Exploration of two natural inhibitors for treating COVID-19 from simple natural products: nature probably has all the Solutions

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Abstract

The plausible interactions of the two novel natural inhibitors; 2-(3,4-dihydroxy-5-methoxyphenyl)-3,5,7-trihydroxychromenylium **(1)** and 2-(3,4-dihydroxyphenyl)-3-hydroxy-7-methoxy-4*H*-chromen-4-one **(2)** (**Figure 1**) with one of the prominent Coronavirus target (Viral SARS-CoV-2 Spike Glycoprotein) which is involved with the survival of the virus was studied through the Glide (Molecular Docking) module of the Schrodinger (Maestro 9.1) software. The docking scores of both the two natural compounds were reported and a probable conclusion for pharmacotherapeutics was drawn from this exploration.

Keywords: Coronavirus, COVID-19, docking, natural inhibitor

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Introduction

On the last date of December 2019, when the whole world was amused with the New Year celebrations and praying to God for the fulfillment of desires in the upcoming year, the most awaited demon outbreak showed its first presence in the Wuhan Province of People's Republic of China (PRC) [1]. Initially, the whole world did not pay any such attention to this Coronavirus outbreak and continued to work regularly without any precautionary measures [2]. Local people have assumed it like a usual disease outbreak and will be managed by the indigenous administrations, just like every specific region usually suffers from viral attacks every year like Ebola widespread in Africa, Zika widespread in Brazil, etc [3]. Many global intellectuals correlated this viral pandemic with that of SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) of 2003 which was quite limited to China, Taiwan, and South-East Asia and also with the MERS-CoV (Middle East Respiratory Syndrome Coronavirus) of 2013 which was also quite limited to the Arabian Peninsula, and they in due course justified its local restrictions without knowing the future consequences [4].

Even World Health Organization (WHO), the only organization that the whole world looks at during any global pandemic conditions, did not take any foremost rapid priority action(s) at very initial stages until it spreads in the European continent and primarily affected Italy, which was followed by a domino effect for the most technologically advanced nations like Spain, United Kingdom, France, Germany, Netherlands, and Belgium [5]. Every Western-European nation imposed a strict lockdown as a measure to prevent community-level transmission of this deadly virus and also to promote social distancing [6]. The imposed lockdown was initially violated by the citizens of these above-stated nations and landed into an uncontrolled pandemic situation. Many youngsters protested for lifting the lockdown across the cities which worsen the local precautionary and preventive conditions imposed by the administrative systems [7].

The healthcare teams tried to control the rise of the pandemic through their present knowledge, current experience, and trial-and-error basis with the available armamentarium [8]. Many independent medical practitioners or their team(s) has claimed the recovery of corona-positive patients through multiple commonly available drug combinations [9]. All major pharmaceutical companies resumed developing potent inhibitors through multi-centered drug discovery laboratories [10]. However, the report of mutations of this deadly coronavirus strain and its associated drug-resistance phenomenon has in the long run discouraged the global researchers. The last option for the prevention or control of this pandemic lies with vaccines [11].

Academicians having sound bioinformatics background continued to study the interaction of several natural, semi-synthetic, and synthetic molecules with the biological target(s) of coronavirus, by using the free tools or sophisticated paid softwares, during the lockdown period. Similarly, as enthusiastic researchers, we tried to study the plausible interactions of the two novel natural inhibitors; 2-(3,4-dihydroxy-5-methoxyphenyl)-3,5,7-trihydroxychromenylium **(1)** and 2-(3,4-dihydroxyphenyl)-3-hydroxy-7-methoxy-4*H*-chromen-4-one **(2)** (**Figure 1**) with one of the prominent coronavirus target (Viral SARS-CoV-2 Spike Glycoprotein) which is involved with the survival of the virus, through Glide (Molecular Docking) module of the Schrodinger (Maestro 9.1) software. The docking scores of both the two natural compounds were reported and a probable conclusion for pharmacotherapeutics was drawn from this exploration.

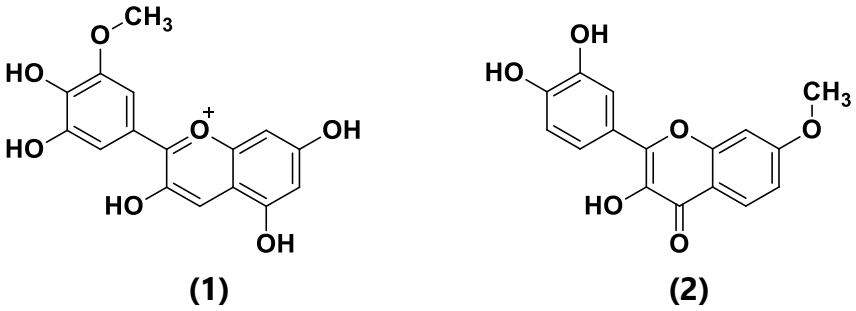

Figure 1. Molecular structures of the natural inhibitors.

Materials and Methods

Sketching of Ligands

The ligands were drawn in a 2D-format initially by utilizing ChemDraw® software v.8.0 and then the file was saved as .cdx format immediately and further saved as .mol file. The LigPrep module was utilized for modifying the ligand torsion of the structures. For docking function, correct protonation conditions were assigned. For each and every ligand, a specific number of stereochemical states of the structure were assigned at 7.0±2.0 pH. The 3D-structure of the ligand was further desalted, then tautomerized, and ultimately optimized utilizing the OPLS_2005 force field. The dielectric constant was assigned 1.0 [12-13].

Preparation and Validation of Protein Targets

For the drug discovery process, the protein structure of the Viral SARS-CoV-2 spike glycoprotein was procured by downloading it from the protein data bank (PDB) where the structure was available as Prefusion 2019-nCoV spike glycoprotein with a single

receptor-binding domain up (PDB ID: 6VSB). For preparing the biological structure for the docking studies, following pre-processing was performed: every aqueous component was removed beyond the distance of 5A°; co-factors, heterogroup, and metal ions were removed; and bond order, disulfide bonds, and formal charges were assigned. The hydrogen atoms and hydrogen-bonding networks were optimized by employing the Impref utility tool and H-bond assignment tool, respectively. For the protein targets, the receptor grids were estimated for the molecular docking where at the predicted active site, the ligands combine. The grids were created in such a way at the centroid of the ligand that it will enclose up the intact ligand. The charge cut off was put at 0.25 and the Van der Waals scale factor was put at 1.0. The ligands depicting the highest score were carried out through XP docking mode and the energy-minimized poses were subjected to final scoring (Glide Score). The induced-fit docking was conducted and the best-docked pose with the lowest Glide score was obtained for each ligand [14-15].

Molecular Docking Studies

The Induced-Fit Molecular Docking (IFD) studies based on the computational method involves utilizing the structure-based drug design technique where the 3D-structure of the free-state low-molecular-weight ligand, having a distinct geometry was docked successfully with an already identified active site of the macromolecular protein, referred to as biological target (such as rigid state receptor or enzyme). The binding of the ligand with the target site was predicted based on the considered quality of the fit. The system calculates low energy values based on appropriate interaction and has its own implication based on the determination of feasible steric clashes. For carrying out the interactions, the RMSD value cut off was fixed to 0.18 A°, restricting the number of ligand poses to 20, Ligand Van der Waals scaling was put 0.5, Receptor Van der Waals scaling was put 0.7, and a decrease in the side chains was performed. The Glide Score was estimated for each and every ligand and grading of the ligands was done based on the obtained biological data [16-17].

Results and Discussion

When *in silico* studies of the two molecules was performed using the Schrodinger software, both the natural inhibitors **(1)** and **(2)** demonstrated strong inhibition of the coronavirus target SARS-CoV-2 spike glycoprotein as evidenced by high Glide Score of -8.407 Kcal/mol and -8.291 Kcal/mol (**Table 1**), respectively. This *in silico* inhibition of this target can be considered or may be correlated to exhibit plausible viral-static activity or even viral-cidal activity to some extent, if tested under the *in vivo* conditions. Both the

compounds showed analogous results when the docking poses were observed. Both the molecules have a number of hydroxyl (-OH) groups that facilitated binding with the amino acid residues.

The inhibitor **(1)** and inhibitor **(2)** contain two active hydroxyl groups at the 2-phenylated domain that interacted successfully with the amino acid residues THR190, GLN192 through 3 strong hydrogen bonds. In addition to it, the 5-OH residue present in inhibitor **(1)** and the 2-OH residue present in inhibitor **(2)** formed strong hydrogen bonding through the amino acid residue CYS145 and GLU166, respectively. Additionally, a single n-n staking was observed through the fused aromatic component of the inhibitor **(2)** with the amino acid residue HIE41 (**Figure 2**).

Table 1: SARS-CoV-2 spike glycoprotein inhibitory perspectives of some natural inhibitors.

Inhibitors	Glide Score (Kcal/mol)	Interacting amino acids residues	Number of Hydrogen bonding
1	-8.407	CYS145, THR190, GLN192	4
2	-8.291	GLU166, THR190, GLN192	4

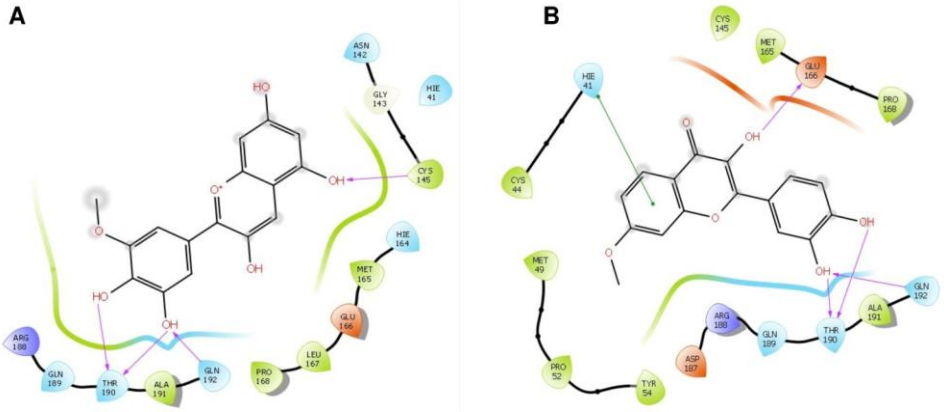

Figure 2. Docking pose of both the natural inhibitors (Inhibitor-1, A; Inhibitor-2, B) against coronavirus target SARS-CoV-2 spike glycoprotein.

Conclusion

The present investigation was a search for inhibitors that will help in recovering the patients suffering from COVID as well as for prophylactic use. This is a nascent step towards the exploration of successful Nature-based safe inhibitors for treating the complex symptoms associated with COVID-19 attack. When the whole world is running for a solution against this demon, probably by the discovery of vaccines, this study will

rejuvenate the minds of scientists that yet there are possibilities that low molecular weight natural ligands have the capability to eradicate this dangerous virus and reduce the global impact created by this pandemic. On the other hand, it can be exclusively perceived from this interesting study that all these natural products that showed minor to moderate or even impressive results, are usually present in food and regular dietary nutraceutical (as flavonoid class, etc.). This eventually concludes that every nature created problem can be completely solved through natural solutions where our diet on these fresh natural foods, extracts, and other elements will help the human mankind in combating the complex situations.

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Conflict of Interest

The authors state that there is no conflict of interest regarding the publication of this manuscript.

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