In-silico bioprospecting of taraxerol as a main protease inhibitor of SARS-CoV-2 to develop therapy against COVID-19

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Research Article

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Abstract

The coronavirus disease outbreak towards the end of 2019 was caused by a novel coronavirus known as SARS-CoV-2. The COVID-19 disease outbreak has been avowed as a global pandemic by the World Health Organization by the end of March 2020. The COVID-19 pandemic was responsible for the crash of the global economy, resulting in the starvation of a large population belonging to economically backward countries. Thus, the global pandemic situation demands the development of a novel antiviral therapy against COVID-19. In the current study, screening of the ligands from the herbal source was performed to explore potential leads through targeting the viral main protease enzyme of SARS-CoV-2. Taraxerol was found to be a potential antagonist of the viral main protease enzyme. Thus, the present article was aimed at investigating taraxerol as a potent herbal lead by toxicity and ADME prediction for the management of COVID-19.

1. Introduction

The Coronavirus disease outbreak during December 2019 in the Wuhan city of China was caused by SARS-CoV-2 and has been declared as COVID-19.[1, 2] COVID-19 was thought to have emerged from a seafood market from an unknown species, causing the virus's emergence and symptoms to be comparable to pneumonia.[1] The confirmation of the human-to-human transmission of the contagious virus was made by the National Health Commission of China in late January. As SARS-CoV-2 began to spread across international borders, affecting the population of multiple countries, WHO designated it an Internationally concerned Public Health Emergency and declared as a global pandemic in March 2020.[3, 4]

Based upon the sequence resemblance of the SARS-CoV-2 nucleotide, it is considered as a Beta coronavirus having high similarity with the well-known and aggressive strains of human coronaviruses (HCOVs). The nuclear material of SARS-CoV-2 was found to be a long positive-sense single-stranded RNA encoding two discrete types of structural as well as non-structural viral proteins.[1, 2] The 5'-untranslated region (5’UTR) and a replicase complex encode for viral structural proteins like spike, nucleocapsid, matrix, and envelope, while 3'UTR and several unidentified open reading frames encode for viral non-structural proteins like protease, phosphatase, and polymerases.[1, 2]

COVID-19 is having initial symptoms of like cough, malaise, fatigue, fever, body aches, loss of smell or taste sensation, inadequacy, and shortness of breath followed by respiratory distress.[5] The persistent viral infection affects not just the lungs, but also other key organs in the body, eventually leading to organ failure.[6–8] Coronavirus transmits from person to person through coughing and sneezing, which spreads to the nasal mucosa via airborne droplets, where it replicates narrowly in ciliated epithelial cells, causing cell damage and inflammation. The transmission of this virus was also observed from infected surfaces to individual’s hands, and then to their bodies.[9]

Globally, more than 216 countries have been affected by the pandemic outbreak of COVID-19 till December 31, 2021. More than 287,022,026 confirmed cases of coronavirus affected people were reported with more than 5,447,886 deaths. According to WHO, China is the first country to report 1,02,083 confirmed cases of COVID-19 with 4636 mortalities. The thoroughgoing number of COVID-19 infections till date has been observed in the US with more than 55 million confirmed cases and 845,745 deaths, followed by India with more than 34 million confirmed cases and Brazil with more than 22 million confirmed cases.[10] Even after eighteen months of the outbreak of the novel SARS-CoV-2 coronavirus, there is still no approved therapy or vaccine available for the cure of this lethal infectious disease. In light of the foregoing, it is critical to design a novel remedy to combat the worldwide epidemic crisis.

The viral main protease enzyme was identified to partake a significant function in the pathogenic entry within the host via ACE2 and may be exploited as a therapeutic antiviral drug target. Inhibition of viral main protease results in the restricting the entry of the pathogen to the host cell terminating the viral infection.[4, 5, 11] As a result, an inhibitor of the main protease is likely to be a successful treatment for COVID-19 pandemics over the world. The proven methodology for in silico screening of herbal leads to identify modest inhibitors of the viral main protease enzyme is depicted graphically in Figure 1.

Herbal medicine is a holistic medicine, being used for the management of several health problems for thousands of years. Herbal medicine inspired several drugs, such as artemisinine, paclitaxel, reserpine, morphine, quinine, emetine, aspirin, and many more, have been discovered for the treatment of numerous diseases. Most of the world population relies on herbal medicine as an alternative and complementary medicine for the management of diseases like COVID-19. In this context, several herbal medicines and their bioactive leads including *Camellia sinensis* (epigallocatechin gallate), *Andrographis paniculata* (andrographolide), *Artemisia annua* (artemisinin), *Betula* sp. (betulinic acid), *Citrus* sp. (hesperidin), *Curcuma longa* (curcumin), *Ficus benjamina* (biorobin), *Glycyrrhiza glabra* (glycyrrhizin), *Mollugo cerviana* (vitexin), *Myristica fragrans* (myricitrin), *Piper nigrum* (piperine), *Radix sophorae* (matrine), *Stephania tetrandra* (tetrandrine), *Tinospora cordifolia* (berberine), *Torreya nucifera* (luteolin) etc. have been explored through computational approaches for the treatment of COVID-19.[12–32] Hence, it inspires us to find such herbal leads through an *in-silico* computational approach for the management of the current pandemic situation. Thus, in the current investigation, putative antagonists of main protease enzyme of the SARS-CoV-2 were acknowledged using docking based computational screening of herbal-based ligands followed by their validation with respect to time by using molecular dynamics simulation in order to develop novel therapy to combat COVID-19.

2. Material And Methods

2.1. Molecular docking simulation

The main protease enzyme of the SARS-CoV-2 complex with an antagonist N3 was procured from the protein databank (6luz). [11,33,34] The three-dimensional macromolecular structure of the viral enzyme is shown in Figure 2. The parted macromolecular structural model was set for docking by amputation of

superfluous water molecules and addition of polar hydrogens, while the reference ligand N3 was prepared by assigning rotatable, non-rotatable and unrotatable bonds.[35,36]

The interacting residues of viral macromolecular enzyme against the complex inhiitor were evaluated by using PyMol software to confirm the macromolecular active site to prepare a grid-box.[37,36] The imaginary grid-box casing the active site of the viral enzyme was demonstrated in Figure 3.

Autogrid software evaluates the chemical configuration of the macromolecule as well as ligand to create maps for various atoms, necessary to accomplish docking simulation.[35,36]

The confirmational search by Autodock for execution of docking process was performed by Lamarckian genetic algorithm. The force-field calculates the ligand's binding energy by integrating intramolecular energies and assessing energetics for bound and unbound states using a comprehensive thermodynamic model. Each ligand molecule's docking parameters are stored in the docking parameter file (DPF).[38,39]

2.2 Virtual screening

In the current investigation, a ligand library of 150 herbal ligands was employed to accomplish in-silico screening against the viral main protease. To find prospective lead compounds, all of these ligands were virtual screened against a validated viral major protease enzyme.[36]

The interactions of the ligands against the macromolecular residues were taken into account while evaluating the docking outcomes for all ligands screened against the viral major protease enzyme. The compounds with the minimum binding energy were selected as the lead molecules based upon the predefined empirical range for the obtained binding energy of -5 to -15 kcal/mol.[40-44]

2.3 Molecular Dynamic Simulation

The selected leads were subsequently screened to choose taraxerol, diosgenin, and amyrin for molecular dynamic to study the stability of their macromolecular complex conformation with respect to time based on their high docking score, safety profile, and non-involvement in normal physiological processes of the human body. For each of the three chosen leads, a molecular dynamics simulation lasting 10 nanoseconds (ns) was performed. Taraxerol was shown to be the most stable lead against the viral main protease enzyme, according to the data, which was verified by magnified simulations over longer time periods of 100 ns. The protein-ligand macromolecular complex was simulated for 100 ns by using Schrodinger's Desmond module at a constant temperature of 300 K. [45-47] Dynamics simulations were performed by solvating the macromolecular complex in an explicit water box of size 10 and modelling the protein-ligand macromolecular complex using the OPLS3e force field.[48-50] Previously, promising and repeatable results were reported using the OPLS3e force field and the SPC water model for the protein targets complexed with the organic ligands. [51] By introducing the ions and subsequently minimizing their energy, the macromolecular complex was neutralized. The Nose–Hoover thermostatic algorithm [52] was used to keep the energy-minimized macromolecular complex at 300 kelvin, while the Martina–Tobias–Klein approach was used to keep the pressure constant throughout the simulations. [53] The

long-range electrostatic interactions between the ligand and the macromolecule were calculated using the particle-mesh Ewald (PME) [54] technique with 0.8 grid spacing and a cutoff radius of 9.0 for Coulomb interactions after the NPT ensemble MD simulation was performed for 100 ns. The simulation interaction diagram tool in the Desmond was used to examine the ligand's precise binding interactions with the macromolecular main protease. [45,46]

The Root Mean Square Deviation (RMSD) of the atoms of both receptors and the complexed ligand were calculated by comparing their reference frame to determine atomic displacement for a certain time frame during the complexation process. During the simulation phase, the macromolecular residues' Root Mean Square Fluctuation (RMSF) was calculated in reference to their initial condition in the crystalline structure. Throughout the simulation technique, the residue index was used to plot the distribution of macromolecular secondary structural elements (SSE) such as alpha-helices and beta-strands. The binding interactions of the ligand within it's the macromolecular site were separated into four groups throughout the simulation procedure: hydrogen bonds, hydrophobic interactions, ionic interactions, and water interactions bridges. The radius of gyration (rGyR), molecular surface area (MolSA), solvent accessible surface area (SASA), and polar surface area of the ligands were all measured (PSA).[55-57] In comparison to its initial frame, the RMSD value of the ligand molecule was determined throughout the whole simulation duration. PSA was determined by taking into consideration the total contribution of oxygen and nitrogen atoms, whereas the ligand's extended length, which correlates to its main moment of inertia, was computed using a 1.4 probe radius.

2.4 ADME evaluation and Toxicity prediction

Osiris molecular property explorer software was used to assess the pharmacokinetics of the shortlisted leads against the SARS-CoV-2 main protease enzyme. Lipinski's Rule of Five has been used to evaluate several physicochemical parameters such as molecular weight, partition coefficient, solubility, hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) sites to determine the pharmacokinetics of the lead compounds.

DataWarrior software was used to predict the presence of any linked hazardous effects in the shortlisted leads. The occurrence of major hazardous effects such as mutagenic-effect, irritant-effect, tumorogenic-effect, and reproductive-effect was assessed in the shortlisted leads.

3. Results

3.1 Molecular docking simulation

A three-dimensional structural model of the viral macromolecule with a resolution of 2.16 was obtained using the X-ray diffraction technique. The protein is made up of a single chain of 306 amino acid residues. N3 comprises 26 rotatable bonds and 9 aromatic carbons, making it a complex inhibitor. In the current computational investigation, all bonds of the inhibitor molecule were kept flexible, and it was also stored in the AutoDock software's pdbqt format.

Wrapping together the ligand N3 and all of the binding residues of the main protease to prepare an three dimensional grid-box. The exact grid coordinates were obtained from our previously published study on the same protein.[58,55,42,44,40] The docking results for the complex inhibitor N3 against viral macromolecular target were tabulated in Table 1.

Table 1. Docking results of ligand N3 against the viral main protease enzyme.

Macromolecule	RMSD	Binding Energy (kcal/mol)	Ki (nM)
6lu7	0.88	-8.22	935.62

3.2 Virtual screening

The lead molecules were chosen based on their affinity for the viral main protease enzyme. The lowest binding-energy obtained for preeminent pose for each ligand and their binding interactions with the macromolecule were used to determine the binding-affinity of the leads. Table 2 shows the binding energy acquired from docking-based virtual screening of the top 10 shortlisted herbal leads.

3.3 Molecular Dynamic Simulation

The putative herbal inhibitor compound taraxerol was further validated using the Schrodinger Desmond module to run a 100 ns dynamics simulation. There are 306 residues in the macromolecular receptor, however the ligand atom contains only one rotatable bond and 30 heavy atoms out of a total of 78. Based on structural validation throughout the operation, the RMSD analysis supports the smooth execution of the equilibrated simulation process. The ligand RMSD demonstrates the ligand’s stability in relation to the macromolecular binding residues during the simulation procedure by aligning their heavy metals.

The RMSD value for the macromolecular residues was found to be well within the 2.8 range, indicating that the majority of the residues do not shift from their starting position during ligand molecule complexation. The ligand molecule's RMSD value has maintained well within 1-2 throughout the simulation run, despite some early swings of up to 9.0 during ligand adjustment within the macromolecular binding cavity, indicating the ligand's strong binding within the macromolecular binding cavity. The ligand taraxerol undergoes a sequence of vibrations after reaching the active binding site of SARS-viral CoV-2's main protease to achieve the most stable confirmation inside the active binding site. As a result, the early oscillations in the ligand's RMSD value of 3-10 ns are caused by these continuing vibrations while performing certain manoeuvres to achieve the most stable confirmation inside the active binding site of the viral main protease enzyme. Figure 4 shows the RMSD of the protein and ligand over the 100 ns period of the molecular dynamic simulation. The RMSF value of macromolecular residues was determined to be well within the allowed range of 3 Å. Few residues changed slightly, with an RMSF value of 2-3 Å; however, the bulk of residues exhibited smaller variations, with an average value of less

than 1 Å. Within the 100 ns period of the molecular dynamic simulation, the RMSF of the viral main protease and the complex ligand taraxerol are shown in Figure 5.

During the simulation process, the SSE analysis revealed that it has 14.94 % alpha helices and 24.21 % beta-sheets, resulting in a total contribution of 39.14 % SSE, which may be conserved for the majority of the simulation. The macromolecular ligand interaction study revealed that Pro168, Leu167, Met165, Cys145, Met49, Gln192, Thr190, and Arg188 interact with the ligand over the course of the 100 ns simulation procedure. More than 8 macromolecular residues were discovered to be consistently interacting with the complex ligand throughout the simulation run. Figure 6 depicts the detailed protein-ligand connections observed during the whole timeframe of the 100 ns molecular dynamic simulation. The ligand's RMSD value was substantially within the range of 1.5 Å, indicating that the ligand fluctuated as little as possible during the simulation process. The ligand's rGyr value was discovered to be in the range of 4.1-4.3 Å. During the modelling phase, no intramolecular hydrogen bonding in the ligand were observed. Throughout the modelling phase, the ligand's MolSA was discovered to be in the range of 372-384 Å2. After some initial variations, the ligand's SASA was found to be in the range of 150-300 2 during the simulation process. During the simulation process, the PSA for the complex ligand was found to be between 35-40 Å2.

3.4 ADME evaluation and Toxicity Prediction

Table 3 shows the pharmacokinetics profiling and ADME evaluation of the shortlisted leads based on physicochemical features such as molecular weight, partition coefficient, solubility, hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) sites.

Table 3: Physicochemical properties of the shortlisted herbal leads for the SARS-CoV-2 main protease enzyme.

S. No.	Name	MW	cLogP	TPSA	HBD	HBA
1	Taraxerol	412	7.01	20.23	1	1
2	Diosgenin	414	4.88	38.69	1	3
3	Amyrin	426	7.28	20.23	1	1
4	Asiaticoside	958	-0.36	315.2	12	19
5	Momordicin	474	5.24	77.76	3	4
6	Hecogenin	430	4.28	55.76	1	4
7	Guggulsterone	312	4.27	34.14	0	2
8	Andrographolide	350	1.88	86.99	3	5
9	Pelargonidin	272	2.39	90.15	4	5
10	Lupeol	426	7.65	20.23	1	1

The prediction of any associated toxic effects in the shortlisted leads by considering the existence of specified functional groups that are already present in those drugs having a main toxic effect like mutagenic-effect, irritant-effect, tumorogenic-effect, and reproductive-effect and the toxicity profiling results of all the shortlisted leads are shown in Table 4.

Table 4: Toxicity evaluation of the shortlisted lead molecules for the SARS-CoV-2 main protease enzyme.

S. No.	Name	Mutagenicity	Tumorigenicity	Irritant	Reproductive effect
1	Taraxerol	No	No	No	No
2	Diosgenin	No	No	No	Mild
3	Amyrin	No	No	No	No
4	Asiaticoside	No	No	No	No
5	Momordicin	No	No	No	No
6	Hecogenin	No	No	No	No
7	Guggulsterone	No	No	No	High
8	Andrographolide	No	No	No	No
9	Pelargonidin	No	No	No	No
10	Lupeol	No	No	No	No

4. Discussion

In-silico computational approach is pioneering for the drug discovery and development. Several drugs have been identified for the treatment of several disease including viral infections. As we know the world is facing health and economic problems due to COVID-19. Still there are no such therapies as well as vaccines have been approved for the treatment of COVID-19. Herbal medicine is very popular throughout the globe for its miraculous effect against health problems. It has been practicing as an alternative medicine for treating the diseases. As per the WHO, 80% population of the world depends upon the herbal medicine for cure and treatment of several diseases. Several drugs have been discovered through natural resources including plants. Therefore, it attracts our mind to identify such potential herbal leads for the management of COVID-19. Numerous leads from botanicals have been recognized thorough computational approaches.

In present study, the lead molecules with binding energy such as taraxerol (-10.17 Kcal/mol), diosgenin (-10.12 Kcal/mol), amyrin (-9.56 Kcal/mol), asiaticoside (-9.54 Kcal/mol), momordicin (-9.51 Kcal/mol), hecogenin (-9.42 Kcal/mol), guggulsterone (-9.23 Kcal/mol), andrographolide (-8.61 Kcal/mol), pelargonidin (-8.49 Kcal/mol) and lupeol (-8.48 Kcal/mol) were identified for inhibiting the viral main protease enzyme. These leads have been reported in medicinal plants including *Clitoria ternatea* (taraxerol), *Dioscorea* sp. (diosgenin), *Eclipta alba* (amyrin), *Centella asciatica* (asiaticoside), *Momordica charantia* (momordicin), *Chlorophytum borivilianum* (hecogenin), *Commiphora* sp. (guggulsterone), *Andrographis paniculata* (andrographolide), *Anagallis monelli* (pelargonidin) and *Carissa spinarum* (lupeol).[59] Hence, these bioactive containing medicinal plants would be effective for the management of the health issue due to SARS-COV-2. In another study, Kar et al. have reported the inhibitory potential of *Clerodendrum trichotomum* containing leads taraxerol, friedelin and stigmasterol against SARS-CoV-2 through in-silico approach. These leads showed inhibitory potential against different enzymes (spike protein, main protease and RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2. Taraxerol exhibited more binding efficiency [spike protein (6LZG), -7.5 ± 0.01 Kcal/mol; main protease, -8.4 ± 0.01 Kcal/mol; RdRp, -7.4 ± 0.02 Kcal/mol) than the friedelin and stigmasterol.[60]

Taraxerol has been reported for several biological activities including antiplasmodial (*Plasmodium falciparum*, IC50, 8.5 μM), antiparasitic (*Trypanosoma brucei*, IC50, 10.5 μM), antioxidant (IC50, 500 μM) etc.[61]

Similarly, Enmozhi et al. have reported the antiviral activity of andrographolide of SARS-CoV-2 main protease enzyme through *in silico* investigation. This investigation includes molecular docking, target analysis, toxicity prediction and ADME prediction for andrographolide. Andrographolid, a bioactive component of *A. paniculata* showed inhibitory effect with binding efficiency (-3.094357 Kcal/mol) against main protease enzyme.[13, 62] Moreover, other lead compounds from plants (epichatechin gallate- 7.24 Kcal/mol, catechin -7.05 Kcal/mol, kaempferol -9.41 Kcal/mol, gingerol -5.40Kcal/mol, zingerol -6.67 Kcal/mol quercetin -8.58 Kcal/mol, curcumin -7.31 Kcal/mol and demethoxycurcumin -8.17 Kcal/mol) have shown inhibitory effects against main protease enzyme.[63] These studies suggested that herbal leads could be promising for the treatment of COVID-19. Further, the potent lead molecules, taraxerol should be explored against SARS-CoV-2 though preclinical and clinical investigation.

5. Conclusion

In-silico virtual screening technique is a highly adequate, prudent and quick approach for identifying a potent herbal lead having therapeutic activity against the viral main protease enzyme of COVID-19. Taraxerol was found to be potential lead against the main protease enzyme of SARS-CoV-2. The structure activity relationship study has revealed that the residue Cys145, Pro168, Met165, Leu167, Gln192, Thr190, and Met49 plays an important interacting role in the ligand binding. The results obtained by molecular docking simulation were further validated by performing 100 ns molecular dynamics simulation and the pharmacokinetic profiling based on their physicochemical parameters were also performed to strengthen the candidature of taraxerol as a safe and optimized inhibitor of viral main protease enzyme. Further, this herbal molecule needs to be validated through preclinical and clinical investigation for its therapeutic applicability.

Declarations

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Code availability: Not applicable

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Tables

Table 2 is available in the Supplemental Files section.

Figures

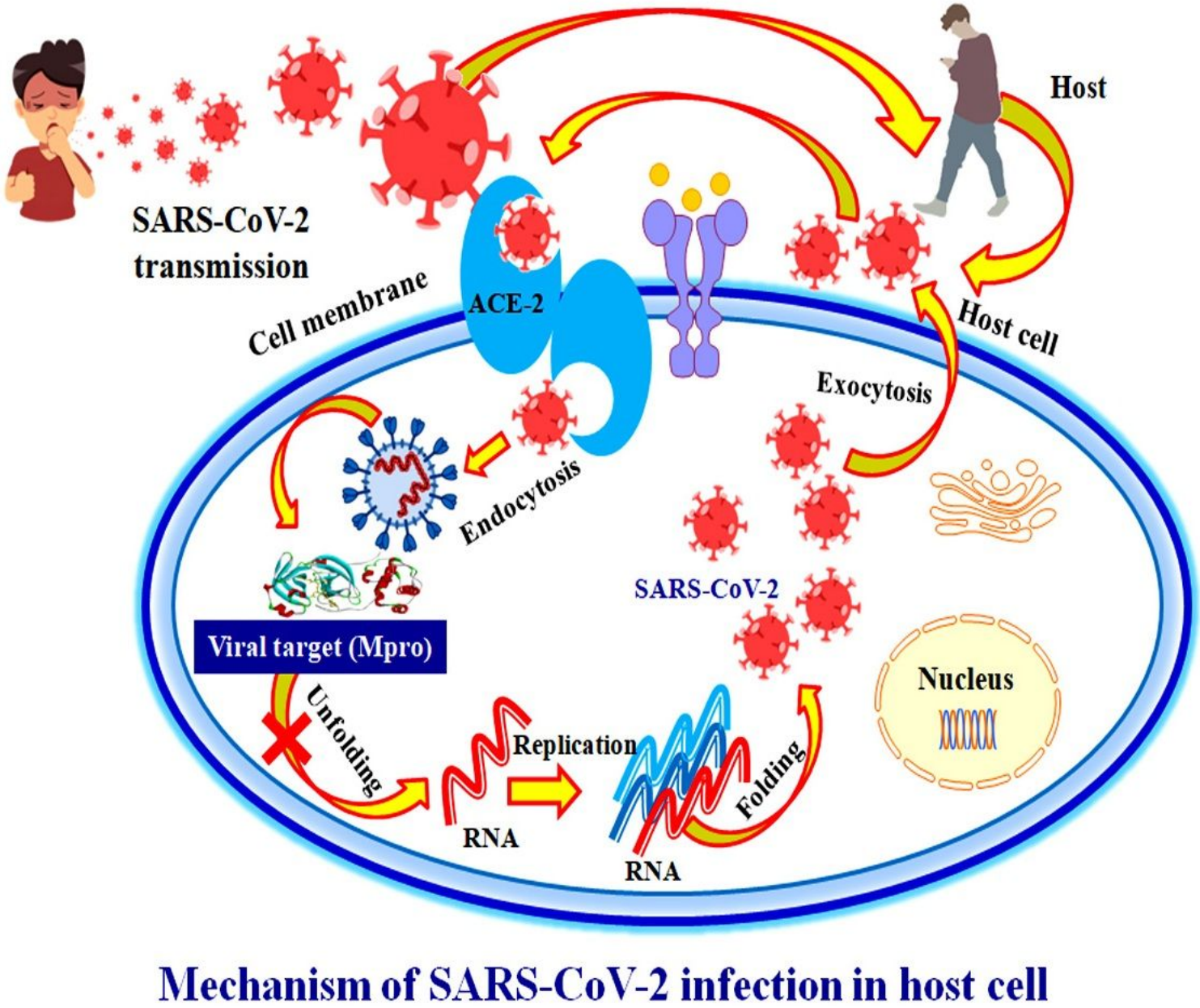

Figure 1

An *in silico* approach for screening herbal leads for potential inhibitors of the viral main protease enzyme in order to discover new antiviral therapies against SARS-CoV-2.

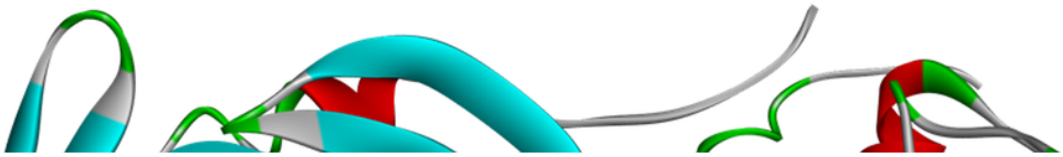

Figure 2

Three-dimensional structural model of the main protease enzyme complex with an antagonist.

Figure 3

Grid-box covering the active site of the viral main protease.

Figure 4

Root Mean Square Deviation: RMSD of the viral main protease enzyme and ligand taraxerol observed during the 100 ns molecular dynamic simulation.

Figure 5

Root Mean Square Fluctuation: During the 100-ns timeframe of the molecular dynamic simulation, the RMSF of the viral main protease enzyme and the complexed ligand taraxerol were measured.

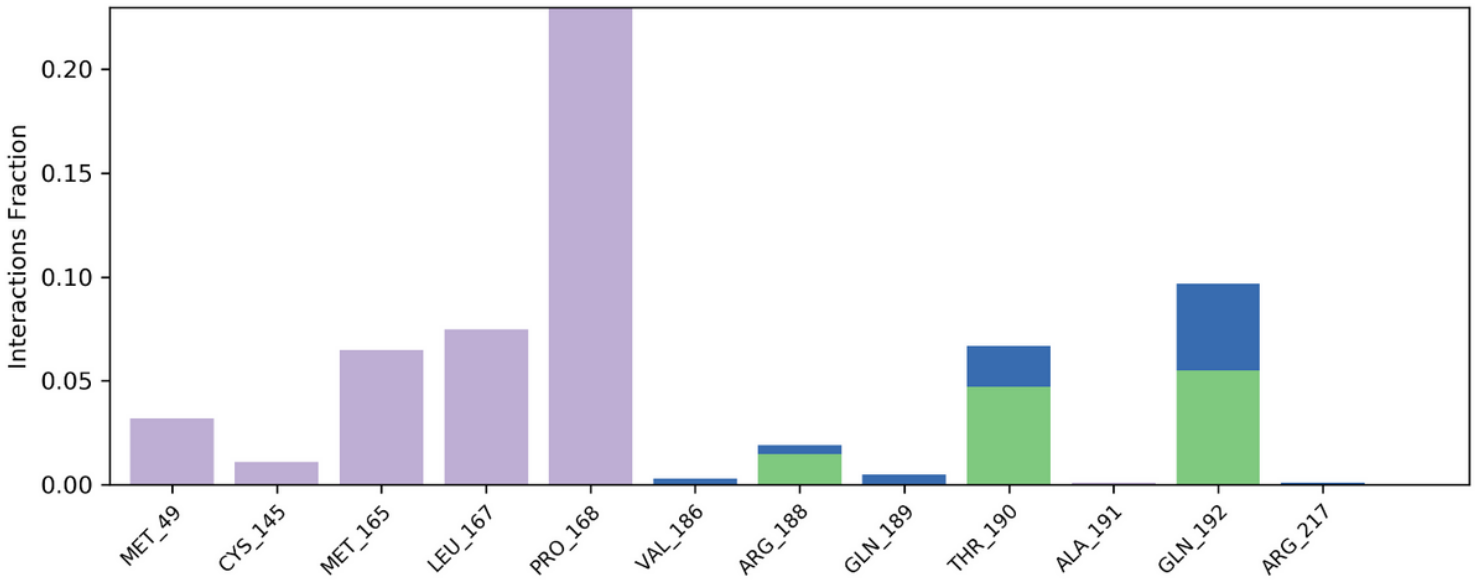

Figure 6

Protein-Ligand Contacts: Detailed protein-ligand interactions were found during the 100 ns molecular dynamic simulation timescale.

Supplementary Files

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- Table2.docx
- Movie.mpeg