BEMS Reports. 2020; 6(1): 9-10.
A Multifaceted Peer Reviewed Journal in the field of Biology, Medicine, Engineering and Science
www.bemsreports.org | www.phcog.net

Research Article

Pharmacology of Chloroquine: Potential Mechanism of Action against Coronavirus

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ABSTRACT

Background: Chloroquine and hydroxychloroquine are recently reported to be effective in treating SARS-CoV-2 illness. The pharmacological mechanisms of this clinical benefit are continued to be explored. **Materials and Methods:** Using molecular docking tools in this study the binding affinity of Chloroquine and hydroxychloroquine were tested against two key SARS-CoV-2 targets i.e., 1) surface glycoprotein (6VSB) involved in viral attachment and 2) main protease (6Y84) involved in viral replication. **Results:** Chloroquine and hydroxychloroquine showed very effective binding affinity against both the SARS-CoV-2 targets. While the binding affinity against main protease was higher, multiple binding sites were observed on the surface glycoprotein of SARS-CoV-2. **Conclusion:** Chloroquine and hydroxychloroquinehave the potential to prevent SARS-CoV-2 attachment, entry and replication by directly binding to SARS-CoV-2 surface glycoprotein and its main protease.

Key words: Chloroquine, Hydroxychloroquine, Protease inhibitors, Coronavirus, Covid-19, Antiviral drugs, SARS-CoV-2, Viral entry.

INTRODUCTION

Chloroquine and hydroxychloroquine are derived from aminoquinolone chemical structure and were-initially developed for the treatment of malaria.[1-3] Subsequently both the drugs were approved for several other clinical indications due to their diverse pharmacological effects (Figure 1).[3-6] The primary mechanism of action of chloroquine against Plasmodium species is achieved by their ability to inhibit the heme polymerase in malarial trophozoites. This prevents the conversion of heme to hemazoin leading to accumulation of toxic heme in the parasite, eventually killing it. In contrast the antiviral activity of chloroquine and hydroxychloroquine is due to their ability to increase intra-cellular/organelle pH by getting protonated. This increased intra-cellular/organelle pH prevents the fusion and entry of virus into the cell. Besides this both chloroquine and hydroxychloroquine are also reported to inhibit the terminal glycosylation of angiotensin-converting enzyme 2 (ACE2).[7] Coronaviruses especially the SARS-CoV and SARS-CoV-2 are reported to bind to the glycosylated ACE2 on cell surface to enter into epithelial cells of the respiratory tract. Thus, chloroquine and hydroxychloroquine by inhibiting the glycosylation of ACE2 can inhibit the entry of SARS-CoV and SARS-CoV-2. Recent studies have shown the benefit of using hydroxychloroquine in the treatment of illness caused by SARS-CoV-2.[4,8] Hydroxychloroquine is also reported to inhibit the release of proinflammatory cytokines such as cytokines like interleukin-1 and tumour necrosis factor, a feature which is likely have synergistic benefit in the treatment of Covid-19.[3-5] Considering the diversity in the pharmacological actions of chloroquine and hydroxychloroquine, it is likely that other potential mechanisms may exist in their action against the SARS-CoV-2 targets. Hence in this study both chloroquine and hydroxychloroquine were assessed for their direct effectsby docking them against the key SARS-CoV-2 targets i.e., (surface glycoprotein and protease).

MATERIALS AND METHODS

The 3D structure of SARS-CoV-2 targets {surface glycoprotein (6VSB) and main protease (6Y84)} were downloaded as PDB files from the protein data bank (https://www.rcsb.org/) and were optimized for molecular docking. The chemical structures of chloroquine and hydroxychloroquine were accessed from PubChem database and were converted to PDB file format and minimised for molecular docking using the Chimera software.[12]Molecular docking was performed to reveal the interactions of chloroquine and hydroxychloroquine with the SARS-CoV-2 targets using AutoDock Vina and the docked protein-ligand complex were visualised using the Chimera and PyMOL v 1.8.2.0 software.[9-12]

RESULTS

The binding affinity (kcal/mol) of chloroquine and hydroxychloroquine against 6VSB and 6Y84 ranged from −4.2 to −5.5; −4.9 to −6.0 and −6.1 to −6.9;

Cite this article : Kumar AHS. Pharmacology of chloroquine: Potential Mechanism of Action against Coronavirus. BEMS Reports. 2020;6(1):9-10.

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History

- Submission Date: 25-02-2020;
- Review completed: 10-03-2020;
- Accepted Date: 20-03-2020.

DOI : 10.5530/bems.6.1.3

Article Available online
http://www.bemsreports.org

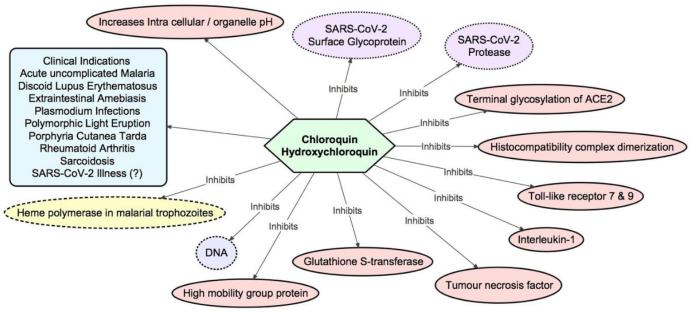

Figure 1: Clinical indications and the pharmacological mechanism of action of Chloroquine and Hydroxychloroquine.

Table 1: Binding affinity of Chloroquine and Hydroxychloroquine against SARS-CoV-2 surface glycoprotein (6VSB) and main protease (6Y84).

Binding affinity (kcal/mol)	SARS-CoV-2 Glycoprotein	SARS-CoV-2 Protease
Chloroquine	−4.60 ± 0.44	−6.48 ± 0.29
Hydroxychloroquine	−5.26 ± 0.33	−6.56 ± 0.42

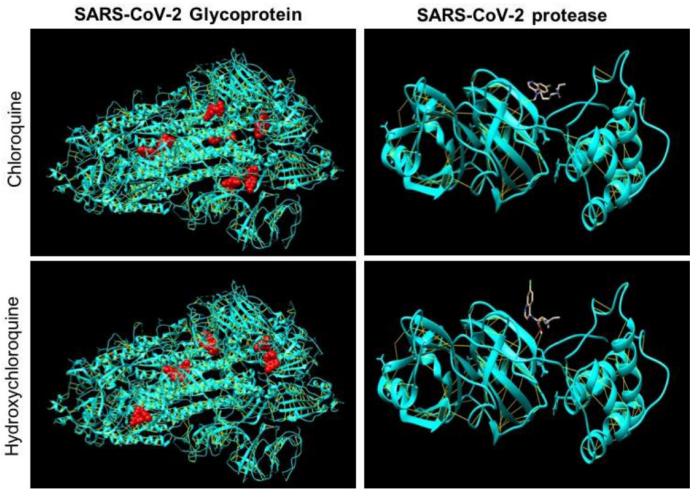

Figure 2: Molecular docking images of Chloroquine and Hydroxychloroquine against SARS-CoV-2 surface glycoprotein (6VSB) and main protease (6Y84) shown with the hydrogen bonds (yellow lines). The docking against 6VSB shows various structural confirmation of the drugs (red).

−6.1 to −7.3 respectively. The binding affinity of both chloroquine and hydroxychloroquine was relatively higher against 6Y84 (SARS-CoV-2 main protease) than 6VSB (SARS-CoV-2 surface glycoprotein). The mean values of the binding affinity are summarised in table 1.

The various structural confirmation of both chloroquine and hydroxychloroquine were observed to docked to 6Y84 at a single location (Figure 2). In contrast the different structural confirmation of both chloroquine and hydroxychloroquine were seen to be binding to 6VSB at different locations (Figure 2).

DISCUSSION

This study provides evidence for the direct effects of the chloroquine and its derivative hydroxychloroquine on SARS-CoV-2 surface glycoprotein and its main protease. Besides the currently know mechanisms of actions of chloroquine like compounds (Figure 1),[1-4,6,8] the ability of these drugs to directly bind to the SARS-CoV-2 surface glycoprotein and its main protease will offer greater efficacy to these drugs by inhibiting SARS-CoV-2 attachment, entry and replication. While the relative binding of the chloroquine's was higher towards the SARS-CoV-2 main protease, their various structural confirmations were observed to bind to different locations on the surface glycoprotein. Hence it is likely that chloroquine's will be equally efficacious in preventing both entry of virus and its replication. Nevertheless, both these features of chloroquine's,together with its other mechanisms[1-3] support its valuable application in the clinical management of SARS-CoV-2 illness.

ACKNOWLEDGEMENT

Research support from University College Dublin-Seed funding/Output Based Research Support Scheme (AHSK), Royal Society-UK (AHSK) and Stemcology (AHSK) is acknowledged.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ACE2: Angiotensin II converting enzyme 2; **6Y84:** (SARS-CoV-2 main protease); **6VSB:** (SARS-CoV-2 surface glycoprotein).

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