Bio/chemoinformatics and formulation insights on the hydroxychloroquine debate on combating COVID-19

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INTRODUCTION

- Chloroquine (CQ) and hydroxychloroquine (HCQ) are undergoing several clinical trials for evaluating their efficacy and safety as antiviral drugs. Yet, there is still a great debate about their efficacy in combating COVID-19.
- This study aimed to evaluate the feasibility of intranasal and/or pulmonary administration of CQ/HCQ for COVID-19 using Bio/chemoinformatics tools.
- Molecular docking was carried out on mucin as well as various receptors including Angiotensin-converting enzyme 2 (ACE-2), heparin sulphate proteoglycan and Phosphatidylinositol binding clathrin assembly protein (PICALM), which are expressed in the lung and intranasal tissues and represent initial sites of attachment of the viral particles to the surface of respiratory cells.

METHODOLOGY

- The simulated gelatin matrix was simulated by molecular dynamics using GROMACS®.
- The targeted receptors and proteins were obtained from the protein data bank (as pdb files).
- Docking scores of the drugs on the simulated carrier and the different targets (ΔG) were obtained using MOE®.
- Calculating the main constitutional, topological and electronic descriptors of the investigated drugs were obtained using Bioclipse®.

RESULTS

- Molecular docking on the gelatin-simulated matrix demonstrated potential high loading values and a sustained release profile.
- The docking has shown good binding of CQ and HCQ to the targeted receptors and proteins.

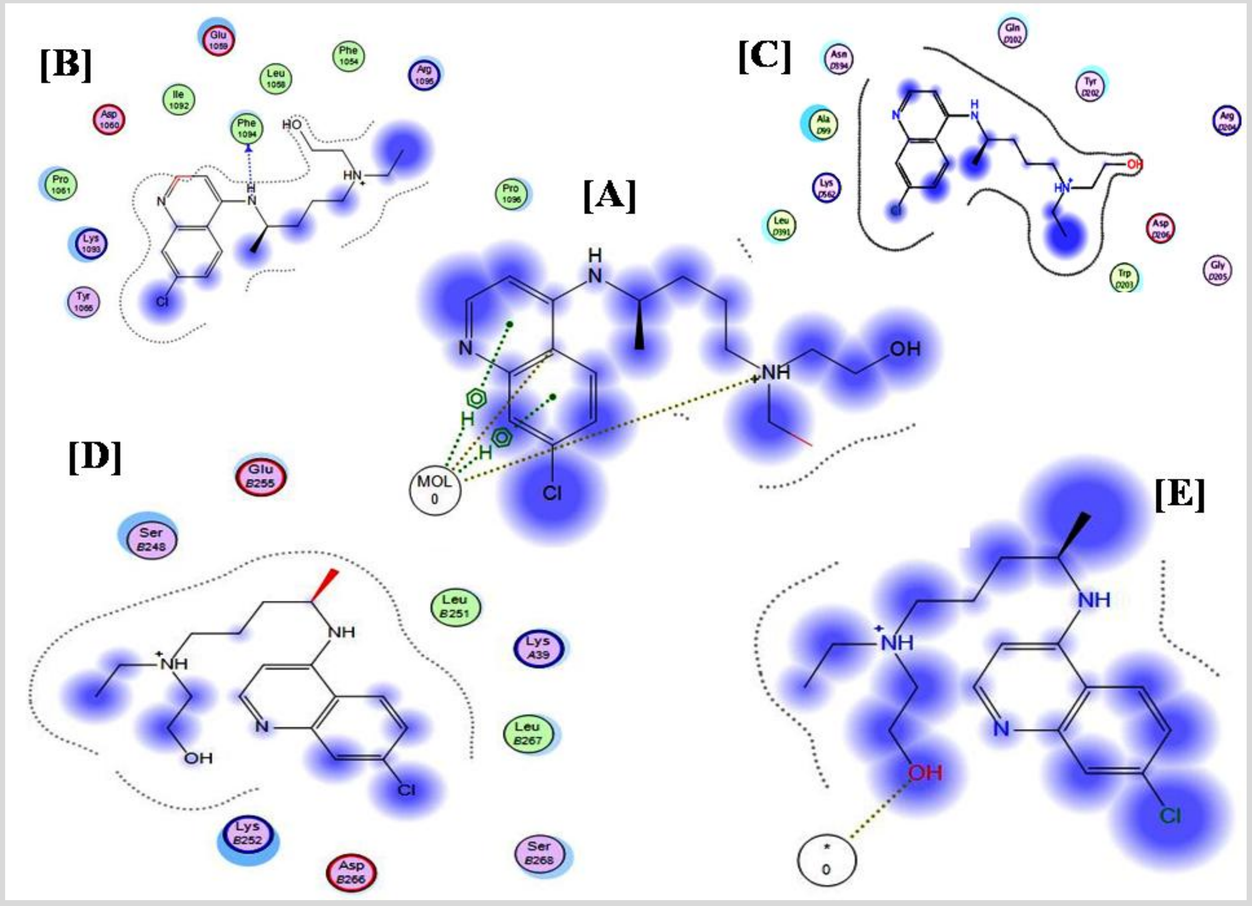
Table 1. Docking binding energy (ΔG) values after docking of the investigated drugs on the related macromolecules.

Macromolecule (Carrier / Protein / Proteoglycan) – PDB code	Binding Energy (kcal / mole)	
	Chloroquine	Hydroxychloroquine
Gelatin matrix (Gelatin nanospheres)	-8.72± 0.1	-10.09 ± 0.01
Mucin – 2ACM	-9.22 ± 0.1	-10.10 ± 0.1
ACE-2 – 6m17	-8.71 ± 0.2	-8.75 ± 0.2
PICALM- 3zyk	-8.29 ± 0.1	-10.49 ± 0.2
Heparan Sulphate Proteoglycan	-8.83 ± 0.1	-11.65 ± 0.1

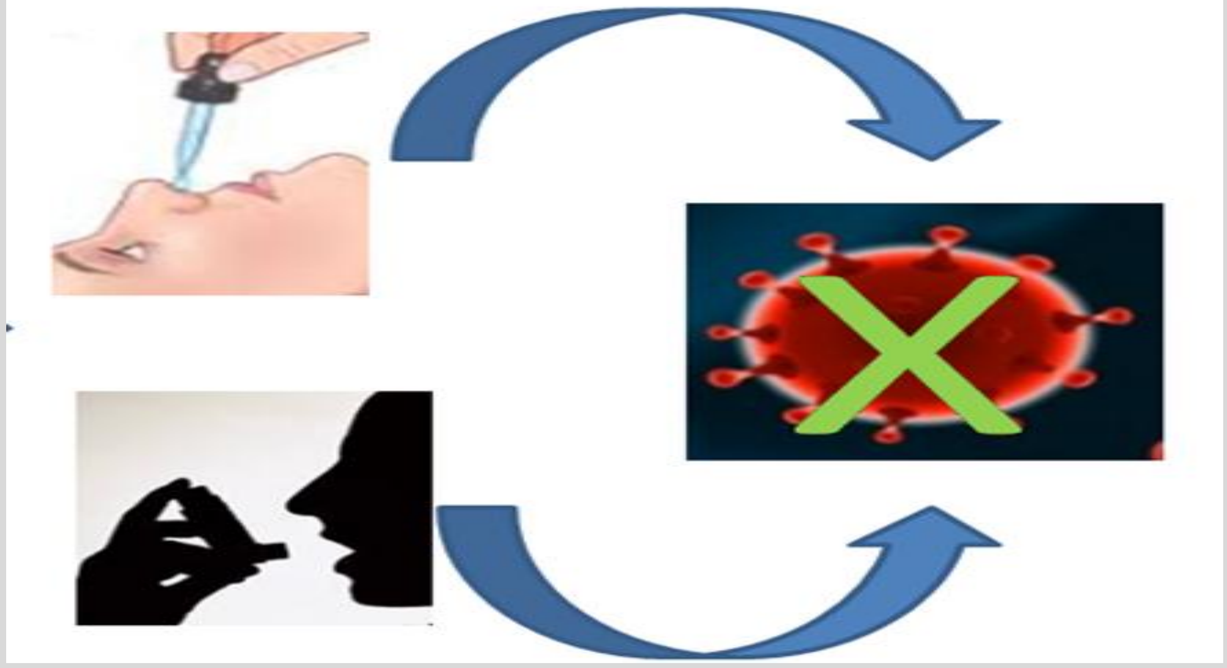
Table 2. The obtained descriptors of the investigated drugs.

Molecule	Canonical SMILES	Total polar surface area	Number of H-bond acceptors	Number of H-bond donors	Molecular globularity	Molecular Flexibility	logP (o/w)	Molecular weight
Chloroquine	Clc1cc2nccc(NC(CCC[NH+](CC)CC)C)c2cc1	28.20	3	1	0.173	5.996	4.287	320.888
Hydroxy-chloroquine	Clc1cc2nccc(NC(CCC[NH+](CCO)CC)C)c2cc1	48.40	4	2	0.186	6.618	3.252	336.89

Figure 1. Docking results of Hydroxychloroquine on [A] Gelatin matrix, [B] Mucin, [C] PICALM , [D] ACE-2 and [E] Heparan Sulphate.



HYPOTHESIZED FORMULATIONS AND PROTOCOL



50 – 100 mg Chloroquine or Hydroxychloroquine loaded in gelatin micro and nanospheres and administered through the nasal and the pulmonary routes

CONCLUSION

- We, hereby, hypothesize the success of the intranasal and the pulmonary routes through a gelatin matrix to overcome several challenges related to CQ and HCQ pharmacodynamics and pharmacokinetics properties and to increase their local concentrations at the sites of initial SARS-CoV-2 entry while minimizing the potential side effects.
- The presented data provide an insight into the use of a novel drug formulation that needs to be tested in adequately powered randomized controlled clinical trials; aiming for a sustained prophylaxis effect and/or a treatment strategy against this pandemic viral infection.

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