ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 15, Issue 2, 2022

Online - 2455-3891
Print - 0974-2441

Short Communication

MOLECULAR DOCKING OF GANOMESTENOL WITH SARS-COV-2 M^{PRO}

VENKATESH

Department of Studies in Food Technology, Davangere University, Shivagangotri 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^{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^{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^{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.

 DOI: http://dx.doi.org/10.22159/ajpcr.2022v15i2.43679. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

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^{pro}) of SARS-CoV-2: M^{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^{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^{pro}) of SARS-CoV-2 is an attractive target which plays a key role in viral replication and transcription [7]. Here, protease (M^{pro}) was used as a possible target of SARS-CoV-2. Previously, the compound Ganomestenol has been isolated and characterized from Genoderma species and also showed good antimicrobial property (Fig. 1) [8]. Ganoderma species is used to treat of viral infection [9]. In the present study, *in-silico* drug designed for molecular docking of N3 inhibitor and Ganomestenol with SARS-CoV-2 M^{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^{pro} [10]. The protein crystal structure of SARS-CoV-2 M^{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].

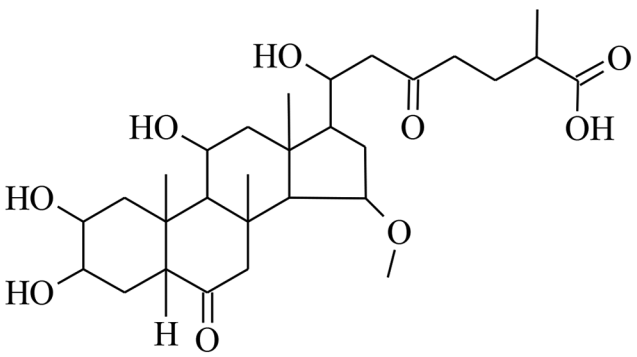

Fig. 1: Structure of ganomestenol

Table 1: Molecular docking of N3 inhibitor and Ganomestenol SARS-CoV-2 M^{pro}

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
2	Ganomestenol	−6.93	−0.26	−11.15	−0.16	5	THR190, GLU166, SER144, GLU166, CYS145

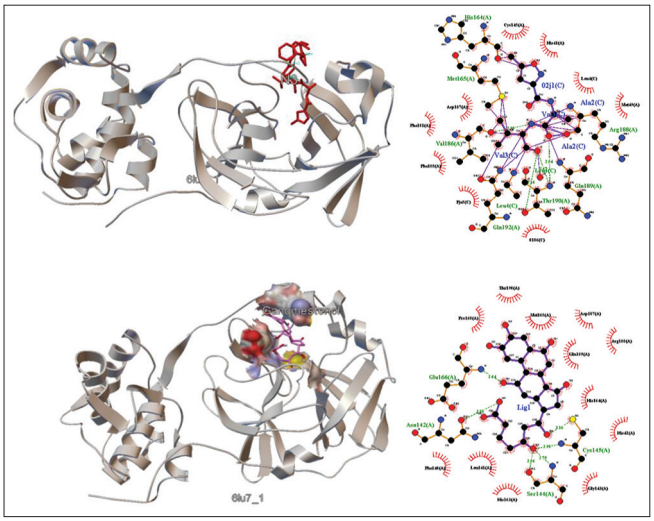

Fig. 2: Molecular docking of N3 inhibitor with SARS-CoV-2 M^{pro} (PDB ID: 6LU7)(a and b) and Ganomestenol with SARS-CoV-2 M^{pro} (c and d) showed in ribbon surface and protein – ligands interaction showed in Ligplot

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 M^{pro} was docked with N3 inhibitor and Ganomestenol. The N3 inhibitor docked with SARS-CoV-2 M^{pro} 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 M^{pro} (PDB ID: 6LU7) and Ganomestenol with SARS-CoV-2 M^{pro} 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.

CONFLICTS OF INTERESTS

No conflicts of interest.

AUTHORS FUNDING

No funding.

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