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Drug Repositioning For The Prophylaxis And Treatment Of Covid-19

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Abstract

Coronaviruses are large, enveloped, single-stranded, positive-sense RNA viruses and belong to the family coronaviridae. Other viruses from the same family include the severe acute respiratory syndrome coronavirus (SARS-CoV), which appeared in 2002 in China, and Middle East respiratory syndrome coronavirus (MERS-CoV), which appeared in 2012 in Saudi Arabia. In december 2019, several patients from Wuhan, China were admitted with symptoms of pneumonia. A new virus was identified and initially called the 2019 novel coronavirus (2019-nCoV). On january 30, 2020, the World Health Organization (WHO) named the disease as "COVID-19" which is coronavirus disease 2019. On March 11, 2020, the WHO described its outbreak as a pandemic.

Chloroquine (CQ), the antimalarial drug, elicit antiviral effects against several viruses. Previous studies reported the antiviral activity of CQ against many human coronaviruses (HCoVs) such as SARS-CoV, MERS-CoV, and HCoV-OC43. Recent in vitro studies (2020) reported that CQ and hydroxychloroquine (HCQ) is effective in inhibiting SARS-CoV-2 infection.

In China, in February 2020 over 100 patients treated with (CQ) resulted in significant improvement of pneumonia. In France, on March 17, 2020, some of the COVID-19 patients were treated with (HCQ) and others treated with HCQ in combination with azithromycin to prevent bacterial infection.

It is well known that Nigella sativa can prevent and treat many diseases including various viral diseases and it has been shown that its adjunct use with CQ gives better results in treating malaria in comparison with CQ alone.

Therefore, we suggest the use of Nigella sativa as an adjunct with HCQ to treat COVID-19 , which can potentiate its effect and reduces its toxicity. Furthermore, as HCQ concentrates more in the lung tissue and remains for about weeks, therefore it could be used as a prophylaxis to prevent COVID-19 infection.

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Introduction

Coronavirus

Human coronaviruses (HCoVs) were first reported in 1965 by Tyrrell and Bynoe, and it was named as B814 [1]. Coronaviruses are the largest RNA viruses, enveloped, single-stranded, and belongs to the family Coronaviridae in the order Nidovirales [2,3]. They are widely distributed among birds, mammals, and humans [2,4,5]. There are six species of coronavirus that cause human illness. 229E, OC43, NL63, and HKU1 are typically associated with common cold symptoms [6]. The other two species are originally zoonotic and included sever acute respiratory syndrome (SARE-CoV) which was the related pathogen for SARE-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 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 [4,7-11].

On December 31, 2019, several patients in Wuhan, China started reporting symptoms that resembled pneumonia [12]. A new virus was identified and initially called the 2019 novel coronavirus (2019-nCoV) [13]. On January 30, 2020, the World Health Organization (WHO) named the disease as "COVID-19" which is coronavirus disease 2019 [14]. Although the COVID-19 started in december 2019 in Wuhan, China, soon it spreads worldwide and on march 11, 2020, the who officially described the COVID-19 outbreak as a pandemic [15].

Chloroquine

Quinines have been in medical use against malaria for over 350 years. The source of these materials is the bark of the Cinchona trees [16,17]. Chloroquine is a 4-aminoquinoline derivative of quinine that was originally synthesized by Hans Andersag in 1934 when he was working for Bayer in Germany through the condensation of 4-7-dichloroquinoline with 1-diethylamino-4- aminopentane [18].

CQ eliminated very slowly from the body, remaining in significant concentrations for several days or even weeks. [19,20]. If it is taken in proper doses, CQ is an extraordinarily safe drug [17,21]. Retinal toxicity has been described with long-term use (years) of CQ and HCQ and may be related to over-dosage of these medications [22-24] which can be avoided by taking the daily therapeutic dose [17]. Gastrointestinal upset has been reported with HCQ intake [25]. Besides, CQ is a safe drug if given to infants and pregnant women [20,26-28]. The synthetic form hydroxychloroquine (HCQ) was introduced in 1955 and differs from chloroquine only by a hydroxyl group which decreases its toxicity, increasing its solubility, while conserving its efficacy [18,29-32].

Chloroquine, the antimalarial drug, elicit antiviral effects against several viruses. This antiviral activity could be by a direct antiviral effect by its concentration in the cell organelles or by indirect effect through its immunomodulatory activity, suppressing the production and release of tumor necrosis factor-alpha and interleukin 6, which mediate the inflammatory complications of several viral diseases [5,33,34]. CQ proved to be effective against several viruses including Dengue Virus [35], hepatitis B virus herpes simplex virus type 1 human immunodeficiency virus type 1[34,36-40].

It has been shown that CQ uptake by the lung tissues is much more than others such as brain, heart, kidney, skeletal muscle, adipose tissue and liver [41]. Moreover, pretreatment with chloroquine increased the organotropic accumulation of particles designed to target the lungs [42]. Which makes it effective in preventing or treating pulmonary COVID-19.

In 2003, Savarino and colleagues hypothesized that CQ might be of some use for the clinical management of SARS [34]. Previous in vitro studies reported that chloroquine is effective in inhibiting the replication of human coronaviruses (HCoVs) such as SARS-CoV, MERS-CoV, and HCoV-OC43 [2,33,43,44]. Furthermore, in 2009, and in vivo study showed that CQ is highly effective against HCoV-OC43 infection in newborn mice and they suggested that CQ may be considered as a future drug against HCoVs [2].

The most recent studies (2020) reported that CQ is highly effective in the control of 2019-nCoV infection in vitro and also been found that HCQ is effective in inhibiting SARS-CoV-2 infection in vitro [45,46]. It was found that HCQ is more potent than CQ at inhibiting SARS-CoV-2 in vitro [47]. Furthermore, an in vivo study, demonstrated that CQ has a strong antiviral activity against HCoV-OC43. Moreover, treatment with daily doses of CQ has a long-lasting protective effect against lethal coronavirus OC43 infection in newborn mice [2].

Therapeutic Dosage of CQ and HCQ

In the early days of the COVID-19 outbreak in China, CQ and HCQ have been used. It was found that HCQ is more effective in treating these patients and its dose was 400 mg/day for five days [48]. 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 10 days. Or 1000 mg CQ daily for 10 days [49]. 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, azithromycin may be added to the treatment [50].

Nigella sativa

Nigella sativa (Ranunculaceae) commonly known as the Black cumin, Kalonji, black seed or Habbatul Barakah. The use of Nigella sativa (NS) seeds and oil in traditional remedies goes back more than 2000 years, and the herb was described as 'the Melanthion' by Hippocrates and Doiscroides [51,52]. Prophet Mohammed (Peace Be Upon Him), more than 1400 years ago, described the curative powers of the black seed as "Hold on to use this black seed, as it has a remedy for every illness except death" [53]. Avicenna, a well-known physician of the 10th century described NS in his book "Canon of Medicine", has recommended the use of NS seeds for dyspnea, enhancement of body's energy and also support during recovery from fatigue and dispiritedness [54]. NS is also mentioned for its curative property in the Holy Bible [55,56].

It has been considered as one of the most treasured nutrient-rich herbs in history around the world and numerous scientific studies are in progress to validate the traditionally claimed uses of NS seeds and oil [57-61].

NS has been used for the prevention and treatment of various diseases. The main active constituent of NS is thymoquinone which has a very antioxidant action. It is very effective against various illness such as diabetes, hypertension, cancer, inflammation, fever, asthma, pain (headache and back pain), infections (bacterial, viral, fungal, and parasitic), eczema, and many other disorders. For references [52,56,61,62].

Combination of NS with different agents

We and others have shown that the adjunct use of NS seeds, oil or its derivatives with different conventional chemotherapeutic agents will reduce their side effects such as hepatic or renal toxicity [63-67]. Furthermore, the co-administration of NS with other drugs might potentiate and improve the therapeutic index [63,68]. This synergistic action of NS or its derivatives might result in reducing the dosage of concomitantly used drugs [56].

In 2014 Emeka and colleagues reported that the use of NS seed and oil extract as dietary supplements in combination with chloroquine (CQ) has potential in enhancing the efficacy of CQ and could be of benefit in the management of malaria [59]. According to this valuable variety of the medicinal uses of NS, we highly support the previous words describing it as the miraculous plant and considered by earliest herbal specialists as "The herb from heaven" [62].

Therapeutic dose of NS

250-500 mg of NS seeds orally (3.5-5 mg/kg/day), and 0.5-1.0 ml/day NS oil capsules. It is more acceptable to be given with honey [69-71].

Conclusion

COVID-19 is spreading across the world at an alarming rate, threatening the lives of millions of people, especially the elderly and immunocompromised patients. 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. With proper therapeutic and preventive measures, the disease can be contained and the population protected.

We are suggesting the use of NS as an adjuvant therapy with HCQ to potentiate the effect of HCQ against COVID-19 infection and to reduce any possible adverse effects of HCQ. Furthermore, HCQ with or without NS could be used as a prophylactic measure against COVID-19 infection.

The following justify giving a single dose of HCQ or CQ (alone or in combination with NS oil) as a prophylactic measure against CoVID-19 infection:

1. Chloroquine eliminated very slowly from the body, remaining in significant concentrations for several days or even weeks.
2. It is concentrated in the lung more than other body organs.
3. It has antiviral activity in general and anti-coronaviruses in specific.
4. Until today CQ and HCQ are used for prophylaxis and treatment of malaria.
5. Both HCQ and NS extracts have very well-known antiviral activities.
6. NS improves the therapeutic index of HCQ.

7. CQ or HCQ are cheap and most available drugs.

The suggested prophylactic dose of HCQ is 200mg of HCQ once only as a preventive measure against COVID -19 disease. While the therapeutic doses of HCQ in the combination of NS have been mentioned above for the treatment of COVID-19 patients.

Conflict of Interest

The authors declare no conflict of interest.

Authors Contributions

Al-Noaemi MC developed the research conception and took the initiatives of this work and drafted the manuscript. Hammoudi AM contributed to collecting, extracting, and organizing the data also revising the review paper and agreed to be accountable for all aspects of the work.

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