pISSN 2302-1616, eISSN 2580-2909
Vol 11, No. 2, December 2023, pp. 249-257
Available online http://journal.uin-alauddin.ac.id/index.php/biogenesis
DOI https://doi.org/10.24252/bio.v11i2.41302

Understanding the structural foundation of mucroporin peptide as a potential anti-COVID-19 candidate: Computational methods

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ABSTRACT. Antimicrobial peptides are gaining attention due to their potential in treating various diseases. Among them, the antimicrobial peptide mucroporin, originated from scorpion venom (*Lychas mucronatus*), has demonstrated the ability to inhibit SARS-CoV. The objective of this research is to utilize computational methods for an *in silico* analysis aimed at identifying, assessing, and examining the affinity and molecular interactions between mucroporin, an antimicrobial peptide, and the SARS-CoV-2 spike protein. This will be achieved through a peptide-protein-based molecular docking approach. Initially, the sequence of mucroporin antimicrobial peptide was modeled using the PEP-FOLD 3.5 server. The most favorable conformation resulting from the modeling was then selected for interaction studies with the SARS-CoV-2 spike protein using PatchDock software. The outcomes of the molecular docking simulation were subsequently analyzed using BIOVIA Discovery Studio 2020 software. The outcomes from the peptide-protein molecular docking experiments revealed that Mucroporin-M1 and Mucroporin-S1, among the antimicrobial peptide molecules tested, displayed the most notable affinity for the SARS-CoV-2 spike protein, with atomic contact energy (ACE) values of −1144.41 kJ/mol and −400.37 kJ/mol respectively. Consequently, it is anticipated that this antimicrobial peptide shows potential as a contender for blocking the SARS-CoV-2 spike protein, potentially contributing to peptide-based treatments for COVID-19.

Keywords: antimicrobial peptide mucroporin; infectious disease COVID-19; *in silico* approach; peptide-protein based molecular docking; SARS-COV-2 spike protein

Article History: Received 31 January 2023; Received in revised form 18 March 2023; Accepted 18 May 2023; Available online 30 December 2023.
How to Cite This Article: Fakih TM, Ramadhan DSF, Rizkita AD. 2023 Understanding the structural foundation of mucroporin peptide as a potential anti-COVID-19 candidate: Computational methods. *Biogenesis: Jurnal Ilmiah Biologi*. vol 11(2): 249–257. doi: https://doi.org/10.24252/bio.v11i2.41302.

INTRODUCTION

The World Health Organization (WHO) has formally announced the emergence of the novel coronavirus disease (COVID-19) as a global health crisis and a pandemic (Czabanowska and Kuhlmann, 2021). This extremely transmissible illness is attributed to the SARS-CoV-2 virus and is marked by symptoms such as fever, cough, pneumonia, queasiness, and weariness. By March 18, 2020, SARS-CoV-2 had swiftly disseminated to close to 24 nations across the globe, leading to an excess of 190,000 officially reported cases (Chauhan, 2020). The rapid global spread of COVID-19 has prompted unprecedented efforts from governments, healthcare professionals, and researchers worldwide to curb the transmission of the virus and find effective treatments. This pandemic has brought about significant disruptions to daily life and has highlighted the importance of international cooperation in addressing public health crises (Chilamakuri and Agarwal, 2021).

From an epidemiological perspective, it is thought that the SARS-CoV-2 virus likely originated in a seafood market situated in Wuhan City, within Hubei Province, China. However, the exact source of the initial transmission to humans remains unknown (Krishnan *et al*., 2021). At present, NCBI GenBank holds a collection of over 100 complete genome sequences from various countries, numbering over 10 in total. The genetic variation in the genome is minimal, at less than 1%. In an attempt to comprehend the origins and evolutionary path of this virus, scientists have also identified parallels with other viruses belonging to the Coronaviridae family, this encompasses the SARS-CoV virus, which was accountable for the SARS outbreak that occurred between 2002 until 2003.

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Although the SARS-CoV-2 virus and the SARS-CoV virus exhibit differing biological attributes, they exhibit noteworthy genetic resemblances (Jacobsen and Klein, 2021; Tun *et al*., 2021).

SARS-CoV-2 bears a significant genetic similarity to SARS-CoV, enabling the application of the known protein structure to swiftly construct a framework for drug exploration concerning this novel coronavirus (Naqvi *et al*., 2020). Traditional drug development strategies may extend over several years; however, currently, available in silico techniques facilitate the quest for potential drug candidates for SARS-CoV-2, with a specific focus on the spike protein inherent to SARS-CoV-2 (Fakih *et al*., 2021; Ramadhan *et al*., 2020). In silico methodologies empower scientists to conduct computational assessments of protein configurations and execute extensive screening of compounds with promising medicinal properties (Emirik, 2022; Manhas *et al*., 2023). This approach has the potential to expedite the identification of drug candidates and the development of therapies targeting SARS-CoV-2.

The spike protein of SARS-CoV-2 adheres to the host cell membrane through interactions facilitated by receptors, allowing it to penetrate the host cell. Earlier computational studies have shown that SARS-CoV-2 employs a mechanism similar to SARS-CoV and displays a strong binding affinity for the ACE-2 (Angiotensin Converting Enzyme 2) receptor (Medina-Barandica *et al*., 2023). Additionally, there is a structural resemblance between the spike proteins of SARS-CoV-2 and SARS-CoV, characterized by a conservation rate of merely 73%, primarily concentrated around the region where interaction occurs with proteins on the host cell (Balkrishna *et al*., 2021). This indicates that, despite genetic disparities, particularly in the region involved in interactions with host cells, the fundamental framework of the spike protein remains relatively alike between SARS-CoV-2 and SARS-CoV. This finding lays a robust foundation for the exploration and creation of therapies designed to disrupt the interplay between the spike protein and host cell receptors, consequently limiting the virus's ability to infiltrate and infect human host cells (Schmidt *et al*., 2022).

Animal toxins, among various natural sources, have demonstrated significant potential in the field of drug development. One such example is mucroporin, extracted from the venom of the scorpion *Lychas mucronatus* (Li *et al*., 2011; Zhao *et al*., 2012). Mucroporin is an antimicrobial peptide (PAM) that exhibits activity against SARS-CoV. This study aims to investigate the molecular interactions between Mucroporin and the spike protein of SARS-CoV-2. Utilizing in silico methodologies, researchers can identify, assess, and scrutinize the binding affinity of PAMs considered as prospective blockers for SARS-CoV-2. As a result, it is anticipated that this research will yield the molecular structure of PAM, making it a hopeful contender for addressing COVID-19.

MATERIALS AND METHODS

In this study, the research utilized Windows 10 and Linux Ubuntu 20.04 Operating Systems, along with specific software tools including MGLTools 1.5.6 coupled with AutoDock 4.2, PEP-FOLD 3.5 server, PatchDock, and BIOVIA Discovery Studio 2020. The hardware employed was a computer equipped with an Intel (R) Core i3-6100 CPU @ 2.30GHz (4 CPUs) processor, 4096 MB RAM, a 320GB hard disk, and an Intel HD Graphics 520 VGA. The primary material investigated was the crystal structure of the SARS-CoV spike protein macromolecule. This target macromolecule, sourced from the Protein Data Bank under the PDB code 6LZG, possessed a resolution of 2.50 Å (Fig. 1) (Wang et al., 2020). The research had a central emphasis on the examination of antimicrobial peptide compounds, notably mucroporin and its various forms (Mucroporin-M1, Mucroporin-S1, and Mucroporin-S2), derived from scorpion venom originating from *Lychas mucronatus*. These peptides had previously exhibited efficacy against SARS-CoV in previous scientific investigations (Fakih, 2021).

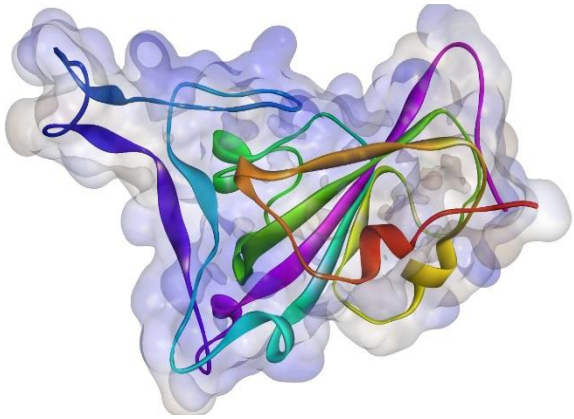

Fig. 1. The structural composition of the spike protein in SARS-CoV-2 at a macromolecular level

This research employs a cutting-edge computational approach through peptide-protein molecular docking simulations. The primary objective is to delve deep into the binding affinity and intricate molecular interactions that take place between the antimicrobial peptide mucroporin, sourced from the venom of the scorpion *Lychas mucronatus,* and the expansive spike protein macromolecule found in SARS-CoV-2. To initiate this in-depth exploration, an extensive array of peptide molecules was initially subjected to sophisticated modeling procedures using the highly advanced PEP-FOLD 3.5 server (Thévenet *et al.*, 2012), while the spike protein macromolecules of SARS-CoV-2 underwent meticulous preparations employing an integration of MGLTools 1.5.6 software alongside AutoDock 4.2 for their subsequent utilization (Forli *et al*., 2012). Following these meticulous preparations, an extensive interaction analysis was performed using the advanced PatchDock software, scrutinizing the interactions between the Mucroporin molecule and the extensive spike protein macromolecule of SARS-CoV-2. Subsequently, the outcomes of the molecular docking simulations, reliant on the atomic contact energy (ACE) values, were meticulously discerned and subjected to comprehensive comparisons. Furthermore, an exhaustive exploration and meticulous evaluation of the intricate molecular interactions formed were executed employing the state-of-the-art BIOVIA Discovery Studio 2020 software (BIOVIA, 2017).

Preparation of the spike protein macromolecules from SARS-CoV-2. This meticulous preparation of the spike protein macromolecule from SARS-CoV-2 is essential to ensure the accuracy and reliability of subsequent analyses, particularly in the context of peptide-protein docking simulations. By eliminating extraneous elements like water molecules and ligands, and by adding polar hydrogen atoms while calculating Kollman partial charges, the molecular structure becomes well-suited for in silico investigations. These steps aim to provide a realistic and biologically relevant representation of the spike protein, enabling a comprehensive exploration of its interactions with antimicrobial peptides like Mucroporin.

Modeling the molecular structure of mucroporin peptides. The utilization of the PEP-FOLD 3.5 server for the molecular modeling of the antimicrobial peptide Mucroporin, as shown in Fig. 2, is a critical step in understanding its structural characteristics. This software is specifically designed for the three-dimensional (3D) modeling of peptides, ranging from 5 to 50 amino acids, employing the de novo method. By selecting the peptide's optimal conformation based on the sOPEP (optimized potential for efficient structure prediction) energy value, and subsequently enhancing it with polar hydrogen atoms and determining Kollman partial charges, we can ensure that the modeled peptide closely approximates its real-life structure. This accurate representation serves as the foundation for further investigations into its interactions with the SARS-CoV-2 spike protein.

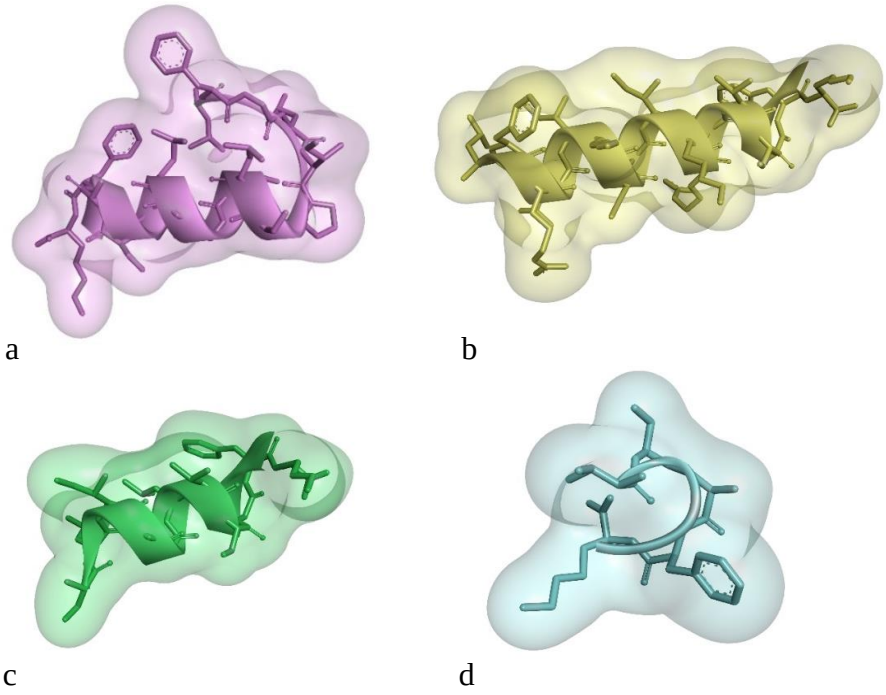

Fig. 2. The molecular configurations of the antimicrobial peptides: a. mucroporin (in red); b. Mucroporin-M1 (in yellow); c. Mucroprin-S1 (in green); d. Mucroporin-S2 (in blue)

Molecular docking simulations based on peptides and proteins. To scrutinize and evaluate the interactions between the antimicrobial peptide mucroporin and the SARS-CoV-2 spike protein macromolecule, we conducted peptide-protein molecular docking simulations, employing the PatchDock software. The software produced ten optimal models with the lowest overall energy, validating their superior binding affinity (Schneidman-Duhovny *et al*., 2005). Notably, this docking simulation maintains a crucial constraint, limiting the distance between mucroporin and the surface of the SARS-CoV-2 spike protein to a maximum of 4.0 Å. The parameters governing this simulation encompass aspects such as the representation of molecular shape, identification of the binding site on the protein macromolecule, as well as the subsequent selection and assessment of potential binding conformations. It is important to emphasize that this molecular docking simulation is carried out with a flexible intermolecular framework, devoid of rigid constraints, thereby ensuring efficiency and flexibility in exploring potential binding configurations.

Examination of the outcomes from molecular docking simulations. Following the completion of the molecular docking simulation, a comprehensive analysis was carried out to dissect and gain insight into the intricate molecular interactions between the antimicrobial peptide mucroporin and the spike protein macromolecule. Of particular interest was the evaluation of the atomic contact energy (ACE) value, a critical metric for assessing the stability and strength of the peptide-protein complex. The ACE score assesses the energy contribution linked to the atomic interactions between the peptide and protein, where a decreased ACE score indicates a more stable and energetically advantageous complex between the peptide and protein. Additionally, the identification of the specific amino acid residues that played pivotal roles in these molecular interactions was conducted utilizing the BIOVIA Discovery Studio 2020 software. This in-depth analysis not only provides a detailed understanding of the binding interactions but also lays the foundation for potential therapeutic applications of Mucroporin in combating SARS-CoV-2.

RESULTS AND DISCUSSION

Presently, there is a pressing need for effective therapeutic options with minimal adverse effects to combat and manage the widespread COVID-19 infection, which has evolved into a global

pandemic (Fouad, 2021). Antimicrobial peptides emerge as a promising selection for antiviral therapy owing to their inherent specificity and distinct attributes when interacting with target proteins. While research on antimicrobial peptides from diverse sources has expanded, there remains a scarcity of comprehensive data regarding the precise extent of their inhibitory capabilities (Das *et al.*, 2022). Consequently, further investigation and scrutiny are warranted. In light of the evolving nature of the COVID-19 pandemic and the ongoing search for effective treatments, the exploration of antimicrobial peptides as potential solutions holds significant promise. Their distinct characteristics, such as selectivity towards target proteins, make them particularly appealing candidates for therapeutic development.

In prior investigations, it was uncovered that the antimicrobial peptide mucroporin, sourced from scorpion venom (*Lychas mucronatus*), exhibited antiviral properties against SARS-CoV with an EC_{50} of 14.46 g/ml (7.12 μM). Given the structural similarities observed in the spike protein between SARS-CoV and SARS-CoV-2, our current study aims to computationally establish the affinity and molecular interactions between the antimicrobial peptide mucroporin and the SARS-CoV-2 spike protein. To accomplish this, we utilized peptide-based molecular docking simulations. The target protein chosen for this interaction analysis was the macromolecular structure of the SARS-CoV-2 spike protein. Our initial step involved preparing the protein macromolecules. This intricate procedure encompassed several crucial steps, starting with the elimination of water molecules and the exclusion of native ligands, followed by the introduction of polar hydrogen atoms and the meticulous computation of partial Kollman charges. To orchestrate this meticulous preparation of the protein macromolecule, we harnessed the capabilities of the advanced MGLTools 1.5.6 software in conjunction with AutoDock 4.2. The overarching goal behind this meticulous process was to guarantee the establishment of a robust and high-affinity interaction site within the protein macromolecule, ensuring the stable binding of the antimicrobial peptide mucroporin.

The antimicrobial peptide mucroporin underwent an elaborate process of three-dimensional (3D) structural modeling, expertly executed using the PEP-FOLD 3.5 server. Subsequent to the conformational modeling phase, the most favorable outcomes were meticulously chosen, guided by the sOPEP (Optimized Potential for Efficient Structure Prediction) energy value. The incorporation of this sOPEP energy value within the PEP-FOLD server plays a pivotal role in enabling the precise prediction of structural conformations for peptide molecules. These conformations closely mimic real-life scenarios and possess the inherent capacity to establish robust and stable interactions within the active site region of the target protein macromolecule. The modeling results presented in Table 1 for the mucroporin antimicrobial peptide suggest its potential to exhibit a strong affinity for the SARS-CoV-2 spike protein. This indicates that the mucroporin antimicrobial peptide, possesses structural attributes conducive to establishing a favorable affinity with the SARS-CoV-2 spike protein. These findings hold promise for potential therapeutic applications in the context of combatting the virus, as they suggest the peptide's suitability for targeting and interacting effectively with the spike protein, a crucial component in the viral infection process.

Table 1. The sOPEP (optimized potential for efficient structure prediction) energy value associated with the antimicrobial peptide mucroporin

Molecule of an antimicrobial peptide	Sequencing of molecules in antimicrobial peptides	The sOPEP energy value
Mucroprin	LFGLIPSLIGGLVSAFK	−27.90
Mucroprin-M1	LFRLIKSLIKRLVSAFK	−36.43
Mucroporin-S1	SLIGGLVSAFK	−14.33
Mucroporin-S2	VSAFK	−2.44

An exhaustive computational investigation was conducted through the implementation of peptide-protein molecular docking simulations, leveraging the cutting-edge PatchDock software. The primary objective was to meticulously assess and scrutinize the optimal binding affinity and intricate molecular interactions between four distinct mucroporin antimicrobial peptide variants and the

sprawling SARS-CoV-2 spike protein macromolecule. The selection of the most advantageous conformation stemming from these rigorous molecular docking simulations was predicated upon the discerning PatchDock score and subsequently subjected to meticulous comparison, taking into account the atomic contact energy (ACE) value. The comprehensive findings, as delineated in Table 2, unequivocally suggest that the antimicrobial peptides Mucroporin-M1 and Mucroporin-S1 outshine their counterparts in terms of binding affinity. This is evidenced by their ACE values of −1144.41 kJ/mol and −400.37 kJ/mol, respectively. These findings provide valuable insights into the specific antimicrobial peptides that might be effective in targeting the SARS-CoV-2 spike protein.

Table 2. The value of atomic contact energy (ACE) between the Mucroporin antimicrobial peptide molecule and the SARS-CoV-2 spike protein macromolecule

Molecule of an antimicrobial peptide	Sequencing of molecules in antimicrobial peptides	The ACE energy value
Mucroprin	LFGLIPSLIGGLVSAFK	217.48 kJ/mol
Mucroprin-M1	LFRLIKSLIKRLVSAFK	−1144.41 kJ/mol
Mucroporin-S1	SLIGGLVSAFK	−400.37 kJ/mol
Mucroporin-S2	VSAFK	509.23 kJ/mol

As Fig. 3 illustrates, the four mucroporin antimicrobial peptide molecules collectively tend to localize within the polar region of the SARS-CoV-2 spike protein macromolecule. This spatial arrangement is made feasible by the inherent flexibility of the antimicrobial peptide Mucroporin. The molecular docking simulations conducted via the PatchDock software do not impose rigid intermolecular bonds. Consequently, mucroporin can dynamically adapt its conformation, allowing it to occupy a specific portion of the SARS-CoV-2 spike protein macromolecule characterized by its polar properties. This adaptability in binding interactions is a significant factor that could influence the peptide's potential effectiveness in inhibiting viral processes.

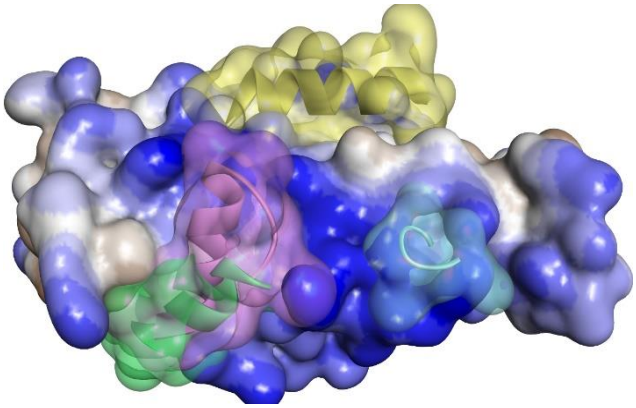

Fig. 3. The specific arrangement in which the antimicrobial peptide molecules, including mucroporin (in red), Mucroporin-M1 (in yellow), Mucroprin-S1 (in green), and Mucroporin-S2 (in blue), are situated at the active site of the SARS-CoV-2 spike protein macromolecule.

The remarkable binding affinity demonstrated by the antimicrobial peptide Mucroporin-M1 can be attributed to the multitude of intricate molecular interactions it establishes with the SARS-CoV-2 spike protein macromolecule. These interactions notably include eight hydrophobic interactions with specific amino acid residues, namely Ala344, Arg346, Ala348, Ala352, Lys356, and Leu452 (as detailed in Table 3). Conversely, the positive ACE value observed in the antimicrobial peptide molecules mucroporin and Mucroporin-S2 is likely a consequence of unfavorable interactions occurring at the active site of the SARS-CoV-2 spike protein macromolecule. Specifically, these interactions involve amino acid residues such as Arg355, Tyr396, Arg457, Lys458, Ser459, Lys462, Ser469, Glu471, Glu516, and Leu517. Given these discerning outcomes, it can be reasonably deduced that antimicrobial peptide molecules such as Mucroporin-M1 and Mucroporin-S1 hold the promise of obstructing the binding of SARS-CoV-2 to the ACE-2 receptor situated on the surface of host cells.

Consequently, this impediment could serve as a deterrent, preventing the virus from infiltrating and infecting host cells effectively.

Table 3. Interactions at the molecular level involving the antimicrobial peptide Mucroporin and the SARS-CoV-2 spike protein macromolecule

Molecule of an antimicrobial peptide	Ala344	Arg346	Ala348	Ala352	Lys356	Tyr396	Pro426	Asp428	Phe429
Mucroprin									
Mucroprin-M1									
Mucroporin-S1									
Mucroporin-S2									

Molecule of an antimicrobial peptide	Leu452	Lys458	Pro463	Phe464	Asp467	Glu465	Glu471	Pro491	Leu518
Mucroprin									
Mucroprin-M1									
Mucroporin-S1									
Mucroporin-S2									

Notes: Hydrogen bond (in green), hydrophobic interaction (in red), electrostatic interaction (in yellow)

The intricate molecular interactions between the antimicrobial peptide mucroporin and the SARS-CoV-2 spike protein macromolecule are predominantly driven by hydrogen bonds, hydrophobic interactions, and electrostatic forces. Hydrogen bonds facilitate the formation of specific and directional connections between atoms within the peptide and protein, contributing to their stable binding. Hydrophobic interactions arise from the aversion of non-polar molecules to water, driving the peptide's hydrophobic residues into the protein's non-polar regions, further stabilizing the complex. Electrostatic interactions, on the other hand, result from the attraction and repulsion of charged particles, such as ions or polar amino acids, and play a significant role in the peptide-protein binding (Liu *et al*., 2022; Wang *et al*., 2022). The collective action of these energy components orchestrates the intricate dance of molecular recognition between mucroporin and the spike protein, potentially influencing their effectiveness in combating the SARS-CoV-2 virus.

CONCLUSION

By employing advanced in silico peptide-protein molecular docking methodologies, it has been substantiated that the antimicrobial peptide molecules Mucroporin-M1 and Mucroporin-S1 exhibit the potential to impede the activity of the SARS-CoV-2 spike protein macromolecule. This inhibition was ascertained by identifying, assessing, and scrutinizing the affinity and molecular interactions formed between these peptides and the spike protein. The outcomes of the molecular docking simulations indicated that these antimicrobial peptide molecules exhibited ACE values of −1144.41 kJ/mol and −400.37 kJ/mol, respectively. Consequently, these findings suggest that these antimicrobial peptides hold promise as potential candidates for inhibiting the SARS-CoV-2 spike protein, thus paving the way for their utilization in the development of peptide-based therapeutics for combatting COVID-19.

ACKNOWLEDGEMENTS

The author expresses gratitude to the Institute for Research and Community Service (LPPM) at Universitas Islam Bandung for their financial support granted under the 2020 Special Research grant scheme, with reference No. 039/B.04/LPPM/IV/2020.

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