kcal/mol. ASGCGDC established eight conventional hydrogen bonds with Gly143 (HN), Ser144 (HN), Cys145 (HN), His41 (HE2), Phe140 (O), His163 (HE2), Gln189 (OE1), and Glu166 (HN) of the M^{pro} (shown in Fig. 1d). Further, one attractive charge interaction and one carbon-hydrogen bond with Glu166 (OE2) and Met165 (HA) were predicted. His172 and His163 formed pi-sulfur interactions with the ASGCGDC peptide.

Fig. 1e shows the docked pose of the M^{pro} with inhibitor N3. The CDOCKER ENERGY value was −103.728 kcal/mol. The inhibitor N3 formed eight conventional hydrogen bonds (Rhe140, His163, His41, Glu166, Glu166, Glu166, Gly143, and Gln189), one pi-alkyl interaction (His41), six carbon-hydrogen bonds (Thr26, His164, Met165, Glu166, and Gln189), and one alkyl interaction (Met165) with the M^{pro}.

The crystal structure of the SARS-CoV-2 M^{pro} contained three domains: Domain I (residues 8–101), Domain II (residues 102–184), and Domain III (residues 201–303). The residue Glu166 and catalytic dyad residues His41 and Cys145 participated in the dimerization of the protein. The substrate-binding site is located in a cleft between Domain I and II [31]. Domain II included the enzyme active site residues Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, and Glu166. His41, Cys145, Met165, and Glu166 of the M^{pro} were selected as key amino acid residues for binding to the ligand [32]. Fig. 1a shows that the docked structure of three peptides and N3 binds firmly at the active site of the M^{pro}. Peptide NDQF was linked to the catalytic dyads His41 and Cys145, forming carbon-hydrogen bonds and a conventional hydrogen bond. Furthermore, peptide NDQF interacted with amino acid residues Gly143, Cys145, His164, Met165, and Glu166 at the active site of the M^{pro}. Although the CDOCKER ENERGY value of NDQF was higher than N3, NDQF interacted with almost all the same amino acids as N3, including the residues Gln189, His164, Gly143, Glu166, Met165, and His41. NDQF firmly gripped the substrate-binding site of the SARS-CoV-2 M^{pro}. Peptides CQDCY and ASGCGDC had significantly lower docking scores. These peptides connected with the catalytic dyads His41 and Cys145 and the active sites Glu166, Met165, and His163, all of which formed multiple hydrogen bonds with the M^{pro}; this results in many hydrogen bonds that anchor the peptide to the ligand-binding cleft of the M^{pro}. These features make peptides NDQF, CQDCY, and ASGCGDC ideal candidates as the most suitable M^{pro} inhibitors.

3.3. Prediction of SARS-CoV-2 spike protein inhibitory activity of the peptides

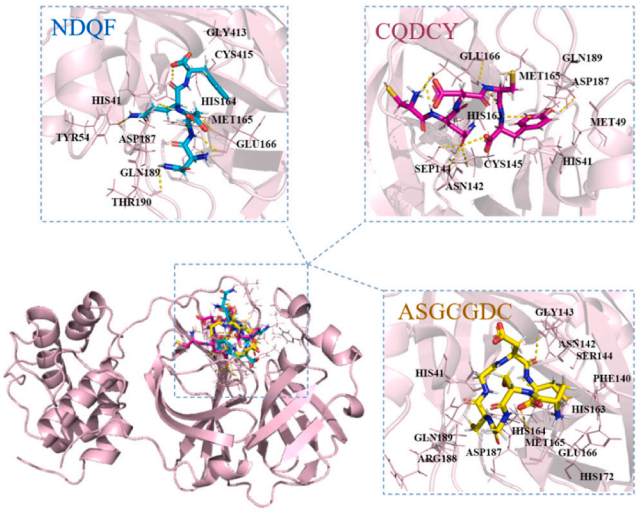
The spike protein is a key factor for virus cell attachment and entry into the host cell, and it can recognize and bind its host receptor, angiotensin-converting enzyme 2 (ACE2). Peptides bound to the spike RBD inhibit the interaction between the spike protein and ACE2, likely decreasing the rate of viral infection. The peptides NDQF, CQDCY, and ASGCGDC, which showed significant inhibition in previous docking with the M^{pro}, were used in the CDOCKER program for molecular docking with the spike RBD.

The SARS-CoV-2 spike RBD docking positions with NDQF, CQDCY, and ASGCGDC peptides are shown in Fig. 2 and Fig. 3. The results demonstrate that NDQF and ASGCGDC effectively combined with the spike RBD. The CDOCKER ENERGY values of NDQF and ASGCGDC were −73.219 and −85.715 kcal/mol, respectively (Table S2). The atoms O65, O66, O26, H18, O25, and O16 of NDQF formed six conventional hydrogen bonds with amino acid residues Gln493, Ser494, Tyr453, and Arg403 of the spike RBD. Furthermore, Ser494 (HB1), Arg403 (HD2), and Arg403 (HD1) of the spike RBD formed three carbon-hydrogen bonds with atoms O66 and O25 of NDQF at distances of 2.65 Å, 2.90 Å, and 2.89 Å. NDQF formed pi-cation and attractive charge interactions with Tyr453 (3.69 Å) and Arg403 (5.22 Å) of the spike RBD, respectively. Two salt bridges (Glu406) with NDQF were observed (Fig. 2b). ASGCGDC formed seven conventional hydrogen bonds and three carbon-hydrogen bonds with amino acid residues Glu484, Gln493, Ser494, Tyr453, Arg403, Gly496, and Tyr495. ASGCGDC also formed two salt bridges with amino acid residues Glu484 (OE2) and Arg403 (HH12) at 2.39 Å and 2.40 Å, respectively (Fig. 3b).

Based on previous literature, a total of 18 residues of the SARS-CoV-2 spike RBD (Lys417, Gly446, Tyr449, Tyr453, Leu455, Phe456, Ala475, Phe486, Ast487, Tyr489, Gln493, Tyr495, Gly496, Gln498, Thr500, Asn501, Gly502, and Tyr505) were found to be in contact with 20 residues of ACE2, which may exploit host infection [26]. One study showed that the Gln493 residue in the spike RBD forms a hydrogen bond with the Glu35 of ACE2, which helps the virus penetrate the host cell [26]. In this study, the peptides NDQF and ASGCGDC interacted with the amino acid residues Tyr453 and Gln493 of the spike RBD, and ASGCGDC also interacted with the amino acid residues Tyr495 and Gly496. In addition, the ProtParam server predicts that ASGCGDC has a half-life of 4.4 h in mammals. NDQF and ASGCGDC formed conventional hydrogen bonds with amino acid residue Gln493 of the spike RBD. These two peptides occupied the spike RBD amino acid residues that might affect binding to ACE2 and inhibit viral penetration of human cells. All these features make the NDQF and ASGCGDC peptides ideal candidates as the most suitable inhibitors against SARS-CoV-2.

3.4. Molecular dynamic simulation studies

MD simulations can show the trajectory of each atom over time in the molecular system [33]. MD simulation was performed to further study the binding mechanisms of the peptides-M^{pro} and peptides-spike RBD in a realistic environment and verify the accuracy of the docking prediction results. The RMSD fluctuation values of the NDQF-M^{pro} system ranged from 0.13 nm to 0.20 nm, and the RMSD fluctuation values of the ASGCGDC-M^{pro} system ranged from 0.19 nm to 0.28 nm, as shown in Fig. 4a. The RMSD of the NDQF-spike RBD and ASGCGDC-spike RBD systems reached equilibrium after 4 ns and fluctuated in the range of 0.12–0.20 nm and 0.27–0.40 nm, respectively (Fig. 4b). The RMSD fluctuation values were in a reasonable range; the results indicated that the peptides NDQF and ASGCGDC can stably bind to the SARS-COV-2 M^{pro} and spike RBD. The RMSF values of amino acid residues were calculated during MD simulations to analyze the fluctuations of amino acid residues of the SARS-COV-2 M^{pro} and spike RBD [32]. As shown in Fig. 4c and d, the amino acid fluctuation trends of the NDQF-M^{pro} and ASGCGDC-M^{pro} systems were similar, indicating that the formation



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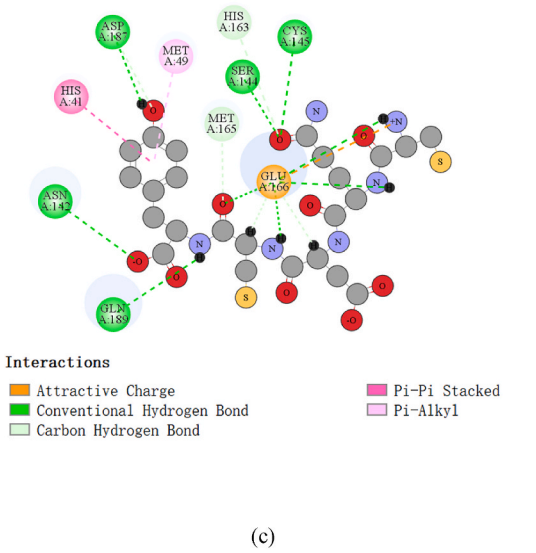

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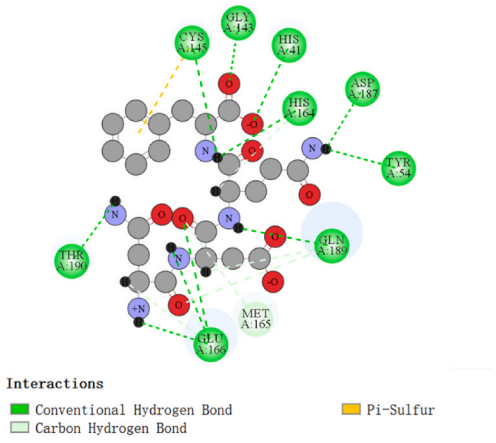

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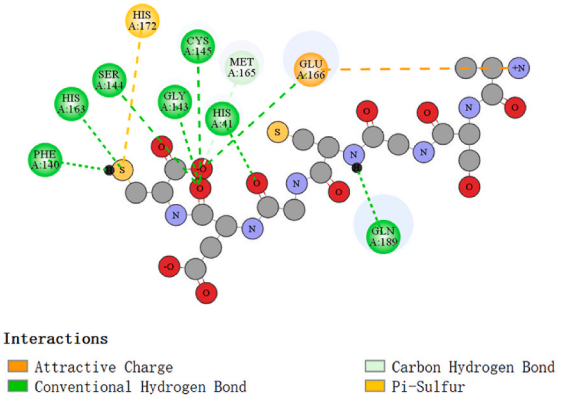

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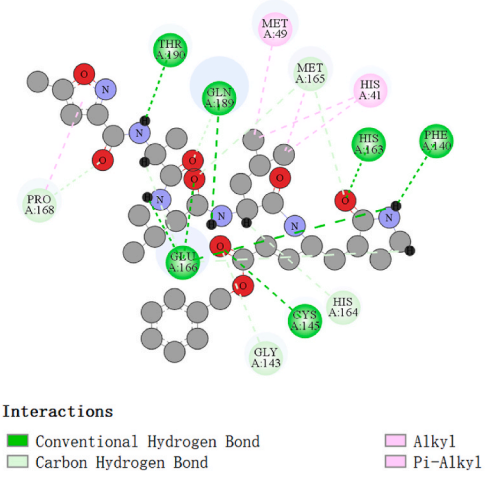
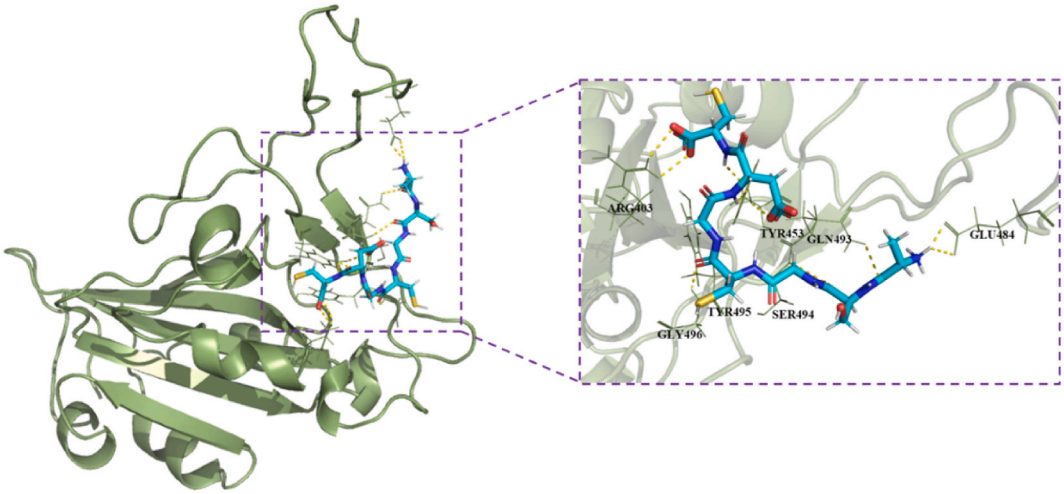


(e)

Fig. 1. Molecular interactions of the peptides NDQF, CQDCY, ASGCGDC, and N3 with M^{pro}. (a) The interaction of peptides NDQF, CQDCY and ASGCGDC with M^{pro} in 3D structure. (b) 2D diagram of the interaction of the peptide NDQF with M^{pro}. (c) 2D diagram of the interaction of the peptide CQDCY with M^{pro}. (d) 2D diagram of the interaction of the peptide ASGCGDC with M^{pro}. (e) 2D diagram of the interaction of the peptide N3 with M^{pro}.



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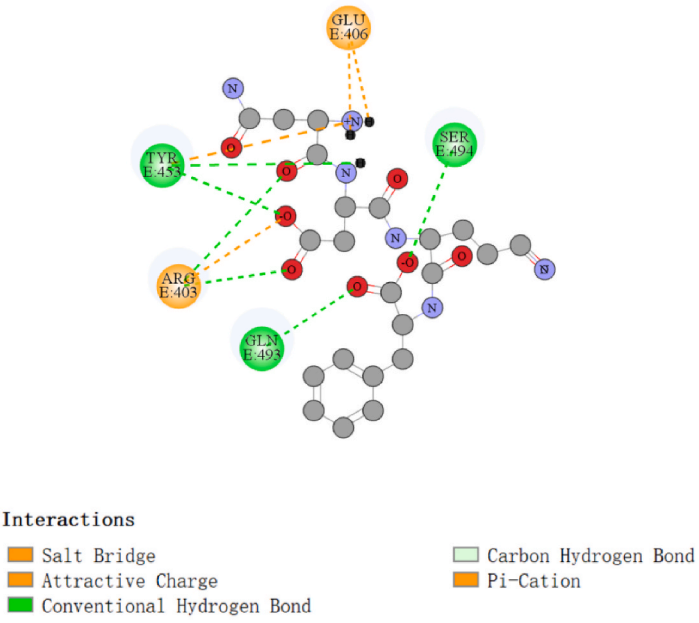
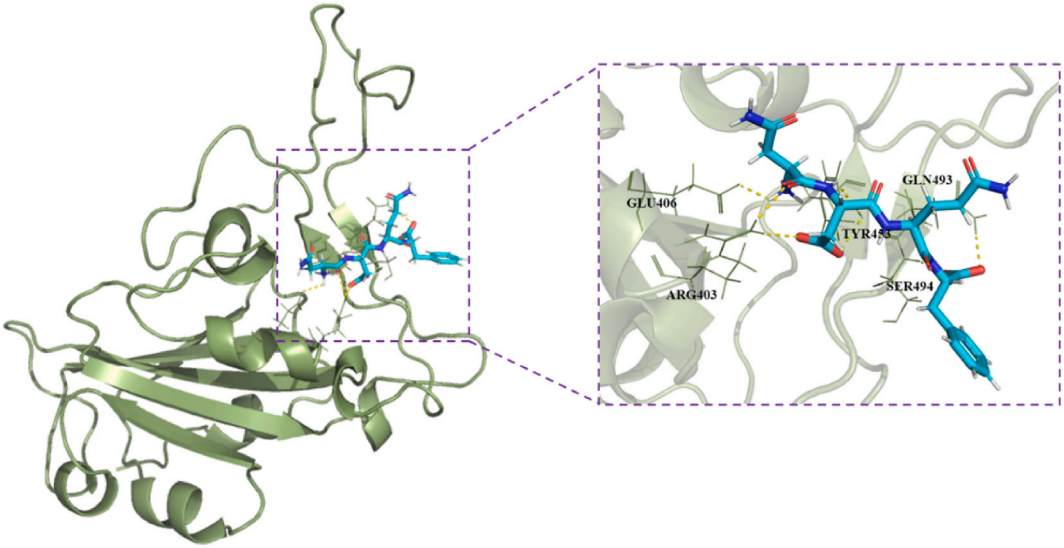


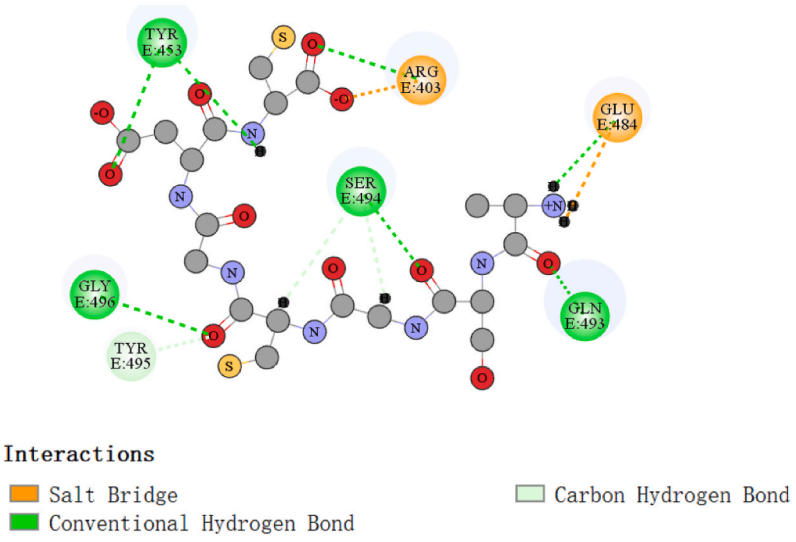
(b)

Fig. 2. The docking resulted for the interaction of peptide NDQF with spike RBD, interactions with residues are shown in different colors. (a) The interaction of peptide NDQF with spike RBD in 3D structure. (b) 2D diagram of the interaction of the peptide NDQF with spike RBD. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

process of the complexes was similar. The results revealed that the NDQF-M^{pro} and ASGCGDC-M^{pro} systems had significant amplitude fluctuations in the residues ranging from the residues 20–30, 40–60, 140–170, and 175–200 corresponding to S1', S2, S1, and S4 pockets, respectively (Fig. 4c) [34]. The fluctuations in the magnitude up to 0.2 nm were observed in the residues forming the binding pocket. These regions with high fluctuations were close to the ligand-binding sites and contributed to ligand interactions. In addition, the amino acid fluctuation trends of the NDQF-spike RBD and ASGCGDC-spike RBD systems were similar and ranged from 0.05 nm to 0.40 nm. Significant amplitude fluctuations were observed at amino acid residues 440–460 and 485–505. These results indicated that peptides NDQF and ASGCGDC interacted with the SARS-COV-2 spike RBD. The results of the MD were consistent with the molecular docking results and validated the accuracy of the predicted molecular docking results. The Rg analysis revealed that the four systems reached equilibrium in 10 ns (Fig. 4e and f). The changes in Rg values of the SARS-COV-2 M^{pro}-peptides complex and SARS-COV-2 spike-RBD-peptides complex were relatively stable with no



(a)



(b)

Fig. 3. The docking resulted for the interaction of peptide ASGCGDC with spike RBD, interactions with residues are shown in different colors. (a) The interaction of peptide ASGCGDC with spike RBD in 3D structure. (b) 2D diagram of the interaction of the peptide ASGCGDC with spike RBD. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

significant fluctuations. Moreover, the stability of the Rg values suggested that the systems were almost equally adopted by the compact protein structures [32]. Thus, the MD results confirmed the accuracy of molecular docking prediction, and the NDQF and ASGCGDC peptides may be potent inhibitory peptides of SARS-COV-2.

4. Conclusion

In this study, the *in silico* method effectively predicted inhibitors of SARS-CoV-2 from 10 nut proteins. The peptides with non-toxic, good biological activity, and water solubility were selected for molecular docking. Peptides NDQF and CQDCY from the peanut and peptide ASGCGDC from the almond bound to the active sites of the M^{pro} with a lower binding energy. Docking analysis suggested that NDQF and ASGCGDC interacted with almost all the same amino acids as N3, including residues His41, Glu166, Met165, Gln189, and Gly143. In addition, NDQF and ASGCGDC can effectively bind to the amino acid residues Tyr453 and Gln493 of the spike RBD. The MD further confirmed the molecular docking results, and peptides could bind stably to the SARS-COV-2 M^{pro} and spike RBD. Therefore, NDQF and ASGCGDC were effective dual-target antiviral peptides against the coronavirus. In summary, nut proteins could be effective as a nutritional supplement against viruses. However, future research in metabolomics and pharmacodynamic evaluation is needed to validate these results due to the limitations of molecular docking itself.

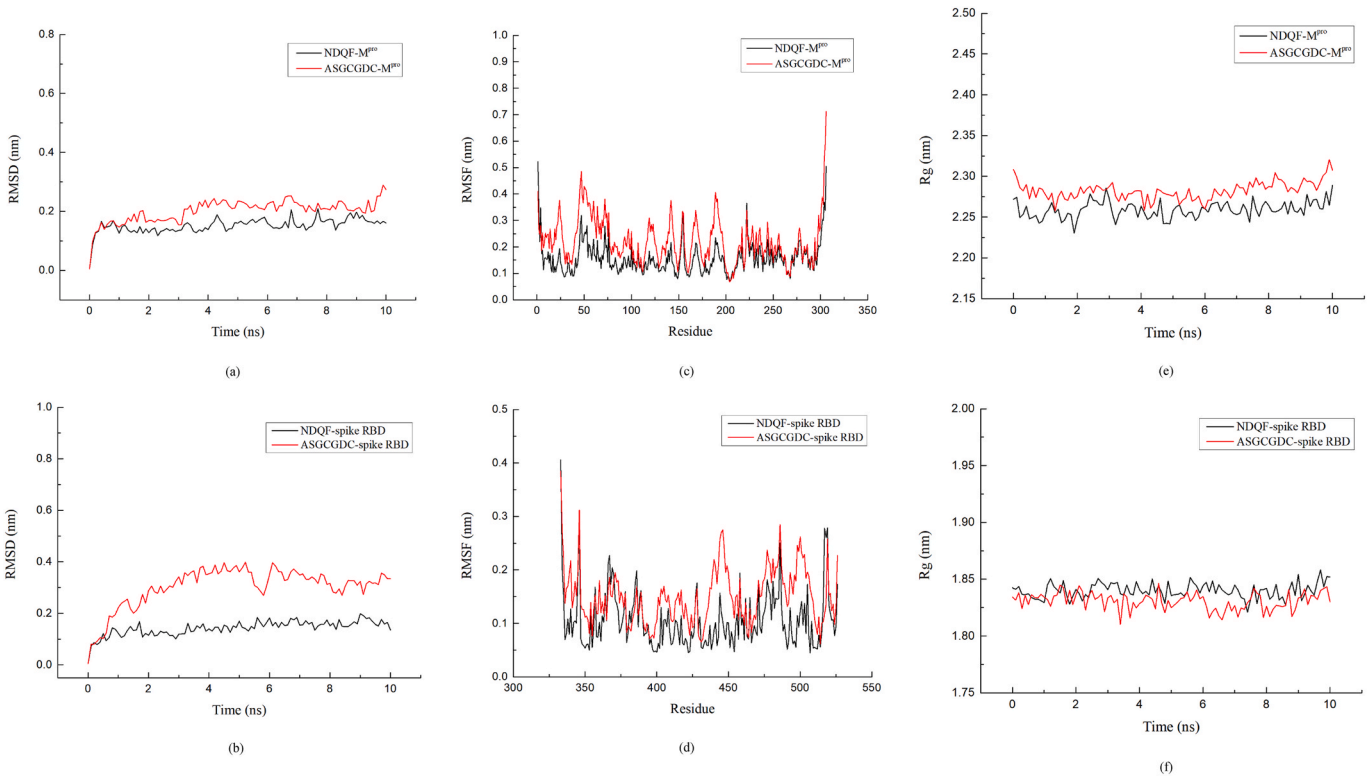


Fig. 4. The Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation (RMSF) and radius of gyration (Rg) curves of the protein backbone (Cα) atoms during MD-simulation. RSMD (a), RMSF (c), and Rg (e) of SARS-COV-2 M^{pro} in complex with peptides NDQF and ASGCGDC. RSMD (b), RMSF (d), and Rg (f) of SARS-COV-2 spike RBD in complex with peptides NDQF and ASGCGDC.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.compbiomed.2021.104937.

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