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# Magainin as an Antiviral Peptide of SARS-CoV-2 Main Protease for Potential Inhibitor: An *In Silico* Approach

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**ABSTRACT**

The new coronavirus (SARS-CoV-2), which caused the global pandemic Coronavirus Disease-2019 (COVID-2019), has infected nearly 206 countries. There is still little information about molecular compounds that can inhibit the development of infections caused by this disease. It is crucial to discover competent natural inhibitor candidates, such as antiviral peptides, because they have a variety of biological activities and have evolved to target biochemical machinery from different pathogens or host cell structures. *In silico* studies will be carried out, including protein-peptide docking and protein-protein docking, to identify, evaluate, and explore the affinity and molecular interactions of the Magainin-1 and Magainin-2 peptide molecules derived from frog skin (*Xenopus laevis*) to the main protease macromolecule (Mpro) SARS-CoV-2, and its effect on the ACE-2 receptor (Angiotensin Converting Enzyme-2 Receptor). Protein-peptide docking simulations show that both peptide molecules have a good affinity for the active site area of the SARS-CoV-2 Mpro macromolecule. These results were then confirmed using protein-protein docking simulations to observe the ability of the peptide molecule in preventing attachment to the ACE-2 receptor surface area. *In silico* studies show that Magainin-2 has the best affinity, with a bond free energy value of −3054.53 kJ/mol. Then the protein-protein docking simulation provided by Magainin-2 prevented the attachment of ACE-2 receptors, with an ACE score of 1697.99 kJ/mol. Thus, through *in silico* research, the Magainin peptide molecule can be further investigated in the development of new antiviral peptides for the treatment of infectious diseases of COVID-19.

Keywords: antiviral peptide; COVID-19; *in silico*; Magainin; SARS-CoV-2

## INTRODUCTION

The emergence of symptoms such as fever, cough, fatigue, sputum production, shortness of breath, sore throat, headache along with several reports of diarrhea and vomiting began to increase as a cause of pneumonia cases since December 2019 and later identified as a new coronavirus in Wuhan, Hubei Province, China (Guan *et al*., 2020; Wang *et al*., 2020). On January 12, 2020, the WHO first named the 2019-novel coronavirus (2019-nCoV) and officially referred to this disease as the coronavirus 2019 (COVID-19) and as a global emergency disease as a result of concern globally. The International Committee of Coronavirus Study Group (CSG) recommends using the name as SARS-CoV-2, published on February 11, 2020 (Guo *et al*., 2020).

Two overlapping polyproteins function to encode the SARS-CoV-2 genome consisting of ~30,000 nucleotides, namely pp1a and pp1ab. Both polyproteins are needed by coronavirus for replication and transcription (Lu *et al*., 2020). Through this polyprotein, a functional polypeptide is released through a proteolytic process involving the main protease (Mpro) of SARS-CoV-2 (Ge *et al*., 2013). Previous studies have shown that the functional structure between SARS-CoV-2 and SARS-CoV is identical based on the genome's complete phylogenetic analysis (Chen *et al*., 2009; Letko *et al*., 2020). By analyzing the order and analysis of the evolution of this coronavirus, it is suspected that bats act as coronavirus's natural hosts. The coronavirus may have been transferred to humans as an intermediate host by binding to the ACE-2 receptor (Angiotensin Converting Enzyme-2 Receptor) (Zhou *et al*., 2020).

ACE-2 receptors act as functional receptors because they can mediate coronaviruses' entry (SARS-CoV or SARS-CoV-2) into host cells. SARS-CoV-2 involves the ACE-2 receptor's surface with an affinity

comparable to SARS-CoV (Kirchdoerfer *et al*., 2018; Walls *et al.,* 2019). A strong bond at the ACE-2 receptor can explain part of the efficient transmission of SARS-CoV-2 in humans, as occurs in SARS-CoV (Park *et al*., 2016). Therefore, the inhibition of the attachment of SARS-CoV-2 to the ACE-2 receptor is a pathway in developing natural inhibitors for infectious diseases of COVID-19.

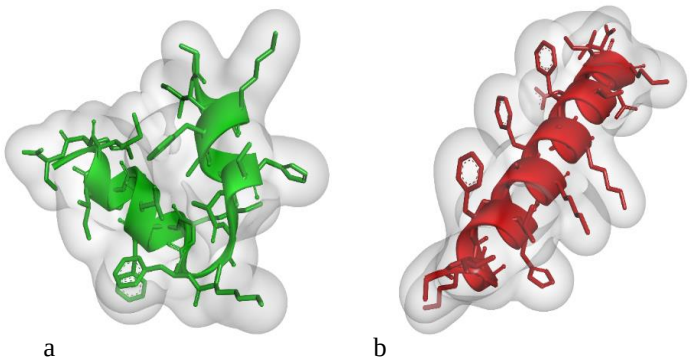
Some literature describes frog skin's antiviral activity (*Xenopus laevis*) because it is considered an abundant source of antiviral peptides. These peptides are produced in skin glands, are deployed in stressful events, and present cationic α-helical secondary structures, with 10-50 amino acids (Marcocci *et al*., 2018; Shartouny & Jacob, 2019). Magainin-1 and Magainin-2 are examples of antiviral peptides with 23 amino acid residues and show efficient inhibition of viruses (Matanic & Castilla, 2004). Previously, several variants of Magainin also presented lysine-rich regions or many lysine residues in their structures, showing the best results in inhibiting viruses. Previous research has suggested that cationic loading associated with amphipathic structures can allow these peptides to interact with anionic phospholipids in viral envelopes, consequently disrupting their structure by several unknown mechanisms and exerting virucidal activity (Dean *et al.,* 2010).

Through this research, the mechanism of action of the antiviral peptides Magainin-1 and Magainin-2 will be proven against SARS-CoV-2 Mpro and their effect on inhibiting the binding of ACE-2 receptors' binding using *in silico*. This *in silico* study can be utilized to identify, evaluate, and characterize potential components of SARS-COV-2 (Kumar *et al*., 2020). In particular, SARS-CoV-2 Mpro has been considered a target because it is a major part of forming coronavirus characteristics. Thus, the results of this research are expected to obtain the structure of a reference antiviral peptide in developing a candidate drug for COVID-19 infection.

## MATERIALS AND METHODS

**SARS-CoV-2 Mpro Macromolecule Preparation.** The macromolecules used are the main proteases (Mpro) of the novel coronavirus 2019 (2019-nCoV or SARS-CoV-2) downloaded from Protein Data Bank (http://www.rcsb.org/pdb) with PDB ID 6LU7 (Jin *et al.,* 2020). SARS-CoV-2 Mpro macromolecules were prepared by removing water molecules and natural inhibitors, adding polar hydrogen atoms, and calculating the Kollman charge.

**Antiviral Peptide Molecule Preparation.** The test molecule used was the sequencing of the antiviral peptide Magainin-1 and Magainin-2 derived from the frog skin (*Xenopus laevis*), which had been modeled using PEPFOLD 3.5 (http://bioserv.rpbs.univ-paris-diderot.fr/PEP-FOLD/) (Figure 1). PEP-FOLD 3.5 is a server that is used to model peptide sequencing into three-dimensional conformation using the de novo method with amino acids between 5 and 50 (Maupetit *et al.,* 2009; Thévenet *et al.,* 2012; Chavan & Deobagkar, 2015; Lamiable *et al.,* 2016). This method can obtain a peptide sequence without the protein database that overcomes the limitations of the methods that rely on peptide mass fingerprinting (PMF) databases. This can be used for non-sequenced organisms, antibodies, posttranslational modification (PTM), and endogenous peptides (Bellows & Floudas, 2010). The results of the peptide molecular modelling will be used as input for protein-peptide docking simulations.



a b

Figure 1. The molecular structure of antiviral peptides: a. Magainin-1 **(**GIGKFLHSAGKFGKAFVGEIMKS**)**; b. Magainin-2 (GIGKFLHSAKKFGKAFVGEIMNS)

**Peptide-Binding Sites in SARS-CoV-2 Mpro Identification.** Identification, evaluation, and exploration of the binding site area most responsible for the antiviral activity of the SARS-CoV-2 Mpro macromolecule were prepared using BIOVIA Discovery Studio 2016 (BIOVIA, 2016). All amino acid residues found around natural inhibitors within a defined radius (between 2 to 4 Å) are prepared for the binding site between the surface of protein macromolecules and peptide molecules in protein-peptide docking simulations.

**Protein-Peptide Docking Simulations.** PatchDock is used for protein-peptide docking simulations (Kaczor *et al.*, 2013; Sathya & Rajeswari, 2016; Aruleba *et al.*, 2018). All antiviral peptide molecules for these simulations are modeled, and polar hydrogen atoms are added using the de novo method. Protein-peptide complex types are selected by default RMSD 4.0 Å grouping. The representation of the Connolly point's surface from the molecule into different components, including convex, concave, and flat patch, is generated through the PatchDock algorithm. PatchDock is optimized, refined, overhauled, and re-selected the side chain interface from the top 10 candidate solutions. It also changes relative molecular orientation by limiting flexibility in the side chains of interacting surfaces and allowing the movement of small, rigid objects. Analysis of the results of protein-peptide docking simulations was carried out using BIOVIA Discovery Studio 2016 (BIOVIA, 2016).

**ACE-2 Receptor Macromolecule Preparation.** The ACE-2 receptor (Angiotensin Converting Enzyme-2 Receptor) macromolecules were downloaded from the Protein Data Bank (http://www.rcsb.org/pdb) with PDB ID 2AJF (Li *et al.*, 2005). This ACE-2 receptor macromolecule is prepared by removing water molecules and natural inhibitors, adding polar hydrogen atoms, and calculating the Kollman charge.

**Protein-Protein Docking Simulations.** PatchDock is used to simulate protein docking of both peptide-protein complexes resulting from the protein-peptide docking methods (Kaczor *et al.*, 2013; Sathya & Rajeswari, 2016; Aruleba *et al.*, 2018). The default RMSD 4.0 Å grouping is used, and the protein-protein complex type is selected. The representation of the Connolly dot surface of the molecule into different components such as convex, concave, and flat patch is generated through the PatchDock algorithm. PatchDock is optimized, refined, overhauled, and reselected the side chain interface from the top 10 candidate solutions. It also changes the orientation of the molecule relative by limiting flexibility in the side chains of the interacting surface and allowing the movement of small, rigid objects. The system's suitability is verified by visualization observations using BIOVIA Discovery Studio 2016 (BIOVIA, 2016).

## RESULT AND DISCUSSION

**Protein-Peptide Docking Simulations.** All antiviral peptides derived from frog skin (*Xenopus laevis*) have been proven to have affinity and interaction with the main protease (Mpro) of SARS-CoV-2, which acts as a target macromolecule using the protein-peptide

docking methods. The docking simulation results in Table 1 show that Magainin-2 has the best affinity with the active site SARS-CoV-2 Mpro compared to Magainin-1 and natural inhibitors, with binding free energy values of −3054.53 kJ/mol, −201.46 kJ/mol, and −1171.44 kJ/mol, respectively. This phenomenon shows a promising sign that Magainin-2 has strong and stable bonds and interactions in the active site area of the SARS-CoV-2 Mpro macromolecule. After that, all the complex results of protein-peptide docking simulations were selected for further studies using protein-protein docking simulations against ACE-2 receptors (Angiotensin Converting Enzyme-2 Receptor).

Table 1. Binding free energy between the peptide molecule and the SARS-CoV-2 Mpro macromolecule

| Peptide Molecule | Binding Free Energy (kJ/mol) |
|---|---|
| Natural inhibitor | −1171.44 kJ/mol |
| Magainin-1 | −201.46 kJ/mol |
| Magainin-2 | −3054.53 kJ/mol |

The peptide molecules Magainin-1 and Magainin-2 show binding positions adjacent to natural inhibitors, and these three molecules can interact in polar patches of SARS-CoV-2 Mpro macromolecules (Figure 2). However, natural inhibitors and the Magainin-1 peptide molecule can only interact with some amino acid residues found in the active sites of the SARS-CoV-2 Mpro macromolecules. Natural inhibitors can only form 5 interactions, consisting of 3 hydrogen bonds (with Met49, Asn142, and Gln189) and 2 hydrophobic interactions (with His41 and Met 165). Then the Magainin-1 peptide molecule can only form 6 interactions, which include 5 hydrogen bonds (with Arg4, Lys5, Lys137, Ser139, and Phe140) and 1 electrostatic interaction (with Ser284).

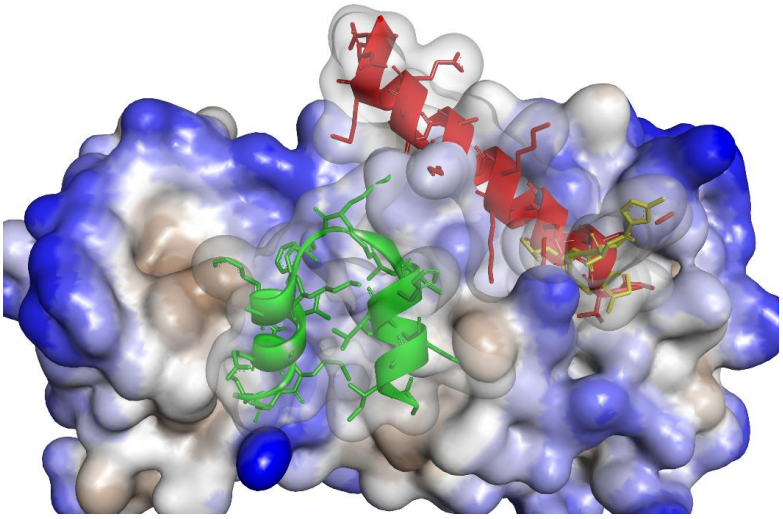


Figure 2. The conformation of natural inhibitor (yellow), Magainin-1 (green), and Magainin-2 (red) molecules in the SARS-CoV-2 Mpro macromolecular binding site

Interestingly, the Magainin-2 peptide molecule has more interaction with the active site area of the Mpro SARS-CoV-2 macromolecule than the natural inhibitor and Magainin-1 peptide molecule. These peptide molecules are capable of forming 13 interactions, including 6 hydrogen bonds (with Thr24, Thr25, His41, Met49, Cys145, and Gln192), 1 electrostatic interaction (with Glu166), and 6 hydrophobic interactions (with Met165, Leu167, Pro168, Ala191, Ala193, and Ala194) (Table 2). Also, the binding position between the Magainin-2 peptide molecule and natural inhibitors has similarities. This phenomenon is proven by forming bonds with several amino acid residues such as His41, Met49, and Met165.

Table 2. Profiles of amino acid residues from SARS-CoV-2 Mpro macromolecules that interact with peptide molecules

| Peptide Molecule | Amino Acid Residues |
|---|---|
| Natural inhibitor | His41***, Met49*, Asn142*, Met165***, Gln189* |
| Magainin-1 | Arg4*, Lys5*, Lys137*, Ser139*, Phe140*, Ser284** |
| Magainin-2 | Thr24*, Thr25*, His41*, Met49*, Cys145*, Met165***, Glu166**, Leu167***, Pro168***, Ala191***, Gln192*, Ala193***, Ala194*** |

Notes: *= hydrogen bond; **= electrostatic interaction; ***= hydrophobic interaction

These interactions can be formed due to hydrogen bonds, especially peptide molecules, which act as hydrogen bond donors and protein amino acid residues as hydrogen bond acceptors. Most hydrogen bonds between protein macromolecules and peptide molecules are relatively strong, with average bond lengths ranging from 3 Å. In addition to hydrogen bonds, interactions between peptide molecules and SARS-CoV-2 Mpro are also dominated by hydrophobic interactions. So it can be predicted that hydrogen bonds and hydrophobic interactions that contribute to protein macromolecules are responsible for stabilizing protein-peptide complexes.

**Protein-Protein Docking Simulations.** Furthermore, identification, evaluation, and exploration using the protein-protein docking methods after the protein macromolecule complex and peptide molecules are formed in the previous stage. The purpose of this docking simulations is to observe the effect of each protein-peptide complex in preventing the attachment of SARS-CoV-2 Mpro macromolecules to the surface area of the ACE-2 receptor. Best affinity with strong and stable interaction of peptide molecules against SARS-CoV-2 Mpro macromolecules is predicted to inhibit the entry of coronavirus into cells and host tissues due to the inability of coronavirus to reach ACE-2 receptors in the signaling process of viral infection. It is also important to explore amino acid residues that play an important role in resisting the formation of molecular interactions between the SARS-CoV-2 Mpro macromolecular binding site and the surface of the ACE-2 receptor.

Table 3. The atomic contact energy (ACE) score of each protein-peptide complex against the ACE-2 receptor

| Protein-Peptide Complex | Atomic Contact Energy (kJ/mol) |
|---|---|
| Natural inhibitor + SARS-CoV-2 Mpro | −204.26 kJ/mol |
| Magainin-1 + SARS-CoV-2 Mpro | 231.75 kJ/mol |
| Magainin-2 + SARS-CoV-2 Mpro | 1697.99 kJ/mol |

Protein-protein docking simulations results in Table 3 show that the Magainin-1 and Magainin-2 protein-peptide complex have positive ACE scores, with values of 231.75 kJ/mol and 1697.99 kJ/mol, respectively. In contrast, natural inhibitors have a negative ACE score, with a value of −204.26 kJ/mol. This phenomenon proves that the ability of the two Magainin peptide molecules to inhibit the attachment of ACE-2 receptors is better than natural inhibitors.

Table 4. Amino acid residues from ACE-2 receptor that play a role in the formation of unfavorable interactions

| Protein-Peptide Complex | Amino Acid Residues |
|---|---|
| Natural inhibitor + SARS-CoV-2 Mpro | Arg115, Lys131, Cys133, Gln139 |
| Magainin-1 + SARS-CoV-2 Mpro | Gly319, Ala387, Arg559 |
| Magainin-2 + SARS-CoV-2 Mpro | Lys313, Val316, Ser317, Ala387, Pro426, Asp427, Asn546, Thr548, Gln552, Phe555, Asn556 |

Moreover, the molecular structure of Magainin-2 is capable of forming many unfavorable interactions on the surface of the ACE-2 receptor. Several amino acid residues that form unfavorable interactions include Lys313, Val316, Ser317, Ala387, Pro426, Asp427, Asn546, Thr548, Gln552, Phe555, and Asn556 (Table 4). This interaction is predicted

to be responsible for preventing the formation of infection signals in SARS-COV-2 (Cheng *et al.*, 2016; Wheeler *et al*., 2016).

## CONCLUSION

Peptide molecules Magainin-1 and Magainin-2 can bind strongly and stably to the binding site area of the SARS-CoV-2 Mpro macromolecule. Interestingly, Magainin-2 has the best affinity and interaction with the SARS-CoV-2 Mpro macromolecule's active site, with a binding free energy value of −3054.53 kJ/mol. The Magainin-2 peptide molecule can also inhibit the formation of interactions with the ACE-2 receptor surface because it has a positive ACE score, with a value of 1697.99 kJ/mol. Therefore, the results of this research indicate that the peptide molecules Magainin-1 and Magainin-2 have the potential to be further developed as natural candidate inhibitors of the SARS-CoV-2 Mpro macromolecules in the treatment of infectious diseases of COVID-19.

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