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Mohammed Chyad Al-Noaemi
Al-Ghad International College for Applied Medical Sciences, Najran, Kingdom of Saudi Arabia

Al-Husein Hammoodi
Department of Clinical Therapies, University of Limerick, Limerick, Ireland

Corresponding Author:
Mohammed Chyad Al-Noaemi
Al-Ghad International College for Applied Medical Sciences, Najran, Kingdom of Saudi Arabia

COVID-19 and Hydroxychloroquine relationship in the Past, Present, and Future

Mohammed Chyad Al-Noaemi and Al-Husein Hammoodi

Abstract
In late December 2019, a very serious outbreak of novel coronavirus pneumonia has been reported in Wuhan, China. The WHO nominated this disease as COVID-19 and described its outbreak as a pandemic. Previous and recent *in vivo* and *in vitro* studies have shown that Chloroquine (CQ) can inhibit coronavirus replication. Therefore, CQ and its derivative hydroxychloroquine (HCQ) repurposed for COVID-19 as an emergency therapy. The Chinese treated COVID-19 patients and reported that CQ has a slight advantage over Lopinavir/Ritonavir. While another group reported that HCQ is more effective in treating COVID-19 patients. Many reports from Italy and France, demonstrated that COVID-19 patients treated successfully by HCQ. HCQ could be used in a single dose for prophylaxis against CoV infection. Besides, it could be combined with *Nigella sativa*, which decreases HCQ adverse effects and potentiates its anti-COVID-19 activity. Such therapeutic measurements will protect and save millions of people.

Keywords: COVID-19, coronavirus, chloroquine, hydroxychloroquine, *nigella sativa*

Introduction
Coronavirus
The first report of a human coronavirus (CoV) was in 1965 when Tyrrell and Bynoe isolated a virus from the nasal washings of a male child, and it was named as B814 [1]. The term "Coronavirus" which described the characteristic morphology of these agents, was accepted in 1968 [2]. The earliest reports of endemic human CoV (HCoV) date back to the 1960s, when HCoV-OC43 and -229E were described [3, 4].
Coronaviruses (CoVs), are enveloped viruses with a single-strand, positive-sense RNA genome approximately 30 kb in size, which is the largest known genome for an RNA virus [5]. The genus CoV belongs to the family Coronaviridae in the order Nidovirales [5-7].
CoV is widely distributed among birds, mammals, and humans [6, 8, 9]. Currently, there are six strains of CoV that cause human illness. 229E, OC43, NL63, and HKU1 are typically associated with common cold symptoms [10]. The other two species are originally zoonotic and included Sever acute Respiratory Syndrome (SARS-CoV) which was the related pathogen for SARS-CoV in Guangdong Province, the republican of China in 2002 and 2003, causes severe lung disorder, leading in some cases to systemic infection and eventually death in about 10% of cases [8, 11-13] and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) that was the causative agent for MERS-CoV disease in the Middle East which was first reported in Saudi Arabia in 2012 [14, 15].
In late December 2019, several health centres in Wuhan, China identified many patients with symptoms that resembled pneumonia of unknown causes. Epidemiologically they linked this disease with the seafood and wet animal wholesale market in Wuhan, Hubei Province, China [16]. After a thorough investigation on these patients done by the Chinese Center for Disease Control and Prevention (China CDC), a new virus was identified and reported that initially called the 2019 novel coronavirus (2019-nCoV) [16-18].
On January 30, 2020, the World Health Organization (WHO) named the disease as "COVID-19" which is coronavirus disease 2019 [19]. Although the COVID-19 started in December 2019 in Wuhan, China, soon it spreads across the world at an alarming rate, threatening the lives of millions of people, especially the elderly and immunocompromised patients, therefore, on March 11, 2020, the WHO officially described the COVID-19 outbreak as a pandemic [20]. Such huge numbers of infected and dead people call for an urgent demand for effective, available, and affordable drugs to control the COVID-19 pandemic.

General CQ Therapy
Quinines have been in medical use against malaria for over 350 years. The source of these materials is the bark of the Cinchona trees [21, 22].

Chloroquine was originally synthesized by Hans Andersag in 1934 when he was working for Bayer in Germany [23].
In addition to its antimalarial activity CQ has also been used for the treatment of amebiasis especially that occurs outside the intestine as hepatic amebiasis [24, 25], rheumatoid arthritis [26, 27], lupus erythematosus [28, 29], and as anti-neoplastic activities [30-33].

The Antiviral activity of CQ
The mechanism of CQ antiviral activity could be by a direct or indirect effect. As CQ is a small, lipophilic, amphiphilic and weakly basic substance, therefore, it penetrates the cell membrane very easily and accumulates in acidic organelles, raisin its pH which blocks the viral activity. Furthermore, CQ interferes with the structure of cell membrane receptors preventing its combination with the viruses. In addition to that, CQ has an indirect effect through its immunomodulatory activity, suppressing the production and release of tumour necrosis factor-alpha and interleukin 6, which mediate the inflammatory complications of several viral diseases [6, 33-36]. Therefore, CQ proved to be effective against several viruses, including Dengue Virus [37], hepatitis B virus [38]. Herpes simplex virus type 1 [39], human immunodeficiency virus type 1 [34, 40-42], and the newly discovered coronavirus (SARS-CoV-2) as it will be discussed later.

The Past CQ Anti-Coronaviruses Activities
In 2003, Savarino and colleagues hypothesized that CQ might be of some use for the clinical management of SARS [34]. Then after, *in vitro* studies reported that CQ is effective in inhibiting the replication of human coronaviruses (HCoVs) such as SARS-CoV [35, 43-45], and HCoV-OC43 [6]. Furthermore, an *in vivo* study showed that CQ is highly effective against HCoV-OC43 infection in newborn mice. They also reported that the daily doses of CQ have a long-lasting protective effect against lethal coronavirus OC43 infection in newborn mice. Therefore, they suggested that CQ may be considered as a future drug against HCoVs [6].

The Present CQ Anti-Coronaviruses activities
The most recent *in vitro* studies (2020) reported that CQ is highly effective in inhibiting the replication of the newly discovered SARS-CoV-2 (previously known as 2019-nCoV) [46], and it has also been reported that HCQ is effective in inhibiting SARS-CoV-2 infection *in vitro* [47]. HCQ was found to be more potent than CQ at inhibiting SARS-CoV-2 *in vitro* [48].

The Current Therapeutic Use of CQ or HCQ for COVID-19
In China, from 27 Jan 2020 to 15 Feb 2020, Huang and colleagues initiated a clinical study to evaluate the efficacy and safety of chloroquine in hospitalized patients with COVID-19. At that time, Lopinavir/Ritonavir had been recommended for treating COVID-19. The dose of CQ was 500mg orally twice daily for ten days. The percentages of patients who became SARS-CoV-2 negative (based on RNA tests) in the CQ group were slightly higher on Day 7, Day 10, and Day 14 and they regain their pulmonary function quicker than those treated with Lopinavir/Ritonavir. These results suggest that Chloroquine has a slight advantage over Lopinavir/Ritonavir [49]. Another group reported that HCQ is more effective than CQ in treating COVID-19 patients, and its dose was 400 mg/day for five days [50].
The Italian scientist treated COVID-19 patients by HCQ in a dose of 800 mg as a loading dose followed by 400 mg daily for ten days or 1000 mg CQ for ten days [51]. While the French scientist, to treat their COVID-19 patients, they used HCQ in a dose of 200mg three times a day for ten days and depending on the clinical condition of the patients, and azithromycin may be added to the treatment [52].

The Future Anti COVID-19 Measurements
For COVID-19 treatment, HCQ can be used in a dose of 800 mg as a loading dose followed by 400 mg daily for ten days.
For COVID-19 prophylactic measure, HCQ can be used in a single dose of 200-400 mg, or CQ 500 mg.
The following justify the use of HCQ or CQ for prophylaxis. 1): its uptake by the lung tissues is much more than others such as brain, heart, kidney, skeletal muscle, adipose tissue and liver [53]. 2): the pretreatment with CQ increased the organotropic accumulation of particles designed to target the lungs [54]. Which makes it effective in preventing or treating pulmonary COVID-19. 3): CQ eliminated very slowly from the body, remaining in significant concentrations for several days or even weeks [55, 56]. 4): the *in vitro*, *in vivo*, and the clinical studies demonstrated potent anti-coronaviruses actions. 5): cheap, safe and available.

The Adjuvant Therapy of *Nigella sativa*
NS is effective in the treatment of various diseases such as asthma, eczema, cancer, inflammation, diabetes mellitus, fever, pain, hypertension, infection (bacterial, fungal, parasitic and viral infections), etc. [57-60] Furthermore, NS reduces the toxicity and adverse effects of drugs and chemicals (61-65). Therefore, *Nigella sativa* oil extract (0.5-1.0 ml/day) could be used as an adjuvant therapy with HCQ, whether for treatment or prophylaxis. NS will reduce any possible adverse effects of HCQ. Furthermore, it will potentiate the effect of HCQ against COVID-19 infection as it has been shown in the treatment of malaria [66].

Conclusion
As COVID-19 is a pandemic disease, it is threatening the lives of millions of people, especially immunocompromised patients. The fast-spreading of the disease globally requires emergency therapy.
Many countries have adopted the use of HCQ for the treatment of COVID-19. In case HCQ is not available, CQ could replace it.
We are suggesting the use of HCQ as the first line, whether alone or with combination with NS oil extract for the treatment of COVID-19. Furthermore, HCQ could be used in a single dose as a preventive and prophylactic measure against COVID-19 whether alone or in combination with NS especially for people at risk of getting the disease as the hospital staff, people which will be in contact with the patients, and people traveling to an endemic area.
With such a therapeutic measurement, the disease can be contained, and the population protected.

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68. Address for correspondence: Tom Smith, Laboratoire de Microbiologie, Centre Hospitalier Universitaire de La Timone, 264 rue Saint Pierre, 13385 Marseille Cedex 5, France; email: tsmith@gmail.com