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Original Article

In silico Prediction of Anti–SARS-CoV-2 Effect of Dermaseptin Peptides from Amphibian Origin

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HIGHLIGHTS

- Three numbers of antiviral dermaseptin peptides from APD database were in silico evaluated against SARS-CoV-2 spike protein.
- The antiviral dermaseptin -S9 peptide showed the highest binding affinity towards the SARS-CoV-2 spike protein macromolecule.
- The hydrophobic property of the distributed amino acids of the derrmaseptin-9 molecule might be related to the binding affinity.

ABSTRACT

The novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has now been declared as a global pandemic by the World Health Organization (WHO). Several drug molecules have been proposed that can be used against the virus. As an alternative to effective drug molecules, the antiviral peptides have the potential for effective application to control the infectious disease. In this work, the anti- SARS-CoV-2 effect of dermaseptin peptide molecules produced by the skin of the frog was evaluated by using the computational method. Three numbers of antiviral dermaseptin peptides were obtained by searching the antimicrobial peptide database (APD). First, the structure prediction of peptides was done by Pep Fold 2.0 server followed by structure validation by PROCHECK program. Then, the protein-peptide docking simulations were performed using the COVID-19 docking server. The peptides' binding affinity with the SARS-CoV-2 spike protein macromolecule was evaluated along with eight negative control peptides and human angiotensin converting enzymes 2 (ACE2). The protein-peptide docking and interaction analysis resulted in finding that dermaseptin-S9 peptide molecule was the most efficient molecule among the selected peptides with a binding energy of -331.54 KJ/mole. Hence, as a follow-up study, the dermaseptin-S9 peptide molecule can be further designed to enhance its specificity and binding affinity for its better use against the SARS-CoV-2 disease.

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Introduction

The amphibian skin glands, considered to contain about 500 types of antimicrobial peptides, have been described by previous researches (Rinaldi, 2002; Neiva et al., 2013). Among them, the dermaseptin family of

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antimicrobial peptides are important and usually produced by the skin of tree frogs that belong to *Phyllomedusa* (Mor and Nicolas, 1994; Mor and Nicolas, 1994; Krugliak et al., 2000; Amiche et al., 2008; Nicolas and El Amri, 2009). Considering the sequence feature, the dermaseptins are 20-35 amino acid long, linear and cationic peptides, and also capable of adopting the amphipathic α-helical structure in the membrane environment (Dathe and Wieprecht, 1999). This particular structure is considered as the essential feature of the peptide for destabilizing the lipid membrane, thereby exhibiting its lytic activity (Epand and Vogel, 1999; Shai, 1999; Feder et al., 2000; Tossi et al., 2000). During the last few years, the dermaseptins have been proved to be similar to antibiotics used for a broad spectrum of action. The antimicrobial activity has been observed against bacteria (Rotem et al., 2006; Rivas et al., 2009; Zaïri et al., 2014), protozoa (Krugliak et al., 2000; Matejuk et al., 2010) and filamentous fungi (De Lucca et al., 1998; De Lucca and Walsh, 1999; Bergaoui et al., 2013). Concerning viruses, dermaseptins show enhanced potential antiviral effect against different viruses such as HIV anti-herpetic activity (HSV type 2) in its mutated from compared to wild- type peptide. Also, insertion of the dermaseptin in the viral envelope disrupts the virus assembly (Aouni et al., 2002; Da Mata et al., 2017). Similarly, it has been reported that the dermaseptin has proven its effectiveness against the dengue, vaccinia, and influenza virus (de Souza Cardoso et al., 2013; Holthausen et al., 2017; Velavan and Meyer, 2020). Recently, the World Health Organization (WHO) has declared the novel coronavirus disease of 2019 as a global emergency and a pandemic for spreading throughout the world (Elnagdy and AlKhazindar, 2020; Mehra et al., 2020; Satpathy, 2020). As per the recent report, several peptides can be utilized as the antiviral therapeutic measure against the deadliest disease (Kam et al., 2009; Mustafa et al., 2019). Recently, the spike glycoprotein of the novel coronavirus is considered as a major target for the design of anti-SARS-CoV-2 drugs. The spike protein is basically responsible for initial binding of the coronaviruses to lung cells and subsequently activated by the proteolytic cleavage. The spike glycoprotein remains on the surface of the virus and having the physical shape of the "spike" giving it the appearance of a crown under the electron microscope, so-called as "corona" virus (Shen et al., 2014; Robson, 2020). Many researchers have studied the mechanism and function for spike glycoprotein with the human ACE2 protein. The protein binds to the cellular receptor such as ACE2 and triggers the cellular entry of the virus (Lan et al., 2020; Letko et al., 2020, Walls et al., 2020).

The objective of the present study is to use the computational docking approach to discover the dermaseptin types of antimicrobial peptides as the effective anti- SARS-CoV-2 agent.

Materials and Methods

Retrieval and structure prediction dermaseptin peptides

The dermaseptin peptides, having antiviral nature were retrieved from Antimicrobial peptide database. The antimicrobial peptide database (APD) is an important repository for the peptides responsible for antimicrobial activities and contains 3250 antimicrobial peptides. This database is freely available at http://aps.unmc.edu/AP/main.php and provides the facility for the keyword search. The database was searched for keyword dermaseptin in the name menu and anti-virus in the activity menu resulted in 3 peptides of this type responsible for antiviral activity. Then the three-dimensional structure was predicted by PEP-FOLD 2.0 server available at https://mobyle.rpbs.univ-paris-diderot.fr/cgi-bin/portal.py#forms::PEP-FOLD. Pep fold server predicts the 3D structures of the peptide from the amino acid sequences. It considers four residues to describe the conformations, and finally completed 3D structure is predicted by using a greedy algorithm and a coarse-grained force field. The Pep fold 2.0 has limitation up to 9-36 amino acids (Maupetit et al., 2009, Kong et al., 2020). The predicted 3D structure was further validated by predicting the Ramachandran plot for the proteins by using the PROCHECK tool available at https://servicesn.mbi.ucla.edu/PROCHECK/.

Docking study of peptides with SARS- CoV-2 spike glycoprotein

To check the antiviral effect of these peptides on SARS-CoV-2 spike glycoprotein, protein-peptide docking was performed. The Spike trimer (open) protein 3D structure of the virus was chosen as the receptor molecule, and the predicted peptide structures were used as the partner protein. The docking process was performed by the on-line server available at https://ncov.schanglab.org.cn/. The online docking resources provide a free and interactive platform for predicting potential peptide and can be used to discover therapeutics molecules against the COVID-19 (Sukhwal and Sowdhamini, 2013). Further, the docked complex was analyzed for the different features for protein protein-interaction such as total stabilizing energy, number of interface residues, number of short contacts, number of hydrophobic

interactions, and number of van der Waals pairs. For these feature analysis purpose, PPCheck server was used and this is freely available at http://caps.ncbs.res.in/ppcheck/methodology.html. PPCheck is an important webserver frequently used to measure the interactions between any two given proteins or chains, whenever fed as a single PDB file (Ou et al., 2017). Further, the amino acid distribution features and hydropathy profile were analyzed by using the Pepinfo module of EMBOSS tool (https://www.ebi.ac.uk/Tools/seqstats/emboss_pepinfo/) and PROTSCALE server (https://web.expasy.org/protscale/).

Moreover, to validate the binding property of the dermaseptin peptides with the Spike glycoprotein of SARS-CoV-2, eight of non- microbial alpha helical peptides from the PDB database were chosen as the negative control followed by docking analysis. In addition to this, the human angiotensin converting enzymes 2 (ACE2) protein structure was retrieved from the PDB and docking was performed with the spike protein. For all the docking purpose, COVID-19 docking server was used. The hydrophobic interaction details of the spike- ACE2 protein complex and dermaseptin-Spike glycoprotein complexes were computed by Protein Interactions Calculator (PIC) server available at http://pic.mbu.iisc.ernet.in/. The server is freely available to compute the intraprotein interaction and protein-protein interaction details.

Results and Discussion

Three antiviral peptides were obtained from the antimicrobial database search that is having origin from the frogs of genus Phyllomedusa (Table 1). All three peptide sequences were fed to PEP-FOLD 2.0 server for 3D structure prediction purposes. Further, the model was evaluated for reliability by computing the Ramachandran plot (Fig. 1).

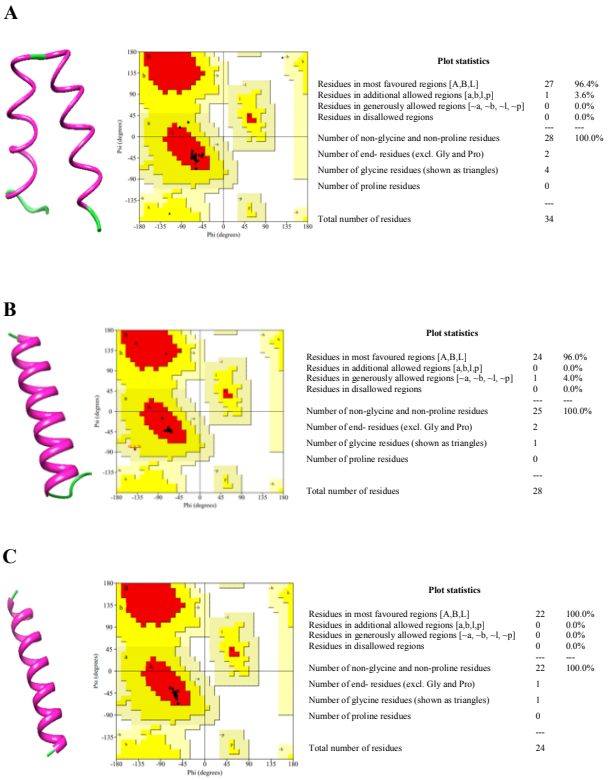

Figure 1. Predicted structure of the peptide along with the Ramachandran plot. (A) Dermaseptin-S1, (B) dermaseptin-S4, (C) dermaseptin-S9.

Further docking was performed by COVID-19 docking server. The COVID-19 Docking Server provides a GUI web interface and facilitates the user for molecular visualization and the results download. The server contains 27 protein target structures essential in the virus life cycle that can be used for docking purposes. The docking process involves multistage fast Fourier transform (FFT)-based method global docking and site-specific docking. The docking score and binding pose have been shown in Fig. 2.

Table 1. Anti-viral dermaseptin peptides obtained from the APD database search

S.N	APD ID	Name of the protein	Sequence length	Sequence	Origin
1	AP00157	dermaseptin-S1	34	ALWKTMLKKLGTMALHAG KAALGAAADTISQGTQ	*Phyllomedusa sauvagii*
2	AP00160	dermaseptin-S4	28	ALWMTLLKKVLKAAAKAALNAV LVGANA	*Phyllomedusa sauvagii*
3	AP00764	dermaseptin-S9	24	GLRSKIWLWVLLMIWQESNKFKKM	*Phyllomedusa sauvagii*

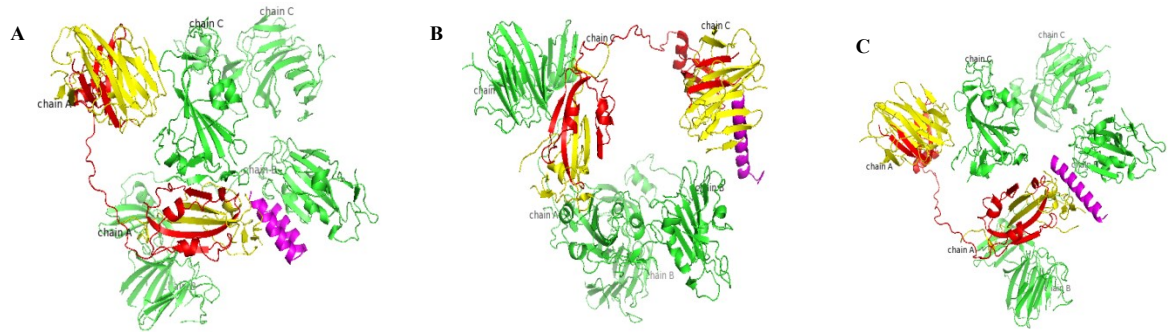

Figure 2. Docking poses and binding pattern of three peptides with specific chains of spike protein trimer in the open position: binding chains are shown in yellow, peptide is shown in pink. Docking energy for (A) dermaseptin-S1: -242.62 kJ/mole, (B) dermaseptin-S4: -295.42 kJ/mole, (C) dermaseptin-S9: -331.54 kJ/mole.

The predicted models, observed to be reliable as more than 95% of the residues are in the favourable position in the Ramachandran plot. The dermaseptin -S1 consists of 2 helix, 1 turn and 29 numbers of hydrogen bonds. The structure of dermaseptin-S4 consists of one helix, 2 turns, and 20 numbers of hydrogen bonds. Similarly, the dermaseptin-S9 consists of only 1 helix and without any turns and contains 20 hydrogen bonds. Considering that the structure of the spike glycoprotein of the SARS-CoV-2 consists of 3 chains that are in open state, it has been chosen for the present docking purpose. After docking the binding energy and position were obtained (Fig. 2).

The COVID -19 docking server contains the open state trimeric structure of the SARS-CoV-2 spike protein (derived from the PDB ID 6VYB) and a facility for peptide antibody docking. The docking process is performed using the CoDockPP program, which uses a fast fourier transform (FFT) based method for screening and scoring purposes. After the docking process is over, the best affinity ligand molecules are evaluated by the root mean square deviations (RMSD) with a cut-off distance of 3.0 Å 2.0 Å in the case of global docking and site-specific docking, respectively (Kong et al., 2019).

The docking process was further validated by taking negative control of some non- antimicrobial alpha-helical peptide molecules from the PDB (Table 2).

From the docking score, the binding affinity of the selected peptides were observed as low, in comparison to the dermaseptin antimicrobial peptide, except the dermaseptin S-1 peptide molecule. The dermaseptin-spike protein docked complex structures were further analyzed by PPCheck tool and the interaction of the dermaseptin peptide was computed for each chain of the receptor protein. Overall interaction resulted in the maximum interaction that occurs with the dermaseptin -S9 peptide with the A chain of the spike protein of SARS-CoV-2 virus (Table 3).

Table 2. Docking details of the selected alpha-helical non- antimicrobial peptide and docking with Spike protein

PDB ID	Name	Length	Sequence	Docking score (kJ/mole)	Remark
1 AL1	Crystal structure of alpha1: Implications for protein design	12	ELLKKLLEE LKG	-219.13	Synthetic amphiphilic alpha helix with a ridge of Leu residues along one helical face
1 DJF	NMR structure of a model hydrophilic amphipathic helical basic peptide	15	QAPAYKKA AKKLAES	-200.78	Synthetic peptide under SDS environment
1 DNG	NMR structure of a model hydrophilic amphipathic helical acidic peptide	15	QAPAYEEAA EELAKS	-213.55	Human Platelet Factor 4, Segment 59-73
1 KZ5	Solution structure of the third helix of Antennapedia Homeodomain derivatives	12	RQIKIWFRK WKK	-262.89	Antennapedia protein
1O53	Solution structure of the N-terminal membrane anchor of *E. Coli* enzyme Iia (Glucose)	15	GLFDKLKSL VSDDKK	-234.88	PTS system, glucose-specific IIA component
1RG4	Sp-B C-terminal peptide in organic solvent (Hfip)	16	GRMLPQLVC RLVLRCS	-272.61	Pulmonary surfactant-associated protein B
2FXZ	Solution structure of 97-109 segment of *Staphylococcal* nuclease	13	KMVNEALV RQGLA	-240.58	97-109 Segment of staphylococcal nuclease
2JMY	Solution structure of Cm15 In Dpc micelles	15	KWKLFKKIG AVLKVL	-255.28	Synthetic construct

Table 3. Interaction details of the peptides with spike glycoproteins

Docked complex	Chain	Total stabilizing energy (kJ/mole)	Interface residues	No of short contacts	No of hydrophobic interactions	No of van der Waals pairs
Dermaseptin-S1 complex with SARS-CoV-2 spike glycoprotein	A	165.88	Total number = 18 10LEU 11GLY 12THR 13MET 14ALA A449TYR A452LEU A453TYR A455LEU A456PHE A490PHE A491PRO A492LEU A493GLN A494SER A495TYR A496GLY A498GLN	22	0	1387
	B	-0.19	Total number = 4 19LYS B405ASP B503VAL B504GLY	0	0	37
	C	No overall interaction	No overall interaction	No overall interaction	No overall interaction	No overall interaction
Dermaseptin-S4 complex with SARS-CoV-2 spike glycoprotein	A	No overall interaction	No overall interaction	No overall interaction	No overall interaction	No overall interaction
	B	-0.42	Total number = 5 18ALA 19LEU B330PRO B331ASN B333THR	0	0	74
	C	44.43	Total number = 20 10VAL 11LEU 12LYS 13AAL 14ALA C121ASN C124THR C125ASN C126VAL C170TYR C171VAL C172SER C203ILE C224GLU C225PRO C226LEU C227VAL C228ASP C229LEU C41LYS	6	3	1014
Dermaseptin-S9 complex with SARS-CoV-2 spike glycoprotein	A	427.25	Total number = 36 10VAL 11LEU 12LEU 13MET 14ILE 15TRP 16GLN 17GLU 18SER 19ASN A402ILE A403ARG A417LYS A418ILE A448ASN A449TYR A450ASN A451TYR A452LEU A453TYR A455LEU A456PHE A490PHE A491PRO A492LEU A493GLN A494SER A495TYR A496GLY A497PHE A498GLN A500THR A501ASN A505TYR A506GLN A507PRO	94	3	4450
	B	-0.18	Total number = 7 10VAL 13MET B408ARG B411ALA B412PRO B413GLY B414GLN	0	0	55
	C	No overall interaction	No overall interaction	No overall interaction	No overall interaction	No overall interaction

The interaction parameters are also in support of docking energy obtained (Fig. 2). Further, the amino acid profile of the three peptides along with their hydropathy plot indicated about the maximum occurrence of aromatic residues that are available in case of the dermaseptin -S9 peptide. Details of the amino acid and hydropathy profiling of the peptides have been shown in Fig. 3.

Domain prediction of the spike protein was performed by Simple modular architecture research tool (SMART) server (http://smart.embl-heidelberg.de/). Three numbers of Pfam: Spike_rec_bind domains were observed. The domain is also known as Beta coronavirus spike glycoprotein S1, receptor binding, representing the receptor binding point and available in the protein as Chain A: 235-410, Chain B: 228- 391, Chain C: 235-405.

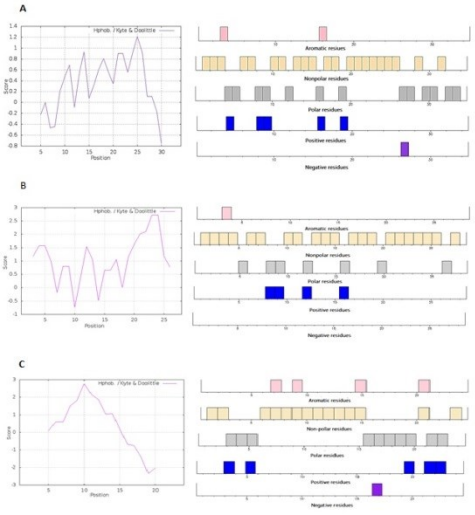

Figure 3. The amino acid distribution and hydropathy plot of the selected peptides. (A) Dermaseptin-S1, (B) dermaseptin-S4, (C) dermaseptin-S9.

Table 4. Specific hydrophobic interaction (within 5 Angstrom)

Spike	ACE2	Spike	Dermaseptin -S9	Spike	Dermaseptin -S4	Spike	Dermaseptin -S1
347 PHE B	**156 LEU**	411 ALA B	9 ILE	92 PHE C	1 ALA	380 TYR B	3 TRP
348 ALA B	**156 LEU**	449 TYR A	14 TRP	104 TRP C	1 ALA	418 ILE A	2 LEU
348 ALA B	**252 TYR**	449 TYR A	15 TRP	104 TRP C	3 TRP	453 TYR A	2 LEU
352 ALA B	**158 TYR**	452 LEU A	15 LEU	104 ILE C	4 MET	453 TYR A	6 MET
352 ALA B	**255 TYR**	453 TYR A	11 LEU	119 VAL C	3 TRP	455 LEU A	29 ILE
491 PRO B	135 PRO	449 TYR A	8 LEU	126 VAL C	3 TRP	455 LEU A	6 MET
491 PRO B	163 TRP	455 LEU A	12 TRP	126 VAL C	6 LEU	456 PHE A	29 ILE
		490 PHE A	15 LEU	126 VAL C	7 LEU	495 TYR A	2 LEU
		495 TYR A	11 TRP	128 ILE C	3 TRP		
		495 TYR A	7 LEU	128 ILE C	7 LEU		
		495 TYR A	8 LEU	170 TYR C	10 VAL		
		497 PHE A	11 LEU	170 TYR C	7 LEU		
		497 PHE A	7 TRP	192 PHE C	1 ALA		
		505 TYR A	7 TRP	192 PHE C	4 MET		
				194 PHE C	3 TRP		
				194 PHE C	4 MET		
				203 ILE C	4 TRP		
				203 ILE C	3 MET		
				203 ILE C	7 LEU		
				226 LEU C	11 LEU		
				226 LEU C	4 MET		
				227 VAL C	11 LEU		
				227 VAL C	3 TRP		
				230 VAL C	7 LEU		

Based on the docking and amino acid interaction analysis, it was observed that the dermaseptin -S9 peptide showed the maximum binding affinity (-331.54 KJ/mole) to the A- chain of the spike glycoprotein. The maximum number of interactions was also predicted along with stabilization energy at the highest 427.25 KJ/mole among the selected three peptides. The major dominant form of the interaction was obtained as the Vander walls interaction. Similarly, the hydropathic index plot showed a consistent increase in the hydrophobicity in residues in the 5-12 position present in the dermaseptin -S9 peptide (Fig. 3). Further comparative analysis was made about hydrophobic interaction between spike-ACE2 and spike–dermaseptin complex computed from the Protein Interactions Calculator (PIC) server (Table 4).

The amino acids of B chain, including 347 Phe, 348 Ala, 352 Ala, and 491 Pro of the spike glycoprotein actively interacts with the ACE2 protein amino acids, including 156 Leu, 252 Tyr, 158 Tyr, 255 Tyr, 135 Pro, and 163 Trp, respectively, out of which the 347 Phe, 348 Ala, 352 Ala of the spike protein is covered under the RBD domain (bold in the table 4), hence important for the viral entry activity to the host cell as studied by many researchers (Chen et al., 2020; Muhseen et al., 2020). However, in the current study, none of the dermaseptin peptides interacts with the RBD domain of the spike protein (Table 4) and shares the binding area of spike-ACE2 (Fig. 4).

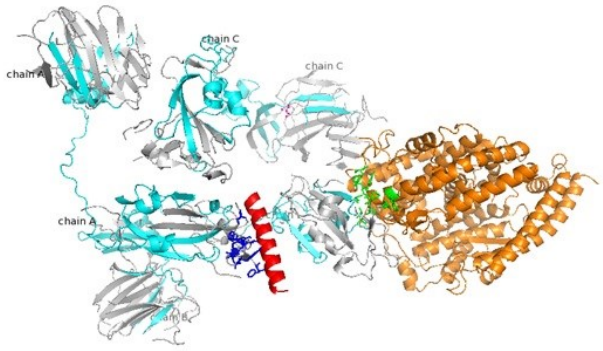

Figure 4. Interaction details about the dermaseptin-S9 (red); docking score = - 331.54 kJ/mole with the ACE2 (yellow); docking score was -267.86 kJ/mole with the spike trimeric glycoprotein (grey), with the RBD (cyan colour), interacting hydrophobic amino acids, with dermaseptin -S9 (blue) and interaction with ACE2 (green).

In the case of dermaseptin -S4, the highest numbers of the hydrophobic interactions were obtained with chain C, followed by dermaseptin -S9 with the chain A and dermaseptin -S1 with the chain A. Also, the maximum number of aromatic amino acid residues was observed in dermaseptin -S9 while comparing the amino acid distribution profile for the three peptides. Considering the overall features, such as docking energy, the number of interface residue interaction, amino acid profiling, and hydrophobic interaction study, the dermaseptin-S9 peptide can be considered as the effective molecule.

Chen et al. have discussed the effects of hydrophobicity on antimicrobial peptides' mechanism of action and it has been established that higher hydrophobicity feature directly correlated with stronger haemolytic activity (Chen et al., 2007). In addition, the presence of more aromatic amino acids might be related to the stability and possible role in the interaction with the receptor molecule. The SARS-CoV-2 spike glycoprotein is a trimeric structural protein and contains two functional subunits, N-terminal S1 subunit and a C-terminal S2 subunit. A 200 amino-acid-long within the S1 subunit of the spike protein mainly involved in its interaction with the receptor of human facilitating the virus's entry process (Castel et al., 2011; Zhou et al., 2020).The spike glycoprotein facilitates the viral entry by binding to the host cell surface receptor protein known as angiotensin-converting enzyme-2 (ACE2) (Castel et al., 2011; Xia et al., 2019; Hoffmann et al., 2020). More specifically, the receptor-binding domain (RBD) of the SARS-CoV-2 spike glycoprotein binds to the conserved extracellular peptidase domain of angiotensin I converting enzyme 2 (ACE2) (Lam et al., 2020; Shang et al., 2020).

In this context, targeting the enzymes by peptide-based drugs may be a better choice due to their higher efficiency and lower toxicity, and little side effects compared to conventional medicines. The spike protein of the SARS-CoV-2 can be used as a potential target of these antiviral peptides (AVPs) that have proven its efficiency by inhibiting viral infection through stopping the viral entry (Mujtaba et al., 2006). Barah et al. described different peptide design strategies and identified key amino acid residues that were responsible for the binding to the viral spike receptor-binding domain (Barh et al., 2020). Mahendran et al. reviewed the potential use of AVPs against COVID-19 based on the documented evidence against SARS-CoV-2, SARS-CoV, MERS-CoV, SARS-related CoVs, and other respiratory viruses. Many chimeric peptides also have been designed to target the spike glycoprotein of the virus (Mahendran et al., 2020). The molecular docking and simulation study of dermaseptin -S4 and dermaseptin -S9 by Fakih has shown that the dermaseptin -S9 having the maximum affinity towards the SARS-CoV-2 spike protein as the receptor, agrees with our result (Fakih, 2020). Recently, Jaiswal et al. described the peptide-based inhibitor design for targeting spike glycoprotein based on the binding site of the ACE2 protein (Jaiswal and Kumar, 2020). In the current study, it can be predicted that the dermaseptin -S9 could be the best useful antimicrobial peptide against the SARS-CoV-2 virus, as it shows a higher affinity towards the SARS-CoV-2 spike glycoprotein in comparison to the ACE2 and other non-microbial helical peptides. But the extent of interaction is to be further analyzed by the molecular dynamics simulation.

Conclusion

Because of the current increasing SARS-CoV-2 infection cases, there is a great demand for the novel antimicrobial peptide. The dermaseptin peptides from the amphibian origin have proven its effectiveness towards the virus and other microbes. Hence, in this study, three numbers of antiviral dermaseptin peptides were obtained by APD database search. The further 3D structure was predicted for the peptide and reliability of the structure was checked by using the Ramachandran plot. Further, the binding affinity of these peptides was evaluated by protein-protein docking methods. This protein-peptide docking analysis proved the antimicrobial peptide dermaseptin-S9 that can be effectively used as an inhibitor of SARS-CoV-2 spike glycoprotein. This is confirmed with the strong binding affinity (-331.54 KJ/mole) towards the target SARS-CoV-2 spike glycoprotein molecule compared to human ACE2 and other non-antimicrobial peptides. Despite possessing a strong binding affinity, none of the dermaseptin peptides show the interaction with the RBD of spike protein. In the future work, in-silico design in the dermaseptin -S9 can be performed to improve its binding coverage towards the RBD domain with maintaining the binding affinity; hence, it can be effectively used as inhibitor against SARS-CoV-2. However, the result presented in this paper is an in-silico report and should be further validated by the experimental research.

Ethical Statement

This article does not contain any studies involving animals or human participants performed by any of the authors.

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Competing Interests

The authors declared that there is no conflict of interest.

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Authors' Contributions

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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