MOLECULAR DOCKING OF GANOMESTENOL WITH SARS-COV-2 M\(^\text{PRO}\)

VENKATESH

Department of Studies in Food Technology, Davangere University, Shivarangotri Campus, Davanagere, Karnataka, India. Email: venka.biotech@gmail.com

Received: 24 November 2021, Revised and Accepted: 05 January 2022

ABSTRACT

Objective: The present study focused on binding mode of the N3 inhibitor and Ganomestenol with receptor SARS-CoV-2 M\(^\text{PRO}\) protease.

Methods: The structure of ligands N3 inhibitor and Ganomestenol were designed and 3-D coordinates were prepared using ACD/ChemSketch 8.0 freeware. Autodock4 software was used to study the orientation of the inhibitor or ligand in the active site of biological receptor SARS-CoV-2 M\(^\text{PRO}\) (PDB ID: 6LU7). The Lamarckian genetic algorithm was applied to both ligand and protein for energy minimization using default parameters. The results were analyzed by Ligplot and Pymol software.

Results: The compound Ganomestenol designed in in-silico for molecular docking with SARS-CoV-2 protease (M\(^\text{PRO}\)). The in-silico results showed significant binding energy (−6.93 kcal/mol) by comparing with N3 inhibitor (−3.51 kcal/mol).

Conclusion: The affinity of Ganomestenol is highly significant compared to N3 inhibitor and also showed efficacy of ligand toward protease under in-silico condition.

Keywords: Molecular docking, SARS-CoV-2, Ganomestenol, N3 Inhibitor.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the viral pneumonia which affects the respiratory infection in human and becomes an epidemic. To date, there are seven human coronavirus (HCoV) strains identified so far and categorized into α-CoV (229E and NL63) [1] and β-CoV (OC43, HKU1, SARS, MERS, and COVID-19 HCoVs). Among these, severe illness can be caused by the Middle East respiratory syndrome (MERS) and human coronavirus (HCoV) and SARS has the highest mortality [2].

The HCoV is a single-stranded 30,000 bp RNA (+ssRNA) virus. The virus consists of two clusters of proteins, namely, (i) the non-structural RNA-dependent RNA polymerase (RRP) that is significant in the replication of the virus, and protease (M\(^\text{PRO}\)) of SARS-CoV-2: M\(^\text{PRO}\) protease enzyme plays a central role in mediating viral replication and transcription and (ii) Spike proteins mediate for fusion and passes into the host, nucleocapsid, matrix, and envelope proteins [3]. Targeting this protease (M\(^\text{PRO}\)) halts the viral replication.

Scientific community vigorously involved to find pathways and targets to suppress the activity of SARS-CoV-2 infection. Some of the drugs such as chloroquine, hydroxychloroquine, and lopinavir relieve the severity of infection. However, still needs an effective drug for suppressing the virulence of the SARS-CoV-2 infection. At present, Remdesivir is an effective drug to a broad range of viruses including SARS-CoV. Remdesivir effective in premature termination during the virus transcription [4] and combination of azithromycin with hydroxychloroquine shows effective treatment of viral infection [5,6]. The protease (M\(^\text{PRO}\)) of SARS-CoV-2 is an attractive target which plays a key role in viral replication and transcription [7]. Here, protease (M\(^\text{PRO}\)) was used as a possible target of SARS-CoV-2. Previously, the compound Ganomestenol has been isolated and characterized from Ganoderma species and also showed good antimicrobial property (Fig. 1) [8]. Ganoderma species is used to treat viral infection [9]. In the present study, in-silico drug designed for molecular docking of N3 inhibitor and Ganomestenol with SARS-CoV-2 M\(^\text{PRO}\).

Autodock4 was used to study the binding mode of inhibitors or ligand or drug bound in the active site of biological receptors. The structure of ligand molecules N3 inhibitor and Ganomestenol was designed and 3-D coordinates were prepared using ACD/ChemSketch 8.0 freeware. N3 is an irreversible Michael acceptor inhibitor, which covalently binds with SARS-CoV-2 M\(^\text{PRO}\) [10]. The protein crystal structure of SARS-CoV-2 M\(^\text{PRO}\) (PDB ID: 6LU7) [11] was obtained from Protein Data Bank (www.rcsb.org/pdb) and edited by removing the heteroatoms, adding C-terminal oxygen. Both ligands and protein molecule are saved in PDBQT . During docking, Gasteigere–Marsili partial charges [12] were assigned to the ligands and non-polar hydrogen atoms were added. All torsions angels were allowed to rotate during docking. The amino acid residues (His41, Phe140, Gly143, Cys145, His163, His164, Glu166, Gln189, and Thr190) of viral protease interacting with ligand N3 inhibitor were considered as active residues for docking [13]. The grid map of protein 6LU7 was centered at the coordinate of x = −10.867, y = 14.128, z = −68.128 were generated with help of AutoGrid [14]. The Lamarckian genetic algorithm was applied to both legend and protein for energy minimization using default parameters. The results were analyzed by Ligplot and Pymol software [15].

![Fig. 1: Structure of ganomestenol](image-url)
The protease plays a key role in viral replication, which resulted potent target to control viral replication in SARS-CoV-2 virus [16]. However, the disruption of protease activity in host cells can lead to various diseases. Hence, the host proteases can be generally used as potential therapeutic targets. In this present study, SARS-CoV-2 Mpro was docked with N3 inhibitor and Ganomestenol. The N3 inhibitor docked with SARS-CoV-2 Mpro exhibits that the binding energy value is −3.51 kcal/mol, which comprises of −3.51 intermolecular energy kcal/mol and 5 hydrogen bonding interactions. The main chain is arginine; leucine, valine, and threonine are involved for interaction with N3 inhibitor. The Ganomestenol showed binding energy of −6.93 kcal/mol and 05 hydrogen bonding with threonine, glutamic acid, serine, and cysteine (Table 1). The interaction of N3 inhibitor with SARS-CoV-2 Mpro (PDB ID: 6LU7) and Ganomestenol with SARS-CoV-2 Mpro showed in ribbon structure (Fig. 2).

**CONCLUSION**

The molecular docking provides virtual information about the mode of interaction with a target molecule by binding to their active site. In this study, Ganomestenol showed significant binding energy to the protease of SARS-CoV-2 virus compared to N3 inhibitor.

**ACKNOWLEDGMENT**

The author thanks to the chairman, Department of Studies in Food Technology, Davangere University, Shivagangotri campus, Davangere, Karnataka for providing facilities.

**REFERENCES**

1. Galante O, Avni YS, Fuchs L, Ferster OA, Almog Y. Coronavirus NL63-induced adult respiratory distress syndrome. Am J Respir Crit Care Med 2016;193:1001.
2. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sci 2020;248:117477.
3. Elfiky AA, Mahdy SM, Elshemey WM. Quantitative structure activity relationship and molecular docking revealed a potency of anti-hepatitis C virus drugs against human corona viruses. J Med Virol 2017;89:1040-7.
4. Mulangu S, Dodd LE, Davey RT Jr., Mbaya OT, Proschan M, Mukadi D. A randomized, controlled trial of Ebola virus disease therapeutics. N. Engl J Med 2019;381:2293-303.
5. Gautret P, Lagier JC, Parola P, Meddeb L, Mailhe M, Doudier B, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;56:105949.
6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Cao B. Clinical features of patients infected with 2019 novel Coronavirus in Wuhan, China. Lancet 2020;395:497-6.
7. Yang H, Yang M, Ding Y, Liu Y, Lou Z, Zhou Z, et al. The crystal structures of severe acute respiratory syndrome virus main protease and its complex with an inhibitor. Proc Natl Acad Sci USA 2003;100:13190-5.
8. Kumar KJ, Venkatesh. Antimicrobial Property of Crude Extracts and spectrum inhibitors targeting Coronavirus main proteases. J Med Virol 2005;3:e324.
9. Liu X, Wang XJ. Potential inhibitors against 2019-nCoV Coronavirus M protease from clinically approved medicines. J Genet Genomics 2020;47:119-21.
10. Gasteiger J, Marsili M. Iterative partial equalization of orbital electronegativity—a rapid access to atomic charges. Tetrahedron 1980;36:3219-28.
11. Jin Z, Du X, Xu Y, Deng Y, Liu M, Zhao Y, et al. Structure of M pro from SARS-CoV-2 and discovery of its inhibitors. Nature 2020;582:289-93.
12. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, et al. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem 2009;30:2785-91.
13. Laskowski RA, Swindells MB. LigPlot+: Multiple ligand-protein interaction diagrams for drug discovery. J Chem Inf Model 2011;51:2778-86.
14. Chang KO, Kim Y, Lovell S, Nathayake AD, Grouats WC. Antiviral drug discovery: Norovirus proteases and development of inhibitors. Viruses 2019;11:197.

**CONFLICTS OF INTERESTS**

No conflicts of interest.

**AUTHORS FUNDING**

No funding.

**Table 1: Molecular docking of N3 inhibitor and Ganomestenol SARS-CoV-2 Mpro**

| S. No. | Compounds         | Binding energy kcal/mol | Ligand efficiency | Intermolecular energy kcal/mol | Electrostatic energy kJ/mol | H-bond | H-Bond with       |
|-------|-------------------|-------------------------|-------------------|--------------------------------|-----------------------------|--------|-------------------|
| 1     | N3 inhibitor      | −3.51                   | −7.2              | −3.51                          | −3.51                       | 5      | ARG188, LEU4, VAL3, THR190, ARG188, THR190, GLU166, SER144, GLU166, CYS145 |
| 2     | Ganomestenol      | −6.93                   | −0.26             | −11.15                         | −0.16                       | 5      |                   |

**Fig. 2:** Molecular docking of N3 inhibitor with SARS-CoV-2 Mpro (PDB ID: 6LU7)(a and b) and Ganomestenol with SARS-CoV-2 Mpro (c and d) showed in ribbon surface and protein – ligands interaction showed in Ligplot.