Detailed comparison between the safety profiles of chloroquine and hydroxychloroquine

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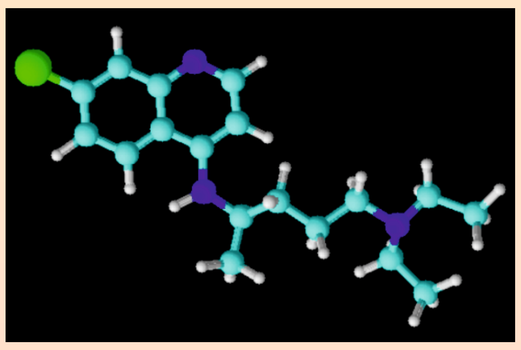
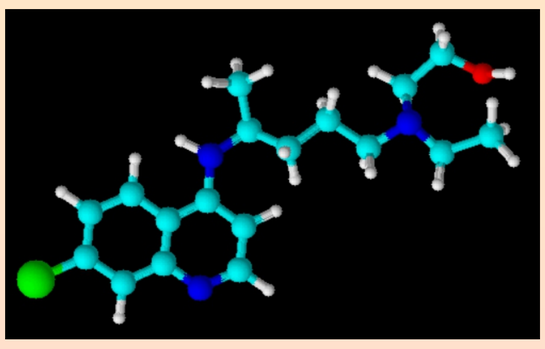
Introduction

The first references to the usefulness of chloroquine (CQ) appeared as early as the 17th century. It was discovered that antimalarial properties could be obtained from quinine bark. The less toxic derivative, hydroxychloroquine (HCQ), was approved for use in 1960. These drugs were also used in March 2020, when the COVID-19 pandemic caused by the SARS-CoV-2 virus was declared by the WHO. CQ and HCQ were approved by the FDA for use in emergency situations. Multiple scientific studies have confirmed that both drugs are highly effective in controlling the infection caused by SARS-CoV-2, reducing the development of pneumonia and thus shortening the duration and severity of the disease. Nevertheless, on June 15, 2020, the FDA made a decision to withdraw the above mentioned drugs from Covid-19 therapy due to the risk of cardiotoxicity. In this study, we analyzed the possible toxic effects of CQ and HCQ using computational chemistry methods. The study was carried out using ProTox II and AdmetSAR software. In order to compare the chemical structure of tested compounds the process of so called superimposition, i.e. overlapping of two molecules, was carried out. The research demonstrated that in silico methods are a useful source of data on drug toxicity. The obtained results confirmed the literature reports on the safety profile of CQ and HCQ.

Analysed structures

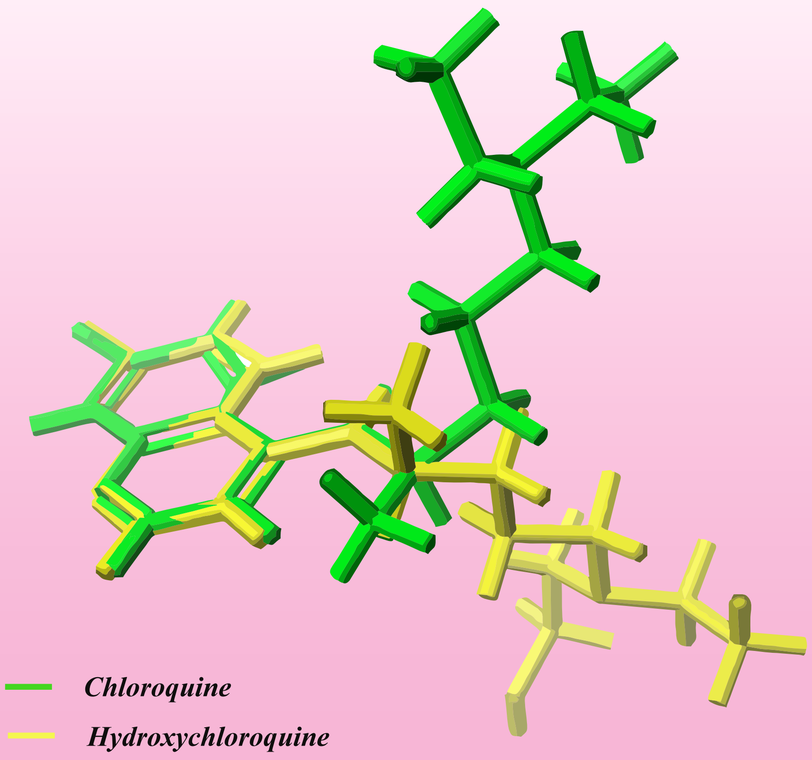


Chlorochina

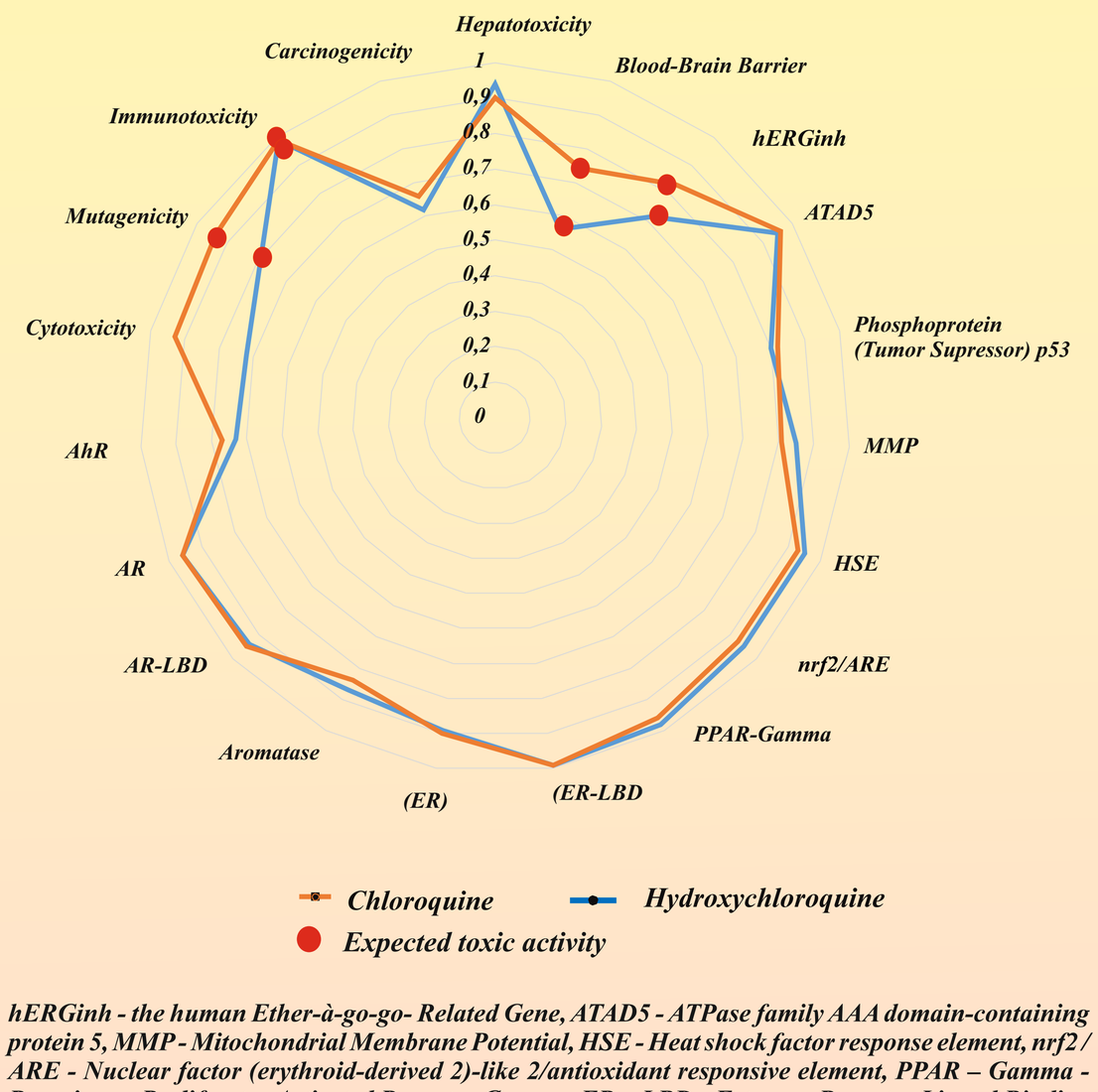


Hydroksychlorochina

Assessment of structural similarity



Evaluation of the toxicity profile



hERGinh - the human Ether-à-go-go- Related Gene, ATAD5 - ATPase family AAA domain-containing protein 5, MMP - Mitochondrial Membrane Potential, HSE - Heat shock factor response element, nrf2 / ARE - Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element, PPAR – Gamma - Peroxisome Proliferator Activated Receptor Gamma, ER – LBD - Estrogen Receptor Ligand Binding Domain, ER - Estrogen Receptor Alpha, AR – LBD - Androgen Receptor Ligand Binding Domain, AR - Androgen Receptor, AhR - Aryl hydrocarbon Receptor.

derivatives.

Materials and methods

1. An analysis of the potential toxic effects of chloroquine and hydroxychloroquine was conducted.

2. Using ProTox II and AdmetSAR software, a comparative analysis of the toxicity probability values of the tested drugs in a particular activity model was completed.

3. The chemical similarity of the structures studied was evaluated, finding similarities and differences in the chemical structure of the

Conclusion

1. Preliminary toxicity evaluation of CQ and HCQ showed that they exhibit toxic effects in a number of areas. Due to the similarity in chemical structure of the molecules (RMS ≈ 1.347 Å), the toxicity ranges of both drugs are at similar levels.

2. The high probability of hERG gene inhibition is of particular concern. Therefore, further and more advanced pharmacological studies on this aspect of drug action are recommended.

3. Studies have shown that drugs easily penetrate the blood brain barrier, so special attention should be paid to toxic effects in the central nervous system.

References

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- *Magdalena Kowalska, Jacek Nowaczyk, Alicja Nowaczyk, KV11.1, NaV1.5, and CaV1.2 transporter proteins as antitarget for drug cardiotoxicity." Int. J. Mol. Sci. 2020, 21: 8099.*