Chandan Sarkar¹, Sarmin Jamadder¹, Milon Mondal¹, Abul Bashar Ripon Khalipa¹, Muhammad Torequl Islam¹,* and Mohammad S. Mubarak²;*

¹Department of Pharmacy, Life Science Faculty, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj 8100, Bangladesh; ²Department of Chemistry, The University of Jordan, Amman 11942, Jordan

**ABSTRACT: Background:** The coronavirus disease 2019 (COVID-19) is a life-threatening viral infection caused by a positive-strand RNA virus belonging to the Coronaviridae family called severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2). This virus has infected millions of people and caused hundreds of thousands of deaths around the world. Unfortunately, to date, there is no specific cure for SARS-CoV-2 infection, although researchers are working tirelessly to come up with a drug against this virus. Recently, the main viral protease has been discovered and is regarded as an appropriate target for antiviral agents in the search for the treatment of SARS-CoV-2 infection due to its role in polyproteins processing coronavirus replication.

**Materials and Methods:** This investigation (an in silico study) explores the effectiveness of 16 natural compounds from a literature survey against the protease of SARS-CoV-2 in an attempt to identify a promising antiviral agent through a molecular docking study.

**Results:** Among the 16 compounds studied, apigenin, alpha-hederin, and asiatic acid exhibited significant docking performance and interacted with several amino acid residues of the main protease of SARS-CoV-2.

**Conclusion:** In summary, apigenin, alpha-hederin, and asiatic acid protease inhibitors may be effective potential antiviral agents against the main viral protease (Mpro) to combat SARS-CoV-2.

**Keywords:** SARS-CoV-2, COVID-19, protease inhibitors, natural products, in silico screening, apigenin.

**1. INTRODUCTION**

Since December 2019, an outbreak of pneumonia of initially unknown causes was detected in Wuhan (Hubei, China), and was quickly determined to be caused by a novel beta-coronavirus, named novel coronavirus 2019 (also called the severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2)). This virus, belonging to the family Coronaviridae and the order Nidovirales, has led to a severe epidemic in China and more than 200 other countries, resulting in a worldwide concern. It is transmitted through direct contact with respiratory droplets of an infected person (generated through coughing and sneezing), fecal-oral, body fluid routes, or touching surfaces contaminated with the virus [1-3]. Coronaviruses (CoVs) are cross-species viruses containing an enveloped positive-stranded RNA genome (Length: 26-32 kb) like pleomorphic particles with crown-like spikes of glycoproteins projecting from their viral envelopes. These envelopes exhibit a corona or halo-like appearance. CoVs include four common cold human coronaviruses [229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus), and HKU1 (beta coronavirus)], and two other types [severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS-CoV)], which cause severe infections [2, 4, 5].

In late December 2019, this unidentified disease was later named coronavirus disease 2019 (COVID-19), where ‘CO’ stands for corona, ‘VI’ for the virus, and ‘D’ for the disease. Patients with COVID-19 reveal insidious onset with fever, cough, and myalgia-with or without diarrhea or shortness of breath, or both [6]. As of Aug 4, 2020, the number of confirmed cases was 18,142,718 and 691,013 deaths around the world [7]. All types of human coronaviruses (hCoVs) encode an enzyme chymotrypsin-like protease (3CLPro), which is also named the main protease (Mpro); thanks to playing a pivotal role in the proteolytic process during the virus multiplication [8]. Proteolytic processing (processing of replicase polyproteins) is one of the crucial steps in the life cycle of many positive-stranded RNA viruses, including coronaviruses. The non-structural protein Mpro generally cuts two replicase polyproteins and also causes some matured proteins that are essential for viral replication and transcription [9]. Thus, the Mpro of SARS-CoV-2 has been considered as an important molecular target for anti-SARS-CoV-2 drug discovery and development.

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Natural products and their derivatives have been used for years in folk medicine to treat several diseases, including viral infections [10], and the scope of herbal medicines in the context of the nutraceuticals market is vast [11]. In addition, the acceptability of plant-based drugs is increasing on a daily basis. Along this line, *Nigella sativa* demonstrated its inhibitory activity against the hepatitis C virus [12]. Furthermore, some natural products exhibit antiviral activity through the inhibition of viral replication [13, 14]. On the other hand, several marine natural products [15], and biotechnologically produced compounds [16] have also been shown to exert antiviral effects against different viruses. There is a vast library of compounds derived from natural sources that could turn into drug leads for the treatment of various ailments, including viral diseases [17]. However, there is a lack of adequate research on the development of anti-CoV agents from such natural products. Such agents are not only important to combat CoV but also play an important role in preventing viral attack. In addition, despite the ongoing research on the development of specific therapies or vaccines against protease of SARS-CoV-2, there is currently no effective prophylaxis or therapy for SARS-CoV-2, which hinders the treatment or control of the viral infection. In this study, we designed an *in silico* study to determine the inhibitory activities of selected natural anti-viral compounds against the protease of SARS-CoV-2 in an attempt to identify the stronger binding affinities. Results of this study could highlight the importance of some natural products as potential drugs for SARS-CoV-2.

2. METHODOLOGY

2.1. Molecular Docking Study

With the aid of Auto Dock vina (version 4; The Scripps Research Institute, La Jolla, CA, USA) in the PyRx platform, molecular docking was performed to elucidate the binding mode of ligands and target structures. For this reason, the atomic coordinate of the protein (PDB ID: 6LU7) was downloaded from Protein Data Bank (PDB). Using Discovery studio visualizer (version 16.1.0.15350; Biovia, San Diego, CA, USA), visualization of the respective protein-ligand complexes, along with non-covalent interactions, were performed. We introduced an updated server called Computed Atlas of Surface Topography of proteins (CASTp 3.0) for the purpose of detecting and characterizing cavities, pockets, and channels of this protein structure.

2.2. Ligand Preparation

After reviewing the literature on different anti-viral drugs, we identified 16 natural bioactive compounds that act on several viral infections in order to predict their inhibitory activities against the protease of SARS-CoV-2 (6LU7) to eventually describe candidate drugs that may exhibit antiviral activity against SARS-CoV-2. We downloaded the 3D structure of each compound in Structure-data file (SDF) format with the aid of the PubChem database.

2.3. Protein Preparation

All information about the proteins has been collected from the Uniprot (http://www.uniprot.org/). The crystal structure of the SARS-CoV-2 main protease in complex with a peptidomimetic inhibitor (PDB ID: 6LU7) was downloaded from the RCSB protein data bank (http://www.rcsb.org) [18]. We used PYMOL (version 1.7.4.5), a magnificent software, to visualize the protein and remove all water molecules from the protein structure (Fig. 1). Void atomic spaces and crystallographic disturbances were corrected through energy minimization using the Swiss PDB viewer v4.1.0. As a final point, optimized protein structure was saved in “.pdb” format [19].

2.4. Binding Pockets Identification of Protein Structure (PDB ID: 6LU7)

Geometric and topological features such as pockets, cavities, and channels were shown with the help of the CASTp 3.0 server thorough the representation of surface atoms participating in their formation (e.g. the stick model shown in Fig. 2 and the sequence panels shown in Fig. 3). In the beginning, the protein structure in the “.pdb” format was uploaded in the CASTp server and a probe radius as input for topographic computation. A default probe radius of 1.4 Å, which is considered as the standard value for computing solvent accessible surface area for obtaining pre-computed results, was used. Finally, all surface pockets or amino acid residues in a protein structure were identified and provided a detailed delineation of all atoms participating in their formation. The final output file was directly downloaded from the CASTp server, which is visualized using the PyMOL plugin.

2.5. Molecular Docking and Binding Site Prediction

In an *in silico* molecular docking study, the appropriate binding orientations and conformations of the ligands with the targeted protein and the preferred orientations of the ligand with maximum binding affinities for the active sites of the protein associated with structural pockets were performed using the AutoDock vina in PyRx platform. Shown in Table 1 is a visualization of the binding of compounds...
with specific amino acid residues, performed by using BIO-VIA Discovery studio visualizer v16.1.0.15350 (Fig. 4), including binding energies (kcal/mol) acquired from PyRx for selected compound-protein complexes.

3. RESULTS

Listed in Table 1 are the results obtained for the determination of the ligand-protein binding affinity and binding pockets. These results indicate that all compounds exhibit typical docking scores with protein and interacting residues against SARS-CoV-2’s M\textsuperscript{pro} (PDB code 6LU7). The binding pockets of SARS-CoV-2’s M\textsuperscript{pro} were identified with the following amino acid residues: THR24, THR25, THR26, LEU27, HIS41, THR45, SER46, MET49, PHE140, LEU141, ASN142, GLY143, SER144, CYS145, HIS163, MET165, GLU166, and HIS172 as shown in (Fig. 1) and Table 1.

Results revealed that alpha-hederin shows better effect than other conventional antiviral compounds due to its lowest docking score (-8.5 kcal/mol) compared with other drugs. However, there was no interaction with pockets of the SARS-CoV-2’s M\textsuperscript{pro}. Additionally, other compounds exhibited effective inhibition such as asiatic acid (-8.2 kcal/mol), apigenin (-7.7 kcal/mol), auricularic acid (-7.3 kcal/mol), sinularin (-7.1 kcal/mol), curcumin (-6.9 kcal/mol), and andrographolide (-6.9 kcal/mol). In this investigation, only apigenin, the inhibitor of swine fever virus infection, interacted with a maximum of 7 amino acid residues (LEU141, GLY143, GLU166, ASN142, LEU141, ASN142, MET165). On the other hand, alpha-hederin, asiatic acid, auricularic acid, and sinularin displayed high binding affinity, although the amino acid residues were not involved in the binding of protease. Therefore, further research is needed to explain the more crystal structure of protease.

4. DISCUSSION

The ability of a virus to engross its cellular receptor, enter the cell, and replicate is a complex process that affords many opportunities for the development of antiviral strate-

![Fig. (2). The pocket panel of protein (PDB ID: 6LU7) through CASTp 3.0 server. (A higher resolution / colour version of this figure is available in the electronic copy of the article).](image1)

![Fig. (3). The sequence panels of protein (PDB ID: 6LU7) through CASTp 3.0 server. (A higher resolution / colour version of this figure is available in the electronic copy of the article).](image2)
Table 1. Comparative docking scores of compounds with protein and interacting residues of selected compounds against 6LU7.

| CASTp predicted amino acid residues of protein structure (PDB ID: 6LU7) | THR24, THR25, THR26, LEU27, HIS41, THR45, SER46, MET49, PHE140, LEU141, ASN142, GLY143, SER144, CYS145, HIS163, MET165, GLU166, HIS172, VAL3, LEU4 |
|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PubChem CID | Anti-viral compounds | Binding affinity (kcal/mol) | Interacting amino acids |
|-------------|---------------------|-----------------------------|------------------------|
| 5280443     | Apigenin            | -7.7                        | LEU141, GLY143, GLU166, ASN142, MET165, CYS145, MET49 |
| 5318517     | Andrographolide     | -6.9                        | SER144, CYS145, GLN189, HIS163 |
| 73296       | Alpha-Hederin       | -8.5                        | TYR239, LEU272, ASP289, ASN238, LEU287, LEU286, MET276, ASN277, GLY278, ARG131, THR199, ALA285 |
| 119034      | Asiatic acid        | -8.2                        | LEU272, LYS137, LEU271, GLY275, LEU287, LEU287, LEU272, TYR237, TYR239 |
| 365764      | Auricular acid      | -7.3                        | ASP153, ILE106, VAL104, PHE294 |
| 54670067    | Ascorbic acid       | -5.4                        | LEU141, GLY143, GLU166, MET165 |
| 969516      | Curcumin            | -6.9                        | GLU166, HIS41, CYS145, LEU141, ASN142, MET165 |
| 54680783    | Citrinin            | -6.5                        | ASP153, SER158, ILE106, VAL104 |
| 10082188    | Hispolon            | -6.3                        | GLU166, HIS163, SER144, CYS145 |
| 643820      | Nerol               | -4.8                        | ASP295, H17, THR111, VAL104, PHE8, PHE294 |
| 5280435     | Phytol              | -4.6                        | THR111, GLN110, OTHR111, ASN151, ILE106, VAL104, PHE294 |
| 5280531     | Retinol palmitate   | -5.2                        | ASN151, VAL297, ILE249, PRO293, PRO252, VAL297, PHE294 |
| 163263      | Sclareol            | -6.1                        | LEU271, LEU272, LEU286, LEU287 |
| 6438436     | Sinularin           | -7.1                        | LEU271, MET276, LEU287, TYR237 |
| 6989        | Thymol              | -5.0                        | TRP218, LEU220, PHE219, LEU271, PHE223 |
| 10281       | Thymoquinone        | -5.2                        | GLN110, ASP153, PHE294 |

gies. The first human cases of SARS-CoV-2 were identified in the Chinese city of Wuhan in December 2019, and spread progressively to more than 200 countries outside China [20]. Worldwide, the number of people who have been infected with the coronavirus is more than 53.7 million [7]. Since the outbreak began in December, more than 1.3 million have died in some 220 locations including China [7]. At present, there are no approved treatments for diseases caused by coronaviruses; however, there are drugs and compounds used to treat HIV and other different types of viruses that are being rapidly tested against the new coronavirus. In this study, we used 16 natural compounds from 60 related articles and analyzed their inhibitory activities through an in silico study against the crystal structure of SARS-CoV-2 main protease (PDB ID: 6LU7), which is obtained from the RCSB protein data bank (http://www.rcsb.org) [18].

Depending on the proteolytic processing events on the polyproteins, maturation of CoVs is performed by a three-domain (I, II, and III) chymotrypsin-fold proteinase, called Mpro or 3CLpro [21]. The structure of the main protease of novel human coronavirus (HCoV) shows two Mpro molecules form an active homodimer. This homodimer plays a significant role in the proteolytic activity when positioned at the interface between domains I and II, where the 2 conserved residues His41 and Cys145 form the catalytic dyad of Mpro [22]. Mpro has recognized as an applicable target for viral inhibitor development toward SARS-CoV-2 treatment due to its pivotal role in virus maturation [23]. According to the chemical structures, the significant inhibitors of Mpro can be classified into two classes — one makes a covalent bond with Cys145 amino acid residue of the catalytic site of that enzyme [24], and the other prevents a substrate entrance.
(Fig. 4) contd…. 
into the active site cavity through bindings to that enzyme [25].

Nature provides massive sources of natural products and their derivatives to develop and explore drugs against numerous ailments including viral diseases [17]. Apart from plant-based compounds [26], several marine natural products [15] along with various biotechnologically produced chemicals [16] are also cited for their antiviral effects against numerous viral infections. In addition, some natural products have been found to provide significant evidence of their ac-

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**Fig. (4).** Nonbonding interaction of selected compounds with Mpro of SARS-CoV-2 through Discovery studio visualizer v16.1.0.15350. Here, we only presented nonbonding interaction for comparatively high binding scored ligand-protein complexes (≥ -6.9 kcal/mol). (A higher resolution / colour version of this figure is available in the electronic copy of the article).
tivity against hCoVs through inhibition of M\(^{\text{po}}\) [27]. Moreover, among the natural products and their derivatives that inhibit M\(^{\text{po}}\) are apigenin [28], amentoflavone [28], aloe emodin [29], beta-sitosterol [29], betulinic acid [30], curcumin [30], honokiol [30], hesperetin [29], indigotin [29], 3-isothecafavimin-3-gallate [31], luteolin [28], myricetin [32], niacinamide [30], quercetin [28], sinigrin [28], scutellarein [32], and tannic acid [31].

Our findings indicate that the inhibitor of African swine fever virus infection [33], apigenin exhibits significant docking performance (-7.7 kcal/mol) and interacts with LEU141, GLY143, GLU166, ASN142, MET165, CYS145, and MET49 amino acid residues of the main protease of nCoV-19. Other inhibitors of the negative-sense RNA viruses (Influenza viruses), namely alpha-hederin exhibited the highest binding energy (-8.5 kcal/mol) and interacted with TYR239, LEU272, ASP289, ASN238, LEU287, LEU286, MET276, ASN277, GLY278, ARG131, THR199, and ALA285 that are totally different from predicted amino acid residues of the main protease through CASTp server [34]. Similarly, asiatic acid, an inhibitor of lentiviruses [35], also showed potent binding affinity (-8.2 kcal/mol) that targets different binding pockets (LEU272, LYS137, LEU271, GLY275, LEU287, LEU287, LEU272, TYR237, and TYR239) of the selected protein. In a similar fashion, the potent West Nile virus NS3 protease inhibitor [36] similarin interacts with LEU271, MET276, LEU287, and TYR237 amino acid residues of M\(^{\text{po}}\) of SARS-CoV-2 that are also mismatched from predicted pockets and showed good docking performance (-7.1 kcal/mol), whereas curcumin, an inhibitor of dengue, hepatitis C, zika, chikungunya, HIV, and ebolaviruses [37, 38] showed less docking performance (-6.9 kcal/mol) than singular in interacting with GLU166, HIS41, CYS145, LEU141, ASN142, and MET165 pockets. On the other hand, andrographolide, an influenza virus inhibitor, displayed a similar effect (-6.9 kcal/mol) compared to curcumin related with 3 amino acid pockets (SER144, CYS145, and HIS163) [39]. Other compounds exhibited moderate performance in this in silico study. However, widespread clinical studies are necessary for protease inhibitors to explain the efficiency against SARS-CoV-2.

CONCLUSION

The complete methodology described in this study highlights the prediction of ligand-protein binding affinity and its binding pockets. In agreement with the results from in silico docking of the constituents against the diverse receptor (PDB code 6LU7), findings showed that several natural products exhibit significant antiviral activity, particularly apigenin, alpha-hederin, and asiatic acid. These compounds could be promising leads in the development of antiviral drugs. However, much more work is required that could involve animal models and perhaps human subjects. In short, information obtained from this investigation could be valuable for future vaccine and drug development.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the study is available within the article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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