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Why not methylene blue over the HCQ and remdesvir

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Abstract
Severity of COVID – 19 pandemic discourse the novel treatment and approach against viral infection. Repurposing of various drugs are exercised to treat the corona infection. Available resources of drugs are not targeting the key ligands of the virus and host interaction. Methylene blue is widely utilized to treat the patients of COVID – 19 in India. *In silico* approach attracted the focus to study its role in binding with different proteins involved in infection. Total ten different proteins were selected to study the efficiency binding of methylene blue. Docking study revealed favorable binding score of methylene blue against the studied proteins. Present study disclosed the methylene blue as a promising molecule to treat the infectivity of virus, after confirmation through *in vitro* and *in vivo* study.

Keywords: COVID – 19, molecular docking, methylene blue

Introduction
Corona Virus Disease of 2019 (COVID-19) pandemic has attracted entire focus of scientific community to understand the pathophysiology of the disease and treatment to fight the global healthcare burden. Many wide ranges of medication are being utilized to treat the COVID-19 patients across the globe. Currently, FDA has approved only Remdesivir (Veklury) to treat COVID-19 and this approval was based on findings that hospitalized patients who got remdesivir recovered faster. Various clinical trials in process to study other potential therapies, such as monoclonal antibodies and repurposing of drugs for COVID-19 are under evaluation. Apart from these, Dexamethasone, Convalescent plasma, Bamlanivimab, Casirivimab and Imdevimab have been tested against COVID -19. NIH has recommended Hydroxychloroquine and chloroquine, Azithromycin, Tocilizumab (Actemra), Kinase inhibitors, Interferons, Kaletra, Ivermectin, Oseltamivir, Favipiravir and Colcrys for COVID -19 treatment. Out of all these medications and other available treatments, Methylene Blue (MB) has been emerged as a new hope for the fighting against COVID-19. Iranian universities have initiated the clinical trials for methylene blue as a potential candidate of COVID-19. Outcome of the trials are promising and opens the new horizon in corona era for the recovery of human life. MB has remarkable advantages to use as a medication i.e. it does not cause endothelial dysfunction, it effect appears in cases without positive NO regulation, it is not a vasoconstrictor, the most used dosage is 2 mg/kg in IV bolus, followed by the same continuous hourly infusion, and most importantly, it has an antioxidant effect [1]. MB needs to be analyzed *in vivo* and *in vitro* for its efficacy as a potential COVID-19 treatment. In view of the, ten potential targets of coronavirus infection have been selected to study the binding affinity of MB. Protein targets were downloaded from database, Protein Data Bank (PDB) (http://www.rcsb.org/pdb/home/home.do). TMPRSS2 (PDB: 1Z8G) [2], SARS-CoV-S in complex with ACE2 (PDB: 2AJF) [3, 4], PLpro (PDB: 3E9S) [5], SARS-CoV-2 3CLpro (PDB: 6LU7) [5], SARS-CoVRdRp (PDB: 6NUR) [6], SARSCoV-2 spike glycoprotein structure (SARS-CoV-2-S) (PDB: 6VSB) [7], binding complex of human ACE2 and RBD (PDB: 6VW1) [8], SARS-CoV-2-S (closed) (PDB: 6VXX)(9), SARS-CoV-2-S with one SB(open) (PDB: 6VYB) [9] and Human angiotensin-converting enzyme 2 (ACE2) (PDB: 1R42) [10] are screened for *in silico* analysis. All water molecules were removed, and in the final stage, hydrogen atoms were added to the receptor molecule. The docking between receptor and ligand was performed using the "Dock a ligand" command. Molecular docking was implemented on 1Z8G, 2AJF, 3E9S, 6LU7, 6NUR, 6VSB, 6VW1, 6VXX, 6VYB and 1R42 receptor against ligands using Argus Lab 4.0.1 (Mark A. Thompson, Planaria Software LLC, Seattle, WA, http://www.arguslab.com) to find the reasonable binding geometries and to explore the protein–ligand interactions. Docking simulations were performed by selecting

"Argus Dock" as the docking engine and their relative stabilities were evaluated using molecular dynamics, and their binding affinities, using free energy simulation, pose and time. Single trajectory method was used for the binding energy calculation. Docking score in terms of free energy (ΔG kcal/mol).

Table 1: Docking score against protein receptors using Argus Lab of Methylene Blue

Sr. No.	Name of Protein (PDB ID)	Docking score (ΔG kcal/mol)
1	1R42	-
2	1Z8G	-6.32
3	2AJF	-5.19
4	3E9S	-7.20
5	6LU7	-4.97
6	6NUR	-6.25
7	6VSB	-5.53
8	6VW1	-5.00
9	6VXX	-6.22
10	6VYB	-6.14

As shown in table 1, docking score represent the maximum selectivity and binding affinity of MB with PLpro followed by TMPRSS2 and SARS-CoVRdRp. These results of docking study are in accordance with the previous findings of same protein targets [11] and utilization of MB [12] as a promising molecule to combat the coronavirus pandemic. As shown in table 1, MB showed selectivity against receptors which are found to be pivotal in attachment and infection of coronavirus in host cells [2, 5, 6]. Additionally, MB exhibited remarkable high affinity binding with protein targets compared to HCQ [11]. Moreover, MB has not been found with any reported side effect like hydroxycholorquine, which is responsible for cardiac arrhythmias [13]. Here, results are promising to propose the mechanism of MB mediated coronavirus killing in human host. These further supports the treatments undergoing for pulmonary infection and COVID-19 [14].

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