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Original Article

MOLECULAR DOCKING STUDY OF NATURALLY OCCURRING COMPOUNDS AS INHIBITORS OF COVID-19

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ABSTRACT

Objectives: The worldwide spread of COVID-19 is an emergent issue to be tackled. Currently, several works in various field have been made in rather short period. The present study aimed to assess bioactive compounds found in medicinal plants as potential COVID-19 Mpro inhibitors using molecular docking study.

Methods: The docking analyses were performed by using Autodock, Discovery Studio Visualiser and Igemdock.

Results: The binding energy obtained from the docking of 6LU7 with native ligand cupressuflavone is -8.9 kcal/mol.

Conclusion: These findings will provide the opportunities to identify the right drug to combat COVID-19.

Keywords: COVID-19, Bioactive compound, Cupressuflavone, Binding energy.

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INTRODUCTION

Coronaviruses are an etiologic agent for severe infections in both humans and animals, which can cause disorders not only in the respiratory tract but also in the digestive tract and systemically. Previous studies of CoVs have reported that CoVs can infect certain species and reptiles [1]. Coronaviruses are members of a virus family called Coronoviridae [2].

The new strain of CoVs was identified with the end of 2019 in Wuhan, China and initially named as 2019-nCoV [3]. The World Health Organization (WHO) declared an outbreak on China on January 30, 2020, which is considered to be a Public Health Emergencies of International Concern (PHEIC) [4]. It was identified to have been caused by a completely unique coronavirus named 2019 novel coronavirus (2019-nCoV), now called COVID-19 (Coronavirus disease 2019) which was named by the WHO on February 11, 2020, based on consultation and collaborations with the World Organisation for Animal Health and the Food and Agricultural Organisation of the United Nations [5].

Nowadays, no specific treatments for COVID-19 are available and investigations regarding the treatment of COVID-19 [4]. Some preliminary studies have investigated potential combination that includes the protease inhibitor lopinavir/ritonavir, which is commonly used to treat human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome patients, for the treatment of COVID-19 infected patients [6]. Other reported antiviral treatments from human pathogenic CoVs include nucleoside analogues, neuraminidase inhibitors, remdesivir, umifenovir (arbidol), tenofovir disoproxii (TDF), and lamivudine (3TC) [4]. The crystalised main protease (M^{pro})/chymotrypsin like protease (3 CL^{pro}) from COVID-19, which has been structured and repositioned in Protein Data Bank (PDB) and is accessible by the public. This protease represents a potential target for the inhibition of CoV replication [7].

Several compounds such as flavonoids from medicinal plants have been reported antiviral bioactivities [8-10]. In the present study, we investigated Cupressuflavone as potential inhibitor candidates for COVID-19.

Computational structures prediction of ligand-protein complexes using docking methods such as DOCK, FLEXx, and GOLD in combination with empirical scoring functions are used to predict ligand interactions in binding sites and binding affinities of ligands to proteins [11-13]. While the binding geometries depend on the binding affinities with ligands to proteins. While binding geometries depends on the docking methods, binding energy estimates rely heavily on the potential functions used to calculate them. Knowledge-based potentials followed rules based on statistical analysis of binding affinities and geometries of experimentally determined protein-ligand complexes. These rules are converted to "Pseudo-potentials" which are then applied to score computer-generated ligand orientations [14,15].

METHODS

Protein

COVID-19 structure was obtained from Protein Data Bank (PDB ID: 6LU7) in.pdb format. PDB was used to archive the crystal structure of biological macromolecule, worldwide [16].

Ligand

The phytochemical Cupressuflavone which is isolated from *Biophytum sensitivum* leaves. The three-dimensional structure of Cupressuflavone (CID_5281609) is obtained from PubChem in.sdf format. The.sdf file was converted into.pdb files using Open Babel.

Molecular docking

The docking analyses were performed by using Autodock, Discovery Studio Visualiser and Igemdock.

RESULTS

Fig. 1 shows the structure of 6LU7. It is the main protease (M^{pro}) found in COVID-19, which has been structured and repositioned in PDB and can be accessed by the public. Fig. 2 shows 3D structure of Cupressuflavone. Fig. 3 shows the interaction between receptor 6LU7 and ligand Cupressuflavone (Table 1).

DISCUSSION

Coronavirus infects humans and vertebrate animals and it affects the respiratory, digestive, liver and central nervous system of humans and animals [17]. The present investigation focused PDB ID 6LU7, as potential target proteins for COVID-19 treatment. The protein sequence

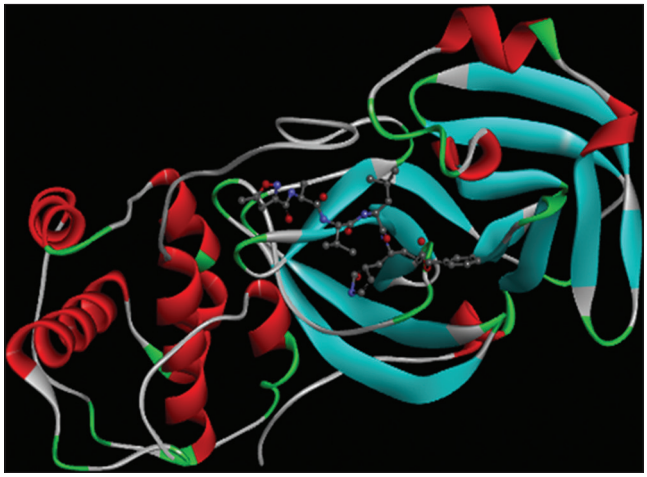

Fig. 1: structure of 6LU7 protein

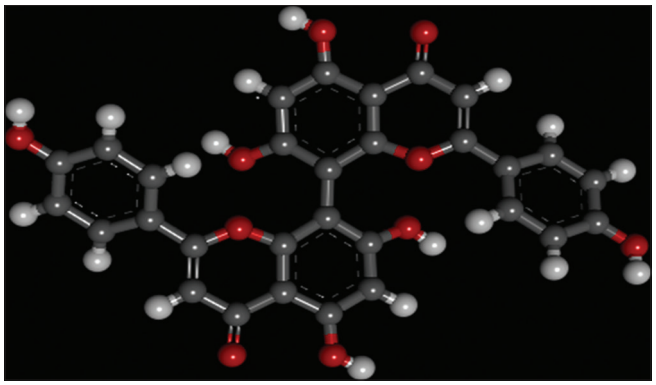

Fig. 2: 3D structure of Cupressuflavone

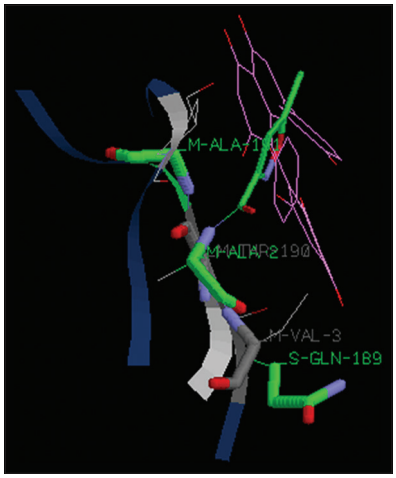

Fig. 3: Interaction between target protein 6LU7 and the ligand Cupressuflavone

of SARS-CoV M^{pro} and 2019-nCoV M^{pro} is 96% identical and the active sites in both proteins remain free from mutations.

The inhibitor Cupressuflavone fit the active site cavity making various close contact with the residue including hydrogen bonding with side chain of Glutamine at position 189 with binding energy -6.4 kcal/mol. Hydrogen bonding with main chain of Alanine at position 191 and Alanine at position 2 with binding energy -2.9 kcal/mol and -4.3 kcal/mol. Vander Waals interaction with side chain of Glutamine at position 189 with the binding energy -6.5 kcal/mol. Vander Waals interaction with main chain of Threonine at position 190, Alanine at position 191, Alanine at position 2, Valine at position 3 with binding energy -8.7 kcal/mol, -9.5 kcal/mol, -15.4 kcal/mol, and -4.5 kcal/mol, respectively. The cluster 1 and element 1 gives a full fitness value of -1628.72 kcal/mol and binding energy is -8.9 kcal/mol.

Table 1: Amino acid residue with binding energy

Amino acid residue	Energy (kcal/mol)
H-S GLN 189	−6.4
H-M ALA 191	−2.9
H-M ALA 2	−4.3
V-S GLN 189	−6.5
V-M THR 190	−8.7
V-M ALA 191	−9.5
V-M ALA 2	−15.4
V-M VAL 3	−4.5

CONCLUSION

There are a number of therapeutics currently in clinical trials in China and more than 20 vaccines in development for COVID-19. The scoring function predicts binding free energies in ligand-protein docking generally with 7-10 kcal/mol shows better activity [18]. Here, we use cupressuflavone isolated from *Biophytum sensitivum*, which is easily available plant. The isolated compound cupressuflavone shows three hydrogen bonding interaction with binding energy −8.9 kcal/mol. Hence this compound may offer therapeutic advantage to the treatment of COVID-19.

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AUTHORS' CONTRIBUTIONS

The authors declared that there is no contribution related to this work.

CONFLICTS OF INTEREST

The authors declared that there are no conflicts of interest related to this study.

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