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Investigating the Inhibition Effect of Portulaca Oleracea against SARS-COV-2 through Molecular Docking Simulation

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Abstract

Recently a new virus strain designated as SARS coronavirus result in a fatal pandemic known as COVID-19. Bioinformatics and drug screening are directed for the assessment of potential inhibitors before their clinical implementation for the treatment of this fatal pneumonia. One of the expected natural potent inhibitors is Portulaca oleracea which has been assigned as an effective drug to different human ailments throughout the whole world. P. oleracea is widely spread in most areas of Egypt. In the current study, hydrophilic polysaccharides were purified from Portulaca oleracea extracts. Molecular docking simulation is implemented to investigate the antiviral effect of the purified polysaccharides to inhibit COVID-19. The viral protease was downloaded from a Protein Data Bank (PDB# 6y84) then docked with the potent inhibitors. The docking results indicate that the purified polysaccharides can bind tightly to the SARS-CoV-2 viral protease, which indicates that P. oleracea is a potential inhibitor for COVID-19.

Keywords: COVID-19; Homology modeling; Portulaca oleracea; and Molecular docking

Introduction

Coronaviruses (CoVs), comprise four species which divided into α-, β-, δ- and γ-coronaviruses [1]. SARS-CoV-2 or synonymously known as (COVID-19) considered a distinct species of β-coronaviruses that infect the whole world with pathogenic viral pneumonia [1-12] that results in a noteworthy threat to the community health [1]. SARS-CoV-2 is a positive single RNA strand with an external envelope, and gene sequence ranging from 26.0 to 32.0 kilobases [13-15]. Coronaviruses (CoVs) consist of two distinguishing proteins; the first category is structural proteins which include Nucleocapsid (N), Spike (S), Membrane (M), and hydrophobic Envelope (E) that covers the entire coronavirus surface [16]. The second category is non-structural proteins which comprise RdRp (nsp12) and proteases (nsp3 and nsp5) [6, 17]. The transmembrane spike (S) glycoprotein gives rise to homotrimers projecting from the viral envelope [18] and stimulates virus entrance into the host cell receptors [19, 20] in addition to promoting the association of the viral and host receptors [21]. Respiratory blobs and close contact in overcrowded associations are conventional transmission facilities for SARS-CoV-2 [22]. On February 5th, 2020, the first high-resolution crystal structure of SARS-CoV-2 protease released on Protein Data Bank (PDB) Doi: 10.2210/pdb6lu7/pdb [19, 23, 24]. On 3rd March 2020, 6y84 was designated as SARS-CoV-2 protease with unbonded active site **DOI:** 10.2210/pdb6y84/pdb.

Currently, medical research continues instantly to identify active antiviral inhibitors that may help to hinder the pandemic spreading of the viral infection. However, no licensed therapeutic vaccine or drug has been targeted till our current times [2, 19, 25, 26]. As a result, the instant approach depends on the utilization of computational methods of bioinformatics, combined structure-assisted drug design, and drug screening [2, 27], as well as the establishment of predictive 3D protein structures of SARS-CoV-2 to recognize new inhibiting vaccine for SARS-CoV-2 protease [23, 28].

Methods of computer-aided drug discovery have arisen as potent tools in the drug discovery process and have been used lately to study protein-drug/ protein-protein interactions and to identify protein inhibitors [29-31]. The targeting of a potent drug into an approved drug is a time-consuming process. Consequently, a set of computational approaches such as molecular docking, virtual screening, binding free energy evaluation, and molecular dynamics simulation, serves as excellent alternatives for recognizing potential drug agents from compound databank [32]. Cava et al. used in silico gene expression profiles to investigate the mechanism of the angiotensin-converting enzyme 2 (ACE2) using the documented potential drug agents for COVID-19 [33]. Wang et al. investigate the antiviral drugs with high binding affinity against 3CLpro through conducting the virtual screening of the used drugs in clinical trials [34]. Zhang et al. identify potential SARSCoV-2 inhibitors through conducting in silico screening approach for traditional Chinese drugs [35]. Liang et al. conducted a molecular dynamic simulation to validate the binding affinity of α-ketoamide inhibitors to the SARS-CoV-2 main protease. In the current study, molecular docking simulation was conducted on polysaccharides derived from the extract of Portulaca oleracea to assess their ability to inhibit the SARS-CoV-2 protease. Portulaca oleracea (duckweed) is an annual succulent in the Portulacaceaefamily with slight hogweed or parsley which may

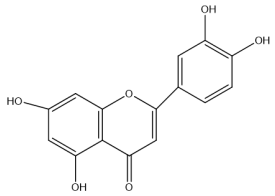
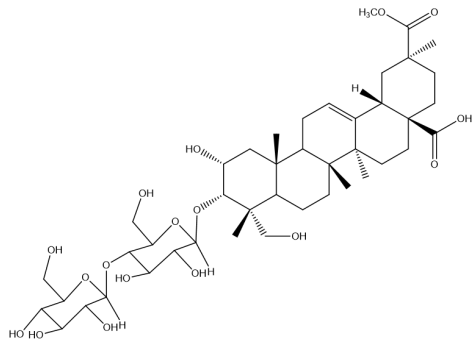
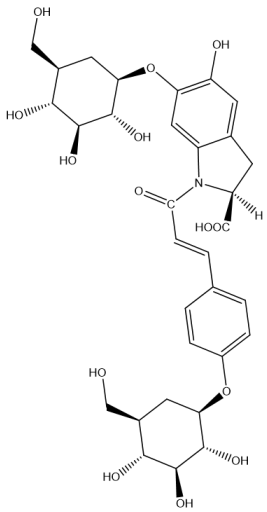
reach 16 inches in height [36]. Molecular docking permits rapid screening of the sequences of amino acid through many coronaviruses' species such as SARS-CoV-2 [23, 37]. The reported docking data were promised and suggest a potential inhibition against the newly pandemic COVID-19 from the currently accessible natural plants [19].

Methods and Reagents

All the reported ligands were built up through the builder module in the docking software, subjected to energy minimization before the commencement of the docking study, then saved as an MDB file in the docking database [25].

The selected ligands comprise the polysaccharides derived from the Portulaca oleracea extract. Table 1 summarizes the structure of the compounds used for molecular docking simulation.

Table1: Summary of the docked inhibitors.

Ligand #	Structure/IUPAC name
Ligand #1	 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4*H*-chromen-4-one
Ligand #2	 (2*S*,4a*R*,6a*S*,6b*R*,9*R*,10*S*,11*R*,12a*R*,14b*S*)-10-(((2*R*,3*R*,4*R*,5*S*,6*R*)-3,4-dihydroxy-6-(hydroxymethyl)-5-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)tetrahydro-2*H*-pyran-2-yl)oxy)-11-hydroxy-9-(hydroxymethyl)-2-(methoxycarbonyl)-2,6a,6b,9,12a-pentamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-4a(2*H*)-carboxylic acid
Ligand #3	 (*S*)-5-hydroxy-6-(((1*R*,2*R*,3*S*,4*R*,5*R*)-2,3,4-trihydroxy-5-(hydroxymethyl)cyclohexyl)oxy)-1-((*E*)-3-(4-((((1*R*,2*R*,3*S*,4*R*,5*R*)-2,3,4-trihydroxy-5-(hydroxymethyl)cyclohexyl)oxy)phenyl)acryloyl)indoline-2-carboxylic acid

Molecular docking study

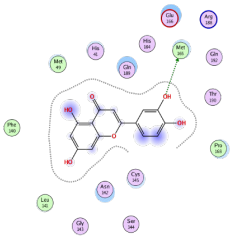
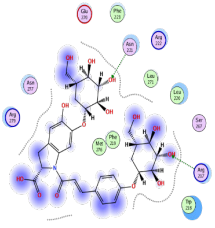
The recently emerged SARS-CoV-2 protease was downloaded from the PDB (PDB ID: 6y84). The non-desired sequence including inhibitors and water molecules were removed from the protease sequence before the commencement of the docking process. The model was validated and energy-minimized in their active physiological settings after the addition of H-atoms to prepare the protonated 3D-structure [6, 38] to achieve a stable and optimized geometrical structure for performing the

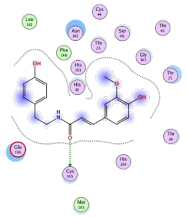
docking study [39]. The system conducted in a triclinic non-periodic cell (1.P1) with a size of 10×10×10 and cell shape 90×90×90. Energy minimized through R-field solvation, Amber10: EHT forcefield with current forcefield charges, cutoff (8,10 Å), and distance-dependent dielectric constant of 4.0 [40]. EHT parameters were applied for small molecules while Amber parameters were subjected to the nucleic acid. The constraints comprise rigid H2O molecules with a gradient of 0.1 RMS kcal/mol/A^2. The Docked complexes were subjected to 500 iterative cycles with a radius offset of 0.4, a gradient of 0.01, and one minimization cycle [40, 41]. The inhibition constants and binding energy are recorded in each docking simulation [37]. The ligands were designated based on the computed binding scores [2].

Results and Interpretations

Ligands with small or negative molecular docking scores will bind tightly with the receptors on 6y84 protein [19]. On the other hand, the shape-scoring function is an empirical relation like the van der Waals' attraction force. The ligand orientation is evaluated with a shape-scoring relation that approaches the binding energy of the ligand-receptor. After the preliminary orientation and scoring assessment, minimization of energy was carried out to identify the nearest energy minimization points within the receptor-binding sites [40]. Most reported ligands bear H- bonding donors or acceptors [42] and display extreme π–π interaction, H-bonds, and/or hydrophobic binding with the 6y84 protease as displayed in Table 2. The ligands interaction with their S- scores and error deviation are provided in supplementary material Table S1. This electrostatic association implies that the reported ligands are potential inhibitors for the COVID-19 [19], as the formed complexes between 6y84 protease and the reported polysaccharides exhibit higher stability with higher binding energy. The formation of extreme H- bonds with the chains and receptor sites of 6y84 protease reveals the ligand's ability to invade the virus main protease and inhibit its viral infection [2]. By screening the docking data, the second ligand (Ligand#2) displays the highest binding score, with a binding energy of -6.58175 kcal/mol, so it can bind firmly to the new COVID-19 protease and diminishes its infectious activity. The docking study assures that the reported polysaccharides inhibit COVID-19, so the Portulaca oleracea plant can be used as a natural source to mitigate the possible infection of the Coronavirus. Figure 1 summarized the interaction of the ligand with the receptor sites on SARS-CoV-2 protease with their isolated surface maps.

Table 2: Illustration of ligand interactions with 6y84 protease.

#	Ligand #	Docking Interaction	Docking Score	Interpretation
1	Ligand #1		-6.00542	H-bonding with Met 165
2	Ligand #2		-6.58175	H-bonding with Asn221 & Arg217

3	Ligand #3		-5.83952	H-bonding with Cys145

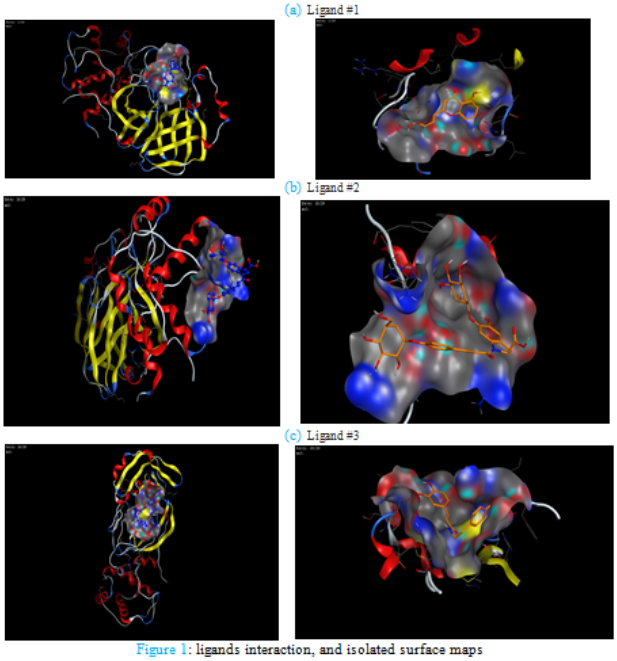


Figure 1: ligands interaction, and isolated surface maps

Conclusion

COVID-19 virus is a severe health fear with high mortality and fatal effect. Although there is no licensed drug till now, efforts directed to investigate a potential therapeutics or drug versus SARS-CoV-2. Computational modeling and virtual screening through molecular docking employed to screen the potent inhibitors against the virus. In this study, the antiviral effects of some potent drugs extracted from the Portulaca oleracea plant were screened for their ability to inhibit SARS-CoV-2 main proteas. The obtained results are based on theoretical docking simulation, without in vivo or in vitro anti-viral assessment. The docking outputs confirmed that the screened polysaccharides bind tightly to 6y84 protease, so can inhibit the infection. Where the 2nd ligand exhibits a binding score of -6.58175, owing to the formation of H-bonding with Asn221 & Arg217, so it is anticipated that it is a potential inhibitor for coronavirus pneumonia.

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