Hydroxychloroquine- A Saviour from The Past - A Review

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Abstract: Hydroxychloroquine is a widely used anti-malarial drug that has been under study for its effect against coronavirus. It has a wide range of applications for various reasons. It also causes certain side effects in the human body when consumed for long. HCQ has been a proven treatment plant for autoimmune disorders like rheumatoid arthritis and SLE. Hydroxychloroquine is a widely used anti-malarial drug. It possesses various benefits and is also used in autoimmune disorders like lupus and rheumatoid arthritis. Hydroxychloroquine sulfate is known to be a derivative of Chloroquine. In this review, we aim to analyze the properties of HCQ, know about the side effects and understand its role in treating COVID-19 and summarize our observations. A systematic search strategy was employed and articles were found using keywords. Literature was taken from databases like PubMed and Google Scholar. Articles that discussed the use of HCQ in COVID-19 were included. Other articles which had data regarding HCQ- side effects, structure and its applications were also included. A total of about 70 articles were collected initially. Multiple articles were added later from other sources. After eliminating articles that did not meet the inclusion criteria, more than 30 studies were finally obtained. This review summarized the use of HCQ in COVID-19. Its structure, and other roles in treatment of Autoimmune disorders were also discussed in detail.

Keywords: Hydroxychloroquine; COVID-19; Chloroquine; Drugs used in COVID-19; Autoimmune disorders

INTRODUCTION
Coronavirus Disease 2019- also known as COVID-19 is a severe acute respiratory disease. It originated in Wuhan province in China. Because of the mode of transmission, it spread very rapidly and soon became a worldwide pandemic. Because of the speed at which it is spreading and its symptoms, it makes it way more dangerous and has consumed lots of lives of people worldwide. There has been no proven cure to the disease. No drugs have been proven to work on this virus and kill it effectively in humans. The only methods that can be employed are maintaining social distancing, sanitizing regularly, wearing a mask, and not ignoring symptoms of this deadly disease. There are multiple symptoms to look out for; breathlessness/breathing difficulty is the major symptom. It is necessary to look out for these symptoms in children as well. Neglect can lead to serious complications. (Gurunathan and Shanmugaavel, 2016)Obstructive airway illnesses are manifested with chronic inflammation affecting the whole respiratory tract.(Dave and Preetha, 2016) Recently, even loss of ability to detect taste and smell is also a sign to be taken seriously. The other symptoms include fever, chills, excess cough, etc. The testing for this disease is being done widely. The only solution as of now is isolation of the patient that has tested positive. Scientists have been looking out for multiple drugs that may have an effect on the virus. Chloroquine and its hydroxy analogue, Hydroxychloroquine are being suggested as treatment options for COVID-19. It was recommended by the Chinese Officials to facilitate use of these drugs as a potential cure to this viral disease. In recent years, resistance to drugs has increased greatly. This makes it difficult to find an ideal drug to cure. (Selvan and Ganapathy, 2016)

Hydroxychloroquine sulfate is known to be a derivative of Chloroquine; it was first synthesized in the year 1946, by the introduction of a hydroxyl group into the structure of the normal Chloroquine. Hydroxychloroquine is a very widely used anti-malarial drug. It is popularly known by its brand name called Plaquenil. It has shown a good activity against a variety of viruses in vitro. (Owens, 2020) It is known to be a very pocket friendly drug and is mostly safe. (Singh et al., 2020) The role of hydroxychloroquine is effective in treatment of Auto-
immune diseases like rheumatoid arthritis. (Liu et al., 2020) Hydroxychloroquine has been demonstrated to have an anti-SARS- and CoV activity which is proven in vitro. This drug has been under study for more than 40 years now, but still is not used as an antiviral. It is being studied for a very long period of time but there is no effect that is known against the virus. (Lover, no date) There is no clear mode of action for this drug, but it is known to reduce the acidity in the endosomes. This reduction in acidity might prevent the endosomes from releasing the virus into the cytoplasm. If this occurs then the spread of the virus can be stopped. Another MOA is that this drug inhibits receptor binding membrane fusion which is required for the entry of coronavirus. (Zhou, Dai and Tong, 2020)

Since Hydroxychloroquine has already been studied thoroughly, we know that it is a proven medication for the treatment of autoimmune diseases such as Lupus and Rheumatoid Arthritis. These autoimmune diseases have to be treated or may proceed to further complications like hepatic fibrosis. (Ezhilarasan, Sokal and Najimi, 2018) After the time of the COVID-19 outbreak, it was suggested by Chinese Health Officials that Hydroxychloroquine may be useful. This suggestion brought about more research being carried out on this drug, its activity on the virus and its side effects caused if any. Many researches have already been done extensively regarding these drugs. Hydroxychloroquine is used in certain cases of diabetes mellitus as well. (Wondafrash et al., 2020) It can bring about toxic effects when it is given in higher doses without proper administration. (Jordan et al., 1999) Lately, the use of Hydroxychloroquine in the treatment of COVID-19 is under study. There is no proven effect of this drug against the virus as of now (Yazdany and Kim, 2020). This drug is also used in lupus pregnancy (Clowse et al., 2006). Some articles also show that hydroxychloroquine may cause ocular toxicity as a major side effect. (Tehrani et al., 2008) The pharmacological properties as well as therapeutic effects of HCQ have been reviewed in many studies. (Rainsford et al., 2015) This review will prove useful because Hydroxychloroquine can be a possible cure to COVID-19. It is necessary to analyze this drug in detail and learn about its effectiveness. This drug is also a known medication for treating rheumatoid arthritis. It is useful in successfully reducing stiffness in cases of arthritis. It is also used by patients having systemic lupus erythematosus. Our team has rich experience in research and we have collaborated with numerous authors over various topics in the past decade (Deogade, Gupta and Ariga, 2018; Ezhilarasan, 2018; Ezhilarasan, Sokal and Najimi, 2018; Jeevanandan and Govindaraju, 2018; J et al., 2018; Menon et al., 2018; Prabakar et al., 2018; Rajeshkumar, Kumar, et al., 2018; Vishnu Prasad et al., 2018; Wahab et al., 2018; Dua et al., 2019; Duraisamy et al., 2019; Ezhilarasan, Poovra and Ashok Vardhan, 2019; Gheena and Ezhilarasan, 2019a; Malli Sureshbabu et al., 2019; Mehta et al., 2019; Panchal, Jeevanandan and Subramanian, 2019; Rajendran et al., 2019; Rajeshkumar et al., 2019; Ramakrishnan, Dhanalakshmi and Subramanian, 2019; Sharma et al., 2019; Varghese, Ramesh and Veeraiyan, 2019; Gomathi et al., 2020; Samuel, Acharya and Rao, 2020).

The most important function of HCQ is that it is an anti-malarial drug. The aim of this review is to learn more about HCQ, its benefits, its drawbacks and most importantly, its role in COVID-19.

COVID-19
Coronaviruses are a group of RNA viruses that are broadly distributed among the human population. They are known to cause diseases in humans (Chen, Liu and Guo, 2020). Coronavirus primarily attacks the respiratory system of humans. The disease is transmitted by droplets of an infected person to a health person. The symptoms of this disease may start appearing in approximately 5 days, but it may take longer to show symptoms or some people that are affected might even be asymptomatic (Rothan and Byrareddy, 2020). The spread of this deadly disease started from Wuhan in China. It rapidly spread to other parts of China and then to different countries and soon spread throughout the world. It was declared as a pandemic in no time. (Lipsitch, Swerdlow and Finelli, 2020). There are a wide range of symptoms that can be observed in patients affected with this virus. Breathlessness is the first sign to look out for in such cases. Other symptoms that follow are sore throat, cough, loss of ability to taste and smell, etc (Sohrabi et al., 2020). At first, this disease was identified as pneumonia but its cause was unknown and not diagnosed accurately (Guan et al., 2020). These groups of coronaviruses are very dangerous to the human body. They can infect the hepatic system as well as the nervous system in humans. Their main mode of action is attacking the respiratory system. As discussed earlier, the mode of spread of this viral infection is person-to-person transmission. This transmission can be from a carrier to an individual or from an infected person to another or even from a doctor to another patient (Bai et al., 2020). A healthy person is one that is in a complete state of physical, mental and social well being (Subashri and Uma Maheshwari, 2016).

Treatment modalities
A variety of drugs have been under study to check for their activity against coronavirus. Multiple drugs from different backgrounds are being studied and researched extensively. They have various diverse active components which are responsible for their properties. (Perumalsamy et al., 2018) In recent years, medicinal plants are being studied to find a substitute to conventional drugs. (Anitha and Ashwini, 2017) Most of these plants have a variety of biological properties that are of great use. (Ashwini, Ezhilarasan and Anitha, 2017) (Ezhilarasan, Lakshmi, Vijayaragavan, et al., 2017) Some of these properties include Anti-inflammatory, Anti-
malarial, Anti-bacterial, Cytotoxic effects etc. (Lakshmi et al., 2015) (Ezhilarasan, Lakshmi, Nagaich, et al., 2017) These plants provide good effects and show beneficial results according to their properties. (Ezhilarasan, 2018) Teicoplanin is a glycopeptide antibiotic that was used in the treatment of bacterial infections. It was found in a study that this drug is active against SARS CoV. This fact was proven in vitro (Baron et al., 2020). Recently, Nanoparticles have gained widespread importance due to their antibacterial, antiviral, anti-inflammatory properties. Various nanoparticles are used widely in treatment protocols. Selenium, Silver, Zinc nanoparticles are some of the examples (Menon et al., 2018)(Rajeshkumar, Kumar, et al., 2018)(Karthiga, Rajeshkumar and Annadurai, 2018) (Rajeshkumar, Agarwal, et al., 2018). These nanoparticles may find a role to play in treatment of this deadly disease. Even nano-carrier drug delivery systems have gained importance and are being used widely (Sharma et al., 2019). Another addition to the list of possible treatment options was antiviral therapy. Antiviral therapy consists of giving a treatment of interferon alpha. This may decrease the viral load in the initial stages of the disease (Shen et al., 2020). Lopinavir/Ritonavir have also been tried and tested but as of now, their efficiency against the virus and safety of use has not been determined (Website, no date). In China, traditional Chinese medicines proved important in the treatment process. It brought about a new hope amongst the population to control the spread of this disease (Dong, Hu and Gao, 2020). Various drugs like Chloroquine, Arbidol, Remdesivir, Favipiravir are under different clinical studies. These studies are being carried out to check their efficacy against the virus (Xu et al., 2020). Certain data showed that the drug Tocilizumab improved the clinical outcome in patients that were severely affected by the virus (Sallard et al., 2020). It is suggested that interferon treatment can be performed in the early stages of viral infection (Baden and Rubin, 2020). Lopinavir and Ritonavir are popularly used antiviral drugs. They are known to have an activity against the enzyme protease. These drugs are also in the stage of clinical trials. (Cunningham, Goh and Koh, 2020) Oligonucleotides have been used previously for treatment of respiratory diseases such as COPD or Asthma. Their role in treatment of COVID-19 is not known as of now (Mehta et al., 2019). Syringic acid has also been under study for its anti-inflammatory and antioxidant activity. It is used as a treatment for certain diseases(Gheena and Ezhilarasan, 2019b). Upcoming research shows that vitamin C is a very effective drug that can help with pain management. It can be an immunity booster in such conditions as well (Chaitanya et al., 2018). In this study, the use of Hydroxychloroquine in curing this viral infection has been discussed in detail. At present, no specific regime, specific medication or specific vaccine has been found as a definitive solution to this virus (Ben-Zvi et al., 2012).

Foreword to Hydroxychloroquine

Hydroxychloroquine is a widely used anti-malarial drug. It possesses various benefits and is also used in autoimmune disorders like lupus and rheumatoid arthritis. Even aloe vera has been proven to be useful in treating skin related problems in diseases (Selvan and Ganapathy, 2016; Subasree, Murthykumar and Dhanraj, 2016). It has great antibacterial and antiviral properties. In cases like cellulitis and others, oral antimicrobials are also given orally as a treatment (Vijayalakshmi and Ganapathy, 2016). These are attributed to its ability of alkalisation. The pH is decreased in the intracellular acidic organelles and this prevents entry of bacteria and virus (Sahraei et al., 2020). It is an orally administered drug, which is the predominant route of drug dosage (G et al., 2017). Its mode of action is through inhibiting the binding to the receptor. This receptor binding is essential for the entry of coronavirus.

Structure of Hydroxychloroquine

The structure of Hydroxychloroquine and Chloroquine are not very different from each other, the difference is just an extra hydroxyl group. In hydroxychloroquine, N- Hydroxyethyl side chain is added and this makes Hydroxychloroquine more soluble than Chloroquine (Fox, 1993).

Overview of Applications

Hydroxychloroquine has a wide array of applications as an antimicrobial, antiplatelet antineoplastic and anti-thrombolytic agent. Anti- platelet drugs are employed to prevent arterial or venous thrombi. It is mainly used as an anti-malarial drug. The other applications of this drug are seen in autoimmune diseases like lupus and rheumatoid arthritis (Stein, Bell and Ang, 2000).

Potential Harmful Effects

As every drug has certain side effects, even Hydroxychloroquine has multiple harmful effects. It is necessary to analyse these effects and understand when to prescribe the drug and what reactions to expect. Hydroxychloroquine is proven to cause Ocular toxicity, Neuro-myotoxicity and retinopathy as well. These effects are dangerous side effects of consuming these drugs for a long period of time. Research is in progress to help overcome these drawbacks. (Touret and de Lamballerie, 2020) (Weiner et al., 1991)
Added Benefits
Focussing on the benefits provided by this drug, we already know that it is a good antimalarial and anti-rheumatic drug. In cases of Lupus, which is an autoimmune disease, the symptoms are skin rashes and other skin related conditions. Hydroxychloroquine is a relatively safe drug to administer in such patients with skin conditions related to SLE. It is an extensively used drug. Recently, it has been found that this drug is also highly effective against the coronavirus and this fact has been proven in vitro (Molina et al., 2020).

Role of hydroxychloroquine in COVID-19
After Hydroxychloroquine was suggested to be a treatment for COVID-19, it was used worldwide. But certain studies show that it has no strong effect on the patients that are suffering from COVID-19 (Rathi et al., 2020). Hydroxychloroquine has been used as a prophylaxis for frontline healthcare workers who are treating the patients that are suffering from this disease (Ferner and Aronson, 2020). As the toxic effects of using Hydroxychloroquine have already been discussed, it is known that the use of Hydroxychloroquine is not guaranteed to be completely safe. In some cases, it may cause adverse cutaneous reactions as a toxic effect. Because of the widespread consumption of Hydroxychloroquine and Chloroquine around the world, it even brought about a shortage of drugs for people that used it for auto-immune diseases like SLE in which Hydroxychloroquine was already proven as an effective treatment choice [(Rome and Avorn, 2020)] Our institution is passionate about high quality evidence based research and has excelled in various fields (Pe, Marimuthu and Devadoss, 2018; Ramesh et al., 2018; Vijayashree Priyadharsini, Smiline Girija and Paramasivam, 2018; Ezhilarasan, Apoorva and Ashok Vardhan, 2019; Ramadurai et al., 2019; Sridharan et al., 2019; Vijayashree Priyadharsini, 2019; Chandrasekar et al., 2020; Mathew et al., 2020; R et al., 2020; Samuel, 2021)

CONCLUSION
The aim of this review was to have an overall knowledge about Hydroxychloroquine. This included a detailed discussion about the side effects, applications and structure of Hydroxychloroquine. The role of HCQ in treatment of COVID-19 is still not clearly stated. There needs to be more extensive research that should be conducted to help understand how HCQ can be helpful in treatment of the viral disease. More researches have to be done to help and find possible solutions to the various side effects caused by this drug.

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