Article

In Silico Analysis Using SARS-CoV-2 Main Protease and a Set of Phytocompounds to Accelerate the Development of Therapeutic Components against COVID-19

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Abstract: SARS-CoV-2, the virus that caused the widespread COVID-19 pandemic, is homologous to SARS-CoV. It would be ideal to develop antivirals effective against SARS-CoV-2. In this study, we chose one therapeutic target known as the main protease (Mpro) of SARS-CoV-2. A crystal structure (Id: 6LU7) from the protein data bank (PDB) was used to accomplish the screening and docking studies. A set of phytocompounds was used for the docking investigation. The nature of the interaction and the interacting residues indicated the molecular properties that are essential for significant affinity. Six compounds were selected, based on the docking as well as the MM-GBSA score. Pentagalloylglucose, Shephagenin, Isoacteoside, Isoquercitrin, Kappa-Carrageenan, and Dolabellin are the six compounds with the lowest binding energies (−12 to −8 kcal/mol) and show significant interactions with the target Mpro protein. The MMGBSA scores of these compounds are highly promising, and they should be investigated to determine their potential as Mpro inhibitors, beneficial for COVID-19 treatment. In this study, we highlight the crucial role of in silico technologies in the search for novel therapeutic components. Computational biology, combined with structural biology, makes drug discovery studies more rigorous and reliable, and it creates a scenario where researchers can use existing drug components to discover new roles as modulators or inhibitors for various therapeutic targets. This study demonstrated that computational analyses can yield promising findings in the search for potential drug components. This work demonstrated the significance of increasing in silico and wetlab research to generate improved structure-based medicines.

Keywords: drug discovery; COVID-19; main protease; phytocompounds; docking; MMGBSA

1. Introduction

Coronavirus is a member of the Coronaviridae family of viruses [1,2]. Human coronaviruses (hCoVs) are enveloped, positive-sense viruses with the largest single-stranded genomes of RNA viruses [3]. The SARS-CoV-2 genome is approximately 30,000 nucleotides long and shares 79% sequence similarity with SARS-CoV. This virus has 14 open-reading frames (ORFs). ORF1a and ORF1ab encode polyproteins that are used to create the replicase-transcriptase complex and 16 non-structural proteins (nsp1–nsp16) [4]. The majority of the proteins encoded by the SARS-CoV-2 virus are similar in length to SARS-CoV proteins except for the spike (S) protein, which is unique to SARS-CoV [5]. Despite minor differences in crucial amino acid residues, the receptor-binding domain (RBD) of the SARS-CoV-2 S protein and SARS-CoV are structurally similar [6]. Researchers focus on the similarities between the SARS-CoV and SARS-CoV-2 viruses across a wide range of research areas, including epidemiology, development of vaccines and novel therapeutic therapies. Several studies focused on the genomic organization, structural and non-structural protein
components, and their potential as suitable molecular targets for the development of therapeutic drugs, convalescent plasma therapy, and a variety of potential vaccines to combat SARS-CoV-2 infection [7–9].

The incubation period of COVID-19 has a mean, median, and mode of 7.83, 7, and 5 days, and, in 12.5% of cases, more than 14 days [10]. Infection with SARS-CoV-2 appears to be more contagious than infection with other coronaviruses [11–13]. R0 is a threshold measure that indicates the severity of infection spread [14]. A value of R0 > 1 implies that the rate of infection in the population may increase, whereas a value of R0 1 indicates that the rate of infection in the population will decrease; however, there are certain exceptions [15]. Several studies have been conducted on the infectivity rate of SARS-CoV-2 [16–18]. Initial estimates of SARS-CoV and MERS-CoV reproduction numbers were estimated for China and the Middle East, with the R0 median = 0.58 (IQR: 0.24–1.18) and R0 mean = 0.69 (95% CI: 0.50–0.92) (106), respectively [19]. However, among the four viruses, SARS-CoV-2 has been shown to be the most contagious, as seen by the R0 value from the Italian outbreak, with a median point estimate of R0 = 3.1 (coefficient of determination, $r^2 = 0.99$) [20]. Nonetheless, a number of viral and host factors influence the severity and clinical nature of the diseases caused by SARS-CoV-2 [21]. Immunity, age, sex, morbidities, and genetic variations are the most important host factors [22].

SARS-CoV-2 variants are a serious threat that could have much further consequences in the future [23,24]. Vaccines are one option, and many have been created to combat COVID-19. To avert more morbidity and mortality, finding potential and effective treatment possibilities will contribute to the improvement of global health.

Viral receptors serve as both entry mediators and signaling event activators. Viruses enter the host through unique receptors to perform distinct activities during their life cycle [25]. Similar to other viruses, receptors play a key role in the infection and pathogenesis of hCoVs [26]. After the initial receptor binding, hCoVs must fuse their envelope with the host cell membrane to enter the viral nucleocapsid into target cells. According to in vitro research, the virus uses this technique to infect human cells, contributing to the spread and dissemination and immune evasion [27]. Angiotensin-converting enzyme 2 is the particular surface protein that allows SARS-CoV and SARS-CoV-2 to enter host cells [28]. The cell surface transmembrane protease serine 2 (TMPRSS2) and the lysosomal proteases cathepsins [29,30] are the two primary proteases implicated in the entry of this virus to the host organism. Both structural and nonstructural proteins are encoded by the viral genome. Replicase-transcriptase proteins are structural proteins that play a key role in viral RNA synthesis [31]. Structural proteins assemble and wrap genomic RNA (gRNA), eventually forming a large number of viral particles that leave the host cell and propagate infection in the host organism.

A series of well-coordinated replication-transcription molecular events result in the synthesis of multiple nested sets of subgenomic mRNAs (sgRNAs), which are translated into several structural and accessory proteins assisting the virus to form its structure and perform various molecular functions [32]. Following the protease-induced cleavage and molecular assembly, these polyproteins assemble to create a functioning viral RNA polymerase, also known as replicase. Polyprotein processing from the viral RNA of SARS-CoV-2 requires the main protease (M$^\text{pro}$), which is also known as nsp5. It interacts with the papain-like protease domain in nsp3. M$^\text{pro}$ plays an important role in infection because it initiates viral replication [33]. The replicase gene encodes a large polyprotein (pp1ab) that is proteolytically cleaved into 16 nsps, which is involved in transcription and virus replication. Thus, M$^\text{pro}$ is important in the processing of polyproteins that mediate the assembly of replication-transcription machinery [34]. Thus, inhibiting nsp5-mediated cleavage would, indeed, prevent nsp protein synthesis and hence viral replication. M$^\text{pro}$ is a key target for the development of antivirals against coronavirus infections since it is unique to the virus and not found in host cells [35]. During the COVID-19 outbreak, proteases, and nsp5 in particular, was identified as one of the most promising therapeutic candidates for treating the infection [36–38]. Many studies have focused on determining the structure of nsp5,
either alone or in complex with potential inhibitors, allowing the identification of a large number of compounds capable of antagonizing nsp5 activity and elucidating the molecular underlying mechanisms behind the inhibition [37–40]. Paxlovid, an oral SARS-CoV-2 M\textsuperscript{pro} inhibitor, was recently approved to treat mild-to-moderate COVID-19 [41]. Many review articles show the effort put in to identify the most effective covalent and non-covalent inhibitors of the SARS-CoV-2 M\textsuperscript{pro} [3,42,43]. All these studies show that M\textsuperscript{pro} is one of the most promising viral targets for SARS-CoV-2 antiviral drug development. As a result, we chose this protein for our research.

After M\textsuperscript{pro} cleaves the viral polyprotein and releases nsp5, a replicase complex is formed, which is responsible for viral replication [39]. nsp7 through nsp16, which are cleavage products of two major replicase polyproteins translated from the coronavirus genome, are the primary regulators of coronavirus RNA synthesis and processing. RNA polymerase (nsp12) and helicase (nsp13) are some of the tasks of the coronavirus replications. There are a variety of domains involved in mRNA capping (nsp14, nsp16) and fidelity control (nsp14, nsp16). Several smaller subunits (nsp7–nsp10) contribute to nsp5 interactions and act as essential cofactors for these enzymes. By stabilizing the N protein–RNA complex inside the internal virion, binding with M protein aids in the stabilization of the N proteins and facilitates the completion of the viral assembly [44]. In the cell culture, nonstructural proteins are assumed to be nonessential for virus replication. These non-essential proteins, which are classified as niche-specific proteins, appear to give the virus a selection advantage in vivo.

The search for drug components using bioinformatics tools is the topic of this research. The importance of bioinformatics and the structural determination has been demonstrated, not only for lead optimization, but also for lead discovery. Structural biology is integrated in the pharmaceutical industry’s drug development pipeline [45]. To identify starting points for their small-molecule R&D initiatives, pharmaceutical companies use high-throughput screening and fragment screening [46]. One technique for speeding up the standard drug development drug discovery process is drug repurposing. This will aid in understanding the reusability of novel therapeutic applications for compounds that have already been demonstrated to be safe and efficacious [47–49]. The increasing and faster spread of SARS-CoV-2, as well as the emergence of novel variants, highlight the importance of potential therapeutic components that serve as effective antivirals in controlling the pandemic. Interrupting the catalytic activity of M\textsuperscript{pro} could be useful in the development of antiviral therapies. With this background in mind, the current work sought to find a few phytocomponents capable of inhibiting the M\textsuperscript{pro} protein. In drug development, phytochemicals are being used as active drug components. Phytochemicals from a wide range of medicinal plants may help improve immune function and fight pathogens in the fight against viral diseases. Numerous studies have shown the importance of phytochemicals and their derivatives, which have antiviral activities, as well as their mode of action in the treatment of viral diseases [50–52]. In this study, six phytocompounds were identified to have significant interactions with the target protein, M\textsuperscript{pro}. Docking-based binding affinity and stability studies were carried out to identify them. Figure 1 depicts the workflow of the various steps used in this study.
2. Materials and Methods

2.1. Structure Retrieval and Protein Preparation Studies

The experimentally solved crystal structure of the M\textsuperscript{pro} is accessible via the Protein Data Bank (PDB), with the accession ID 6LU7. The receptor structure contains 306 amino acids. This structure has been downloaded for our investigation. The structure was prepared using the Protein Preparation Wizard in Maestro Schrödinger Release 2021-1 (Schrödinger, LLC, New York, NY, USA). The preparation of receptor proteins involves steps such as the assignment of hydrogen bonds, bond ordering, addition of hydrogens, optimization, minimization of the protein, and deletion of waters beyond 5 Å from the het group. Partial charges were assigned using the OPLS-3e force field (Maestro Schrödinger Release 2021-1, Schrödinger, LLC, New York, NY, USA). Restrained minimization was used to optimize the hydrogens and heavy atoms.

2.2. Identification of Active Site Residues

The SiteMap module (Schrödinger Release 2021-1, Schrödinger, LLC, New York, NY, USA) was used to determine the highly possible binding locations of the ligands on the receptor structure. The top three ranked possible ligand-binding sites were identified on the target structure, M\textsuperscript{pro}. The OPLS2005 force field was employed using a restrictive hydrophobicity definition, a standard grid (1.0), and a restrictive hydrophobicity definition, which are default settings in SiteMap. In addition, SiteMap assigns scores for each site. SiteMap positions a mapping box for each site based on the site points. This box represents a grid. The van der Waals interactions and electrostatic interactions of the probes placed at each grid point were then used to produce van der Waals and electric-field grids. The probe was a van der Waals sphere with a radius of 1.6 Å that simulates a water molecule.

2.3. Phytocompounds Selection and Ligand Preparation

The molecules we have chosen as the ligands were plant-based chemicals, also known as phytocompounds. A total of 124 compounds were selected for docking. The SDF file for each drug was downloaded from PubChem, NCBI. The LigPrep module in Maestro Schrödinger (Schrödinger Release 2021-1, Schrödinger, LLC, New York, NY, USA) was used to prepare the ligands for docking, and each ligand’s tautomeric and ionization states were determined.
2.4. Receptor Grid Preparation and Docking Studies

The protein receptor grid was created using Glide module, (Schrödinger Release 2021-1, Schrödinger, LLC, New York, NY, USA). This helps to locate the ligand binding site for docking. This grid box was designed to ensure that the \( \text{M}^{\text{pro}} \) target to the center of each docked ligand had the identical binding box dimensions. Glide’s xtra precision (XP) mode was used to conduct the docking process based on the OPLS-3e force field. The best docked structure from the output was determined using the Glide docking score. The interactions of the docked complexes were analyzed using a ligand interaction diagram in Maestro, Schrödinger Release 2021-1 (Schrödinger, LLC, New York, NY, USA) and BIOVIA (Dassault Systèmes, DS visualizer, San Diego, CA, USA, 2020). Following the identification of ligand interactions, ligand receptor complex figures were generated and saved.

3. Results and Discussion

Several studies using bioinformatics and cheminformatics methodologies are being conducted to identify the inhibitors of SARS-CoV-2 \( \text{M}^{\text{pro}} \) [53–55]. Many studies on the SARS-CoV-2 proteins focus on natural and phytocompounds [56–58]. Wetlab investigations are an unavoidable aspect of discovering the best lead compounds, though in silico studies generate substantial data. Bioinformatics is made easier with structural biology. Structure biology can assist with the elucidation, storage, and retrieval of structural data, which aids drug development by defining a goal for target selection and drug identification. To conduct our research, we used data from the PDB, a repository for structural proteins. According to the literature, SARS-CoV-2 \( \text{M}^{\text{pro}} \) is the main enzyme of coronaviruses that plays a critical role in viral replication and transcription, making it a promising therapeutic target. The target protein of the main protease, \( \text{M}^{\text{pro}} \) (PDB ID: 6LU7), was found in the PDB [59]. When the target protein \( \text{M}^{\text{pro}} \) was prepared using the protein preparation wizard tool, the H-bonds were optimized, and the geometry was minimized. SiteMap, a tool, was utilized to identify the potential binding sites and predict their drug ability. Three of the top-scoring active site regions were found by the SiteMap [60]. SiteMap locates energetically favorable locations by calculating the interaction energies between the protein and grid probes. In drug development investigations, this method can also be used to characterize binding sites and critically evaluate potential ligands.

We used a collection of 124 phytocompounds to explore if they could be used as therapeutic components against the SARS-CoV-2 main protease. Plant components have been used in medicine since antiquity and are well-known for their potent medicinal properties [61]. Many phytocompounds have been used in traditional medicine to treat ailments possibly caused by viruses [62–64]. Several studies evaluated the pharmacological nature of the phytocompounds and COVID-19 proteins [65–67].

LigPrep assigns proper bond ordering and corrects the protonation and ionization states of the compounds. During ligand preparation, after converting the 2D structures to 3D, tautomerization, and ionization, the LigPrep produced a number of 3D molecular structures. These minimized 3D energy models were used to undertake the docking investigations with the crystal structure of the target. Ligand docking is not possible before establishing a grid. A constructed protein structure with the appropriate bond order and charges is required for receptor grid generation [68]. After creating the grid box with the prepared target protein, the created 3D molecular structures were docked into the main protease, the target protein, using Maestro. The Glide, Schrodinger, program was used to perform the molecular docking.

Many successful drug delivery strategies have emerged as a result of breakthroughs in the fields of computational, proteomics, and genomics in the last decade. Docking is one of these approaches. It infers protein–ligand flexibility and alternative binding conformations based on the nature of the structures and ligands [69]. Docking studies are a useful tool for determining the correct mechanism of interaction between multiple poses of a molecule. The strength of a protein–ligand complex is usually determined by how well it binds to a
receptor. The binding affinity values and interaction residues display how the six selected phytocompounds bound to the receptor major protease (Table 1).

Table 1. Docking scores of six phytocompounds bound with the target M\textsuperscript{pro} protein of SARS-CoV-2. These six phytocompounds are ranked according to their best docking scores.

| S. No | Compound Name       | Glide g-Score | Glide e-Model | Interacting Residues                      |
|-------|---------------------|---------------|---------------|-------------------------------------------|
| 1.    | Pentagalloylglucose | −12.349       | −114.370      | Leu141, Asn142, Glu166, Pro168, Thr169, Gln189, Thr26, Phe140, Asn142, Glu166, Pro168, Gln189, Thr190 |
| 2.    | Shephagenin B       | −11.811       | −136.263      | Phe140, Leu141, Asn142, Gly143, Glu166, Thr190 |
| 3.    | Isoacteoside        | −10.679       | −96.920       | Phe140, Leu141, Asn142, Gly143, Thr190 |
| 4.    | Isoquercitrin       | −9.834        | −74.011       | Leu141, Thr190 |
| 5.    | kappa-Carrageenan   | −9.021        | −72.718       | Asn142, Glu166, Thr190 |
| 6.    | Dolabellin          | −8.617        | −83.021       | Gly143, Glu166, Thr190 |

The binding and interaction of the selected drugs in the active pocket of the enzymes were investigated individually using the ligand interaction diagram in Maestro, Schrodinger, and Biovia DS visualizer. To explore the nature of the H-bond at the target protein’s inhibitory site, the total number of the hydrogen bonds (H-bond), the key interaction factor in the docked complex, was analyzed. For each molecule, hydrogen bonding, hydrophobic bonding, and electrostatic interactions were investigated. As described in Table 1, six phytocompounds, namely, Pentagalloylglucose (PGG), Shephagenin, Isoacteoside, Isoquercitrin, Kappa-Carrageenan, and Dolabellin, were docked into the active site of the SARS-CoV-2 M\textsuperscript{pro}. PGG, Shephagenin B, and Isoacteoside had a highly negative docking score of −12 to −10 kcal/mol, and Isoquercitrin and Kappa-Carrageenan had a comparable docking score of −9 kcal/mol, and thus interpreted as having a strong binding affinity.

Table 2 shows the selected phytocompounds and their biological properties. PGG exhibited the best docked score value (−12.349) and the best screened ligand with SARS-CoV-2 main protease followed by Shephagenin B (−11.811), Isoacteoside (−10.679), Isoquercitrin (−9.834), Kappa-Carrageenan (−9.021), and Dolabellin (−8.617).

Table 2. The biological properties of six selected phytocompounds docked with the target M\textsuperscript{pro} protein of SARS-CoV-2.

| S. No | Compound Name       | Reported Biological Activities                                                                 |
|-------|---------------------|--------------------------------------------------------------------------------------------------|
| 1.    | Pentagalloylglucose | Polyphenolic molecule, anti-inflammatory, anti-diabetic, and enzymatic resistance features.     |
| 2.    | Shephagenin B       | Antiviral activity against the human immunodeficiency virus.                                     |
| 3.    | Isoacteoside        | Antioxidant and anti-cholinesterase activity, Matrix metalloproteinases inhibition              |
| 4.    | Isoquercitrin       | Antiviral activity, anti-inflammatory activity                                                   |
| 5.    | Kappa-Carrageenan   | Antiviral activity against coronaviruses, dengue virus, and herpes simplex virus.               |
| 6.    | Dolabellin          | Toxicological, and antiviral characteristics against HIV, HCMV, and other infections              |

PGG is a polyphenolic molecule with anti-inflammatory, anti-diabetic, and enzymatic resistance characteristics [70,71]. This is one of the most potent antioxidants in the tannins group, and it has antibacterial and antiviral activities [72,73]. PGG may be a promising antiviral compound against the COVID-19 spike receptor-binding domain (RBD), according to a recent study [74]. PGG makes interactions with Leu141, Asn142, Glu166, Pro168, Thr169, and Gln189 in the binding pocket of M\textsuperscript{pro}. Figure 2A,B show the interaction between PGG and the target M\textsuperscript{pro} protein of SARS-CoV-2.
Shephagenin B interacts with Thr26, Phe140, Asn142, Glu166, Pro168, Gln189, and Thr190 after docking with the MP\textsuperscript{pro}. Shephagenin B, found in Shepherdia argentea leaf extract, is a member of the tannin family. According to research, it acts as an antiviral component against the human immunodeficiency virus (HIV) [75]. Figure 3C,D show the interaction between Shephagenin B and the target MP\textsuperscript{pro} protein of SARS-CoV-2.

Isoacteoside interacts with Phe140, Leu141, Asn142, Gly143, Glu166, and Thr190 residues of MP\textsuperscript{pro}. Isoacteoside is a phenylethanoid glycoside of the phenylethanoid family and an α-Amylase inhibitor [76,77]. This also has antioxidant and anti-cholinesterase prop-

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**Figure 2.** (A,B) Illustrations of the interaction between PGG and the target MP\textsuperscript{pro} protein of SARS-CoV-2.

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**Figure 3.** (C,D) Illustrations of the interaction between Shephagenin B and the target MP\textsuperscript{pro} protein of SARS-CoV-2.
Isoacteoside interacts with Phe140, Leu141, Asn142, Gly143, Glu166, and Thr190 residues of Mpro protein of SARS-CoV-2. Figure 4E,F show the interaction between Isoacteoside and the target Mpro protein of SARS-CoV-2.

Figure 4. (E,F) Illustrations of the interaction between Isoacteoside and the target Mpro protein of SARS-CoV-2.

Only two residues, Leu141 and Thr190, formed interactions with Isoquercitrin. Isoquercitrin is a flavonoid found in fruit and vegetables and has antiviral properties against the human herpes and Zika virus [79,80]. This chemical has anti-inflammatory properties as well [81]. Figure 5G,H show the interaction between Isoquercitrin and the target Mpro protein of SARS-CoV-2.

Figure 5. (G,H) Illustrations of the interaction between Isoquercitrin and the target Mpro protein of SARS-CoV-2.
Kappa-Carrageenan interacts with Asn142, Glu166, and Thr190. Carrageenans are a type of linear sulfated polysaccharide that is discovered and isolated mostly from the cell walls of specific species of red seaweeds [82]. These polysaccharides show antiviral activity against a variety of viruses, including coronaviruses, dengue virus, and herpes simplex virus. Many studies have been conducted to investigate the role of Kappa-Carrageenan in influenza virus [83,84]. Kappa-Carrageenan has a 3,6-AG bridge and one sulfate ester group. Because of this, it is less hydrophilic and less soluble in water [85]. Figure 6I,J show the interaction between Kappa-Carrageenan and the target M\textsuperscript{pro} protein of SARS-CoV-2.

Dolabellin forms interactions with Gly143, Glu166, and Thr190. Dolabellin is a cytotoxic bisthiazole metabolite derived from the Sea Hare *Dolabella auricularia* [86]. These compounds could be used in biological research since they have the potential to be used as therapeutic components. Many of the Dolabellin derivatives have pharmacological, toxicological, anti HIV and antimalarial characteristics [87,88]. Figure 7K,L show the interaction between Dolabellin and the target M\textsuperscript{pro} protein of SARS-CoV-2.

Based on these findings, we could see that the residues namely Glu166, Gln189, and Thr190 may be critical amino acids for targeting the M\textsuperscript{pro} of SARS-CoV-2. Despite the fact that the docking process did not confirm the appropriate compounds for wetlab research, additional steps are required to assess the outcomes. The MM/GBSA technique was also an additional step in the docking evaluation process. This method was used to validate the stability of the docking complexes. This MM/GBSA approach is frequently used in biomedical research to predict the free energy of the binding of molecules. Compared to molecular docking score approaches, this scoring system is more accurate [89]. The MM/PBSA and MM/GBSA approaches are based on the molecular dynamic simulations of the receptor–ligand interaction [88]. Because MM/GBSA scoring is based on MD simulations of the receptor–ligand complex, it can be considered an accurate method for ligand receptor complex scoring [90]. This technique ranks as intermediate in terms of precision and computational methods. To determine the relative binding energies of the ligands, we used Schrodinger’s prime MM-GBSA module. The energy of the optimum free receptors, free ligand, and a complex of the ligand with a receptor was calculated (Table 3). The MM/GBSA scoring process of the compounds revealed a high binding affinity with the inhibition site, indicating that PGG, Shephagenin, Isoacteoside, Isoquercitrin, Kappa-

![Image](image-url)
Carrageenan, and Dolabellin have high conformational stability and binding energy when docked into the main protease inhibition site of SARS-CoV-2 (Table 3). These studies may reveal the capability to bind with the main protease of SARS-CoV-2 and their inhibitory effect. To determine the efficacy of these drugs against COVID-19, wetlab investigations will be valuable, based on the findings of this study.

Table 3. MM-GBSA scores of the six selected phytocompounds docked with the target \( M^{\text{pro}} \) protein of SARS-CoV-2.

| S. No | Compound Name         | MMGBSA dG Bind | Prime Energy |
|-------|-----------------------|----------------|--------------|
| 1.    | Pentagalloylglucose   | −79.76         | −12,827.8    |
| 2.    | Shephagenin B         | −76.12         | −12,828.5    |
| 3.    | Isoacteoside          | −66.49         | −12,857.7    |
| 4.    | Isoquercitrin         | −47.12         | −13,056.8    |
| 5.    | Kappa-Carrageenan     | −32.64         | −12,802.2    |
| 6.    | Dolabellin            | −72.43         | −12,925.1    |

4. Conclusions

Proteomics research on SARS-CoV-2 is uncovering a growing number of possible therapeutic targets and possibilities in drug discovery research. The findings imply that six naturally occurring phytocompounds could be repurposed as therapeutics against \( M^{\text{pro}} \) of SARS-CoV-2, as they show potential binding ability. Our findings indicate that the binding mode analysis is useful in developing therapeutic leads with clinical promise in response to emerging infectious diseases for which no specific medicines or vaccines are available. We intend to continue our wetlab research to develop potential SARS-CoV-2 treatment. Our future research will focus on in vitro assays using the SARS-CoV-2 protease enzyme and molecules identified from the study. This could be significant, especially if a new variant emerges in the near future.
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