

Molecular docking study of hyaluronic acid against interleukin-6 (7DC8 protein) in COVID-19 patients with periodontitis

Ade Ismail¹, Syafrudin Aulia Azhar^{2*}

¹ Periodontic Specialist Program, Faculty of Dentistry, Sultan Agung Islamic University, Semarang, Indonesia

² Department of Periodontics, Faculty of Dentistry, Universitas Gadjah Mada, Yogyakarta, Indonesia

Abstract

Coronavirus disease 2019 (COVID-19) is a new disease caused by a *coronavirus*, namely SARS-CoV-2. This virus was entered inside the host by angiotensin-converting enzyme receptors (ACE2). Recent evidence suggests that sulcus fluid in the periodontal pockets of patients with periodontitis may be a source of SARS-CoV-2 and a potential reservoir for increasing oral viral load in patients with confirmed COVID-19. ACE-2 is expressed in stratified squamous epithelium mainly on the dorsal tongue and gingiva. The gingival sulcular epithelium is the entry point for SARS-CoV-2 into the periodontal pocket epithelium through the *gingival crevicular fluid* (GCF). Hyaluronic acid (HA) is a high molecule of heavy polysaccharide (*glycosaminoglycan*) which has several functions, such as anti-inflammatory and accelerated wound healing. It could decrease the levels of several cytokines. This study aims to analyse the interaction of HA against the IL-6 coronavirus receptor in periodontitis through a molecular docking study using MOE 2015.10 software with IL-6 receptor (7DC8) as the protein model to predict the binding of HA with 10 poses. The 7DC8 protein was prepared by adding charge and the validation method was performed with RMSD <2Å which indicates this method is valid. The results of this study showed that there are interaction between HA and the IL-6 receptor via amino acid residue interaction at the Leucine 98 (bond energy -0.7 kcal/mol), Serine 52 (bond energy -1.7 kcal/mol), Glycine 53 (bond energy -1.5 kcal/mol), and Glycine 299 (bond energy -1.6 kcal/mol). HA has an interaction with coronavirus at the IL-6 receptor of periodontitis based on *molecular docking* study and can potentially be used as a therapeutic option in COVID-19 with periodontitis. In conclusion, hyaluronic acid has the potential as an anti-inflammatory drug of choice in COVID-19 patients with periodontitis.

Received:

8 March 2023

Revised:

18 July 2023

Accepted:

25 July 2023

Published Online:

31 July 2023

How to cite this article:

Ismail, A., & Aulia Azhar, S. (2023). Molecular docking study of hyaluronic acid against interleukin-6 (7DC8 protein) in COVID-19 patients with periodontitis. *IIUM Journal of Orofacial and Health Sciences*, 4(2), 140–144. <https://doi.org/10.31436/ijoh.s.v4i2.219>

Article DOI:

<https://doi.org/10.31436/ijohs.v4i2.219>

*Corresponding author

Address:

Tmn Pelangi, BSB, Semarang

Telephone:

+081215209191

Email address:

rudiraulia22@mail.ugm.ac.id

Keywords: COVID-19, hyaluronic acid, molecular docking, periodontitis

Introduction

Coronavirus disease 2019 (COVID-19) has been declared a worldwide pandemic (Indonesian Lung Doctors Association, 2020). This disease causes progressive respiratory failure leading to death (Zhou *et al.*, 2020). ACE-2 is the main receptor for the entry of SARS-CoV-2 into human cells located in the lungs, nasopharyngeal mucosa, salivary cells, and oral epithelial

cells (Badran *et al.*, 2020). In oral epithelial cells, ACE-2 is expressed in the stratified squamous epithelium of the dorsal tongue and gingiva. The gingival sulcular epithelium is the entry point for SARS-CoV-2 into the periodontal pocket epithelium through the gingival crevicular fluid (GCF) (Sakaguchi *et al.*, 2020).

Periodontitis is a chronic inflammation that attacks the supporting tissues of the teeth

and has a high prevalence in the adult population with the main clinical manifestations of periodontal pockets. Sulcus fluid in the periodontal pocket of patients with periodontitis can be a source of SARS-CoV-2 and a potential reservoir for increasing the viral load in the oral cavity of patients with confirmed COVID-19 (Bertolini *et al.*, 2020).

In periodontitis patients there is an increase in the level of interleukin-6 (IL-6) which is a mediator in the process of periodontal destruction (Molayem & Pontes, 2020). Gingival fibroblasts are capable of producing increased levels of IL-6 when exposed to polysaccharides (LPS) or IL-1. IL-6 is involved in osteoclastogenesis and is used as a potential marker to predict the progression of COVID-19 patients (Molayem & Pontes, 2020.; Wang, 2020). High levels of IL-6 have been associated with a higher risk of pulmonary complications.

Non-surgical periodontal treatment to reduce cytokine levels is considered to be able to reduce lower IL-6 levels and inflammation due to periodontal treatment has the potential to protect COVID-19 patients from life-threatening respiratory complications (Molayem & Pontes, 2020). Hellman *et al.* (2020) has conducted a study that in patients with COVID-19 hyaluronic acid was seen in the alveolar walls and pulmonary perivascular tissue.

Hyaluronic acid (HA) has bacteriostatic and anti-inflammatory effects that play a role in the wound healing process. HA works by weakening the bonds of tissue cells that are chronically inflamed so that they are easily released and replaced by the regeneration of new healthy tissue cells (Wijayanto *et al.*, 2014). HA significantly suppresses the secretion of inflammatory cytokines IL-6 and IL-8 (Rooney *et al.*, 2015). HA reduces the proliferation of epithelial cells such as fibroblasts and lymphocytes which play an active role in chronic inflammatory conditions thereby accelerating the regeneration of new cells (Mesa *et al.*, 2004). There have been no scientific studies related to the interaction of hyaluronic acid with IL-6 in COVID-19 patients with periodontitis

using molecular docking study. Molecular docking is a genetic-based method that can be used to find the most appropriate and involving interaction patterns between two molecules, namely receptors and ligands. The test was carried out to see the docking score and the interaction between hyaluronic acid and the IL-6 receptor (GDP: 7DC8) using Molecular Operating Environment (MOE) 2015.10 software.

Materials and Methods

Software and program

Molecular docking test using Molecular Operating Environment (MOE) 2015.10 software.

Preparation of protein structures for Interleukin-6 (7DC8)

Interleukin-6 receptor protein obtained from protein data bank (PDB), with ATP agonist ligand (PDB: 7DC8) via <https://www.rcsb.org/structure/7DC8>. The protein was chosen based on the element of origin of this protein which is human (*Homo sapiens*), with an unmutated protein, and has an active single ligand. The docking method used is the optimal method that has the best RMSD value. The receptors were prepared using MOE 2015.10 software by removing unnecessary molecules, such as water. Redocking of antagonist ligands is carried out on the ligand receptor to obtain the active site of the receptor.

Preparation of hyaluronic acid ligand

Hyaluronic acid SMILES code obtained from PubChem at <https://pubchem.ncbi.nlm.nih.gov/compound/Hyaluronic-acid-sodium-salt>. The HA structure was prepared directly using Molecular Operating Environment (MOE) software 2015.10 and saved in .mdb format.

Molecular docking

The test was carried out to see the docking score and the interaction between hyaluronic acid and the IL-6 receptor (GDP:

7DC8) using Molecular Operating Environment (MOE) 2015.10 software. First, the redocking process was carried out to see the position of the complete protein with its native ligands before and after docking. The redocking process will look at the value of the Root-mean-square-deviation (RMSD) as a method validation parameter with an ideal value of $<2 \text{ \AA}$. The docking positions tested were 10 best positions of hyaluronic acid (HA) against the IL-6 receptor. Manually selected a ligand position that has the best docking score. The docking score of the test ligand was compared with that of the agonist

ligand to compare the binding affinity of the two to the receptor.

Result and Discussion

The molecular docking was carried out using the IL-6 target protein obtained from PDB, namely 7DC8. Redocking of IL-6 (GDP: 7DC8) with ATP agonist ligand is shown in Figure 1; and obtained the value of RMSD = 0.9807. Since $\text{RMSD} < 2 \text{ \AA}$ (Jain and Nicholls, 2008), the PDB:7DC8 method and receptor are valid for use in molecular docking assay ligands.

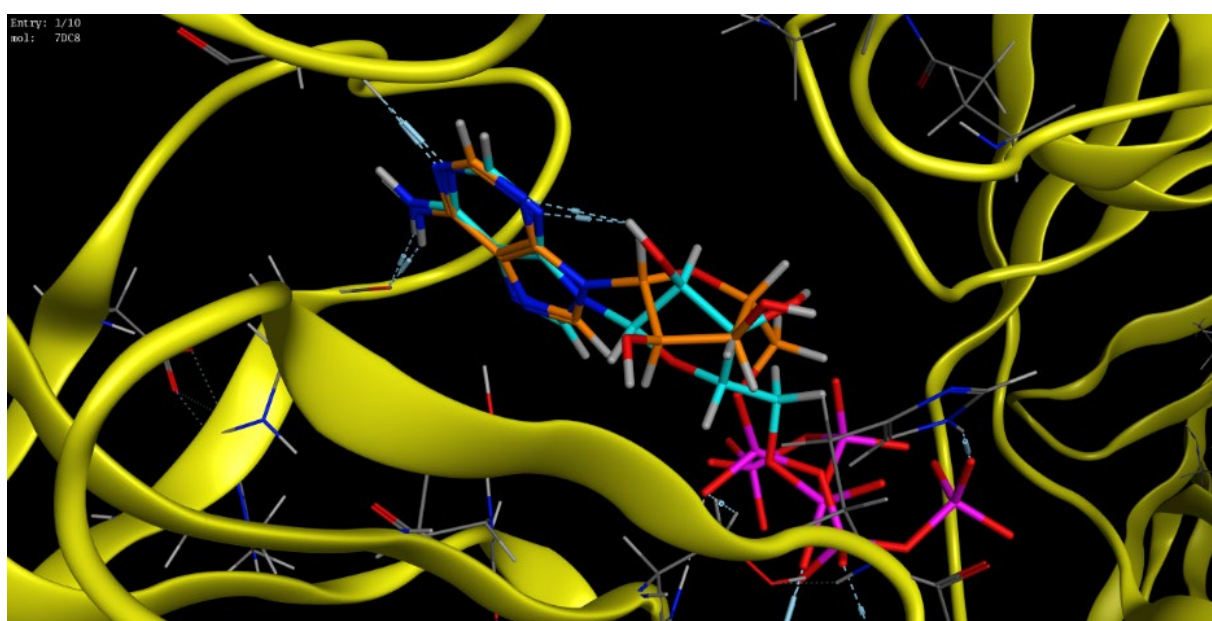


Figure 1. Redocking of IL-6 (PDB-7DC8) (light blue) with ATP agonist ligand (orange).

The molecular docking agonist ligands ATP on the amino acids from IL-6 are *Phenylalanine* (Phe) 298, *Glycine* (Gly) 96, *Leucine* (Leu) 100, Leu 98, *Tyrosine* (Tyr) 95, *Serine* (Ser) 52, and *Glutamine* Gln 53 (Table 1). The hyaluronic acid test ligand has a bond with the amino acids Gly 299, Leu 98, Ser 52,

and Gln 53, so that hyaluronic acid has the potential to inhibit IL-6. Molecular docking of IL-6 with agonist ligand (ATP) and test ligand (hyaluronic acid) is shown in Table 1. While the overlay of molecular interactions of IL-6 with agonist ligand and test ligand (hyaluronic acid) is presented in Figure 2.

Table 1. Molecular interaction of IL-6 (GDP: 7DC8) with hyaluronic acid test ligand

Ligand	Docking Score	Amino Acids	Interaction	Distance(Å)	E (kcal/mol)
Agonis (ATP)	-5.4722	PHE 298	H-donor	3.26	-0.7
		GLY 96	H-donor	2.87	-2.2
		LEU 100	H-donor	3.07	-1.9
		LEU 98	Pi-H	3.68	-1.0
		TYR 95	Pi-pi	3.96	-0.0
		SER 52	H-acceptor	2.50	0.9
		GLN 53	H-acceptor	2.76	-5.4
Test (Hyaluronic acid)	-7.3179	GLY 299	H-donor	2.99	-1.6
		LEU 98	H-acceptor	3.05	-0.7
		SER 52	H-acceptor	2.95	-1.7
		GLN 53	H-acceptor	2.86	-1.5

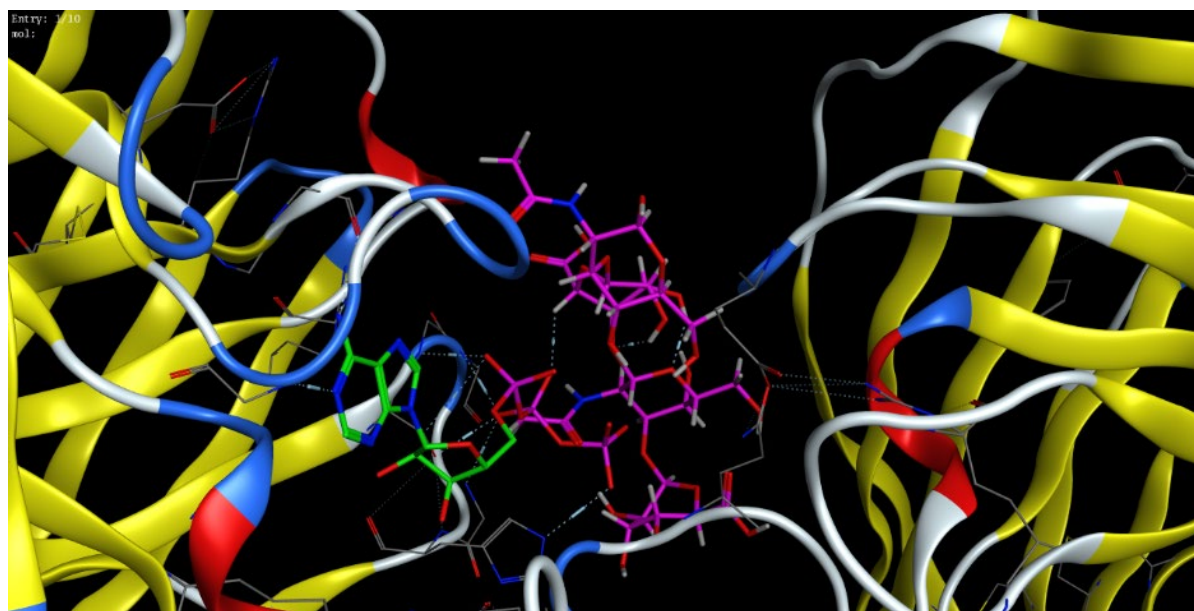


Figure 2. Overlay of IL-6 molecular interaction with agonist ligands (magenta)

Hyaluronic acid inhibits ATP in increasing inflammation through increase IL-6 receptors on the amino acids Leu 98, Ser 52, and Gln 53. This indicates that hyaluronic acid has potential as an anti-inflammatory in COVID-19 patients with periodontitis. The molecular interactions of the test ligands that have the potential as inhibitors are shown in Figure 3.

Docking Score is the scoring function used to predict the binding affinity of both ligand and target once it is docked. Docking score the ATP agonist ligand was -5.4722 and the test ligand (hyaluronic acid) was -7.3179. The lower the bond energy value between the ligand and the target protein, the more stable the complex formed. This indicates that hyaluronic acid has potential as an anti-inflammatory in COVID-19 patients with periodontitis through inhibition of IL-6 receptors.

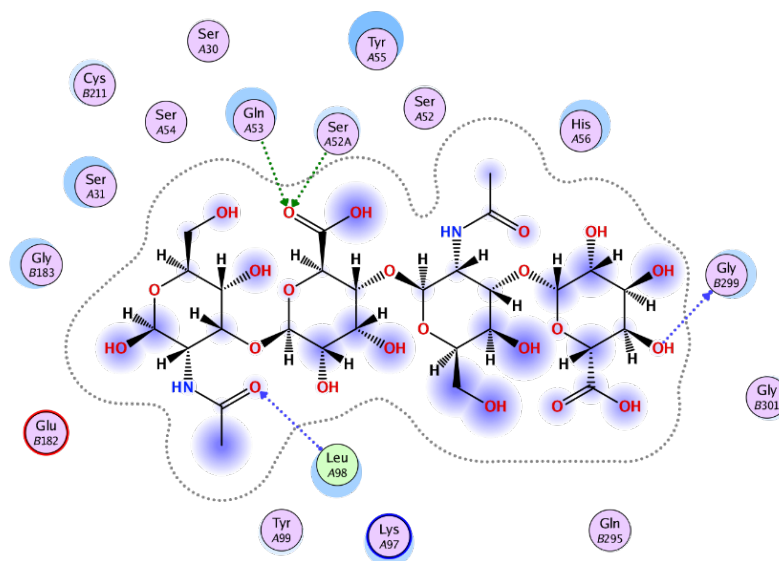


Figure 3. Molecular interaction of test ligands on IL-6

Conclusion

Hyaluronic acid (HA) can interact with IL-6 receptors in COVID-19 patients with periodontitis using molecular docking. Molecular interaction of hyaluronic acid to inhibition of IL-6 (GDP: 7DC8) with a docking score of -7.3179 was able to inhibit the attachment of agonist ligands by -5.4722 to the amino acids Leu 98, Ser 52, and Gln 53. So, hyaluronic acid has the potential as an anti-inflammatory drug of choice in COVID-19 patients with periodontitis.

References

- Perhimpunan Dokter Paru Indonesia (2020). *Panduan Praktik Klinis: Pneumonia 2019-nCoV*, PDPI: Jakarta.
- Zhou, P. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 579, 270-273.
- Badran, Z., Gaudin, A., Struillou, X., Amador, G., and Soueidan, A. (2020). Periodontal pockets: a potential reservoir for SARS-CoV-2?. *Medical Hypotheses*, 143, 109907.
- Sakaguchi, W., Kubota, N., Shimizu, T., Saruta, J., Fuchida, S., Kawata, A., et al. (2020). Existence of SARS-CoV-2 entry molecules in the oral cavity. *International Journal of Molecular Sciences*, 21, 6000.
- Bertolini, M., Pita, A., Koo, S., Cardenas, A., and Meethil, A. (2020). Periodontal disease in the COVID-19 era: Potential reservoir and increased risk for SARS-CoV-2. *Pesquisa Brasileira em Odontopediatria e Clínica Integrada*, 20(suppl1):e0140.
- Molayem, S. & Pontes, C. (2020). The mouth-COVID connection: Il-6 levels in periodontal disease — potential role in COVID-19-related respiratory complication. *Journal of the California Dental Association*, 7, 1-44.
- Wang, C., Horby, P. W., Hayden, F. G., and Gao, G. F. (2020) A novel coronavirus outbreak of global health concern. *Lancet*, 395, 470-473.
- Hellman, U., Karlsson, M.G., Engström-Laurent, A., Cajander, S., Dorofte, L., Ahlm, C., et al. (2020). Presence of hyaluronan in lung alveoli in severe Covid-19: An opening for new treatment options? *Journal of Biological Chemistry*, 295(45),15418-15422.
- Wijayanto, R., Herawati, D., & Sudibyo (2014). Perbedaan efektivitas topikal gel asam hyaluronat dan gel metronidazol terhadap penyembuhan jaringan periodontal setelah kuretase pada Periodontitis Kronis. *Jurnal Kedokteran Gigi*, 5(2086-0218), 307-325.
- Mesa, F.L., Aneiros, J., Cabrera, A., Bravo, M., Caballero, T., Revellas, F. (2002). Antiproliferative effect of topic hyaluronic acid gel. Study in gingival biopsies of patients with periodontal disease. *Histology and Histopathology*, 17, 747-753.
- Rooney, P., Srivastava, A., Watson, L., Quinlan, L.R., Pandit, A. (2015). Hyaluronic acid decreases IL-6 and IL-8 secretion and permeability in an inflammatory model of interstitial cystitis. *Acta Biomaterialia*, 19, 66-75.
- Jain, A.N. & Nicholls, A. (2008). Recommendations for evaluation of computational methods. *Journal of Computer-Aided Molecular Design*, 22, 133-139.
- Attique, S. A., Hassan, M., Usman, M., Atif, R. M., Mahboob, S., Al-Ghanim, K. A., et al. (2019). A molecular docking approach to evaluate the pharmacological properties of natural and synthetic treatment candidates for use against hypertension. *International Journal of Environmental Research and Public Health*, 16(6), 923.