Section 1

Reviews, lectures

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THE 500 YEARS STORY OF HYDROXYCHLOROQUINE AND ITS IMPLICATION ON OUR MEDICAL KNOWLEDGE: FROM MALARIA TO COVID-19

Quinine is a famous class of drugs over the last 500 years of the history of medicine. It does not treat disease symptoms, but rather modifies the underlying mechanism of the disproportionate effect of inflammation and immunity. Thus, it is described under the rubric of DMARD (Disease-Modifying Anti-Rheumatic Drugs). The mutation of SARS-CoV-1 to SARS-CoV-2 has given the virus the advantage of bypassing many defenses, allowing the virus to spread widely, causing the current pandemic. During this progressive global crisis, the medical community began to repurpose many of the available drugs to treat SARS-CoV-2 infection. Many antiviral drugs have been proposed. Using hydroxychloroquine for the prevention and treatment of COVID-19 has received significant attention in 2020. The idea of using hydroxychloroquine came from previous experience during the initial outbreak of MERS in 2012 when physicians and other scientists conducted random observations on various approved medication to identify potential treatment for HIV, ZIKA virus-infected Ebola infected patients and MERS infection. Despite earlier encouraging findings from in vitro and early observational studies, randomised clinical trials showed the opposite. Thus, a need to reflect our interpretation of all the scientific findings at differ stages and settings.

Keywords: Malaria, Quinine, hydroxychloroquine, COVID-19, pandemia.

Quinine in history

Native South American civilisation, mainly the Incas, discovered that the barks of quinaquina tree could treat various febrile illnesses[1,2]. The famous taxonomist Carl Linnaeus renamed the tree in 1740 to Cinchona tree. The Spanish invaders of Peru in the 16th Century were excited with this remedy, using it to treat Malaria. They started to harvest a large amount of the barks and shipping them to Spain. They called it “Jesuit bark” or “Peruvian bark”. It was a sensational drug in European folk medicine but also was a subject of arguments among physicians and intellectuals (Figure 1).

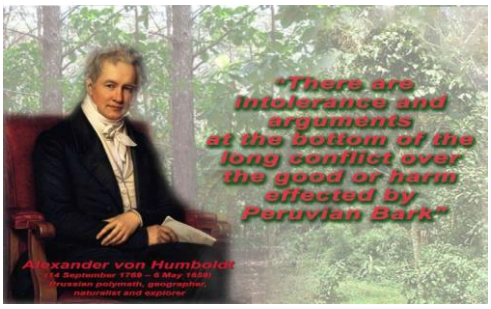

Figure 1: A quote from a prominent 18th Century natural philosopher recognised the beneficial and toxic effects of the Barks (quinine).

This great demand caused extensive harvesting and even implantation of the tree in other subtropical areas. Today few remaining specimens of this endangered tree remain in Peru and the Andes region. By the early 19th Century French scientists isolated quinine as the effective component of the tree bark [2,3]. The quinine powder was vital and precious, for example, by the 1840s British citizens and soldiers in India were using annually 700 tons of cinchona bark for their health protection. They dissolved the powder in carbonated water, adding sugar and lemon to smoothen the bitterness of quinine, creating "Tonic Water", which when added to the Gin resulted in the cocktail of "Gin and Tonic". Winston Churchill once declared, "The gin and tonic has saved more Englishmen's lives, and minds, than all the doctors in the Empire."

The need for quinine uses as anti-malaria medication expanded, but there were not enough barks to cover the European colonial expansions of Asia and Africa. Accordingly, efforts were started to synthesise quinine in the laboratory by the third decade of the 20th Century (figure 2). Meanwhile, extensive use started to show some toxicity and tolerance. The demand for the protection against Malaria among the fighting troops in the Pacific during WW-II required that more/better products be synthesised. Chloroquine was synthesised circa 1945. In a few years, hydroxylation of the chloroquine moiety led to the development of hydroxychloroquine (Figure 2). These forms, chloroquine and hydroxychloroquine, are less toxic and showed better tolerance and are in use today[5].

Physicians began to experiment with the medication and, in the early 1950s, they observed their beneficial effect in the treatment of rheumatoid arthritis and lupus erythematosus using various doses. Combination with other medication(s) reduced potential toxicity and side effects. Thus, hydroxychloroquine has made its name in combination therapy today. They are relatively cheap, and it has an established clinical profile. The World Health Organization (WHO) included them in the WHO list of essential medicines.

In the last thirty years, chloroquine or hydroxychloroquine have been reported to possess potentials activities against various viruses, such as human immunodeficiency virus (HIV), hepatitis A and C virus, influenza A and B viruses, H5N1 virus, Lassa virus, Ebola virus and many others. Initial uncontrolled studies suggested it might have a utility in fighting COVID-19. This was coupled with political and media wrangling, which led to many further clinical trials which more recently showed that they are not as effective as potentially promised and with some toxicity[2][5].

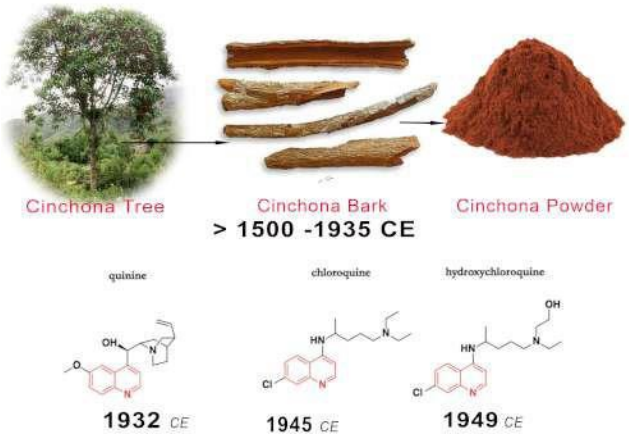

Figure 2: For almost 400 years, nature was the source of quinine It was only in the 20th Century that synthetic forms were made and used.

Mechanisms of action of hydroxychloroquine

Despite the long history and the widespread clinical use of various forms of quinine, insights into the mechanism of action is still evolving [4]. [5] Quinine interferes with the malaria parasite's ability to digest haemoglobin by inhibiting their toxic products. chloroquine or hydroxychloroquine regulate the activity and the excessive reaction of the inflammation and immune system. They neutralise the acidic lysosomal environment, thus interfering

with endocytosis or autophagy preventing the production of harmful substances. They also alter the membrane and intracellular signalling as well as transcriptional pathways, reducing the production of proinflammatory mediators and various cytokines. These mechanisms modulate and smoothen the inflammatory and immunological reaction (figure 3).

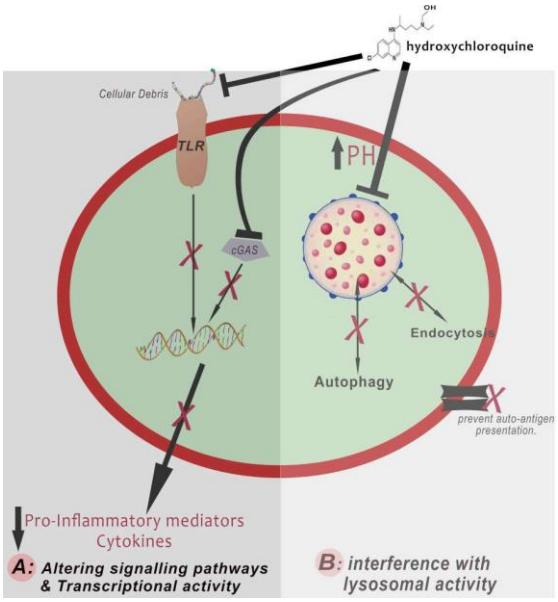

Figure 3: Simplified schema of the potential mechanism of action of quinine, in particular hydroxychloroquine. Panel (A) (the Pink box to the left) quinines interfere with some membrane receptors, like Toll-like receptor (TLR) or ACE2, preventing binding to their ligands, and by inhibiting the intracellular nucleic acid sensor cyclic GMP-AMP synthesis (cGAS). These will alter the signalling and transcriptional pathway that produces proinflammatory cytokines, interleukins, or interferons. Panel (B) (the yellow box to the right) quinine decrease the acidic environment of the Lysosome, hindering the functionality of lysosomes as a waste disposal organelle. Thus, preventing their mechanism of endocytosis (which is essential in viral infection) or autophagy, reducing the presentation of the antigens to the immune cells.

The adverse events

Since the early days of using this class of drugs, the benefits and toxic effects were recognised (Figure 1). There are some differences in the side effects between different forms and salts. Hydroxychloroquine is better tolerated and has lesser side effects than other forms of quinine, including chloroquine. The adverse events are related to the dose, plasma level and are more frequently seen with long-term use. [6-9].

The main side effects are headache, indigestion, nausea and diarrhoea, skin rashes and pigmentations, which are worse in sunlight, besides the bleaching of the hair or mild hair loss. Muscles weakening and tinnitus are also recorded [9] .

One of the significant side effects is colour vision disturbances and altered central vision because of the impact on the retina. The retinopathy may progress and is often irreversible even after stopping the medication. Therefore, ophthalmologic follow-up is a critical component when taking these medications [10-11].

The effects on the Cardiovascular system

The cardiovascular effects have been extensively discussed in scientific literature and in the media, even more so following the advocacy to use hydroxychloroquine to compact COVID-19 infection [12].

There is a dual effect on the cardiovascular system. The use of chloroquine or hydroxychloroquine reduce cardiovascular risks in patients with rheumatic diseases. This effect seems to be most relevant in patients with a thrombotic complication owing to systemic inflammation. The combination with aspirin enhances this beneficial effect. It is unknown if we can see these benefits in patients without rheumatic diseases. On the other hand, there are many reports of serious cardiotoxicity[13,14], mainly heart conduction abnormalities, cardiac arrhythmias, and cardiomyopathy, especially in patients taking high dose or in combination with other drugs. These are not frequent complications, though they are more frequent in women and with long treatment use. Fortunately, most of these adverse

events are reversible upon drug discontinuation. Reports of Cardiomyopathies were presented as left ventricular hypertrophy, hypokinesis, exacerbation of left ventricular diastolic dysfunction and heart failure. Some centres recommend investigating these complications with cardiac magnetic resonance imaging and endomyocardial biopsy to provide prognostic insights and confirm the diagnosis of hydroxychloroquine-induced cardiomyopathy [15,16].

The most morbid cardiovascular effects are the effects on ventricular repolarisation, that is prolonging the action potential of cardiac cells [17,18]. Quinine can block many cardiac ionic membrane channels which regulate the electrical properties of the cardiac cells, specifically the potassium channel known as "Inward rectifier K+ channel" causing a delay in the recovery of the cardiac cell action potential. This increases the likelihood of ventricular ectopy and ventricular arrhythmias; mostly Torsade de pointes, a short but disorganised ventricular arrhythmia that can degenerate to ventricular fibrillation causing sudden death. The clinical manifestation of this toxicity is by prolonging the QT interval of the electrocardiograms, an indicator of prolonging cardiac action potentials. This prolongation is often seen with electrolyte disturbances or when hydroxychloroquine is given with the other medications such as azithromycin, as used in some quarters for prophylaxis and management of COVID-19. Although Torsade de pointes is not common, recent uncontrolled use of these drugs leads to an increase of these arrhythmias, with more deaths. Many medical centres recommend continuous or frequent assessment of corrected QT (QTc) interval on the electrocardiogram, which should not exceed 440 milliseconds. As for all QT prolonging medicines, consider discontinuing these drugs if there are concerning increases in QTc or QTc change from baselyne [19,20].

The history of hydroxychloroquine during COVID-19 Pandemic.

During 2020, there were over 75 million confirmed cases and more than 1.7 million deaths worldwide because of SARS-CoV-2 infection (COVID-19). During this progressing crisis globally, the medical community started to repurpose many available drugs to manage the SARS-CoV-2 infection. Many antiviral drugs were suggested. However, quinine and its derivatives, like hydroxychloroquine, emerged as a targeted medication in the early months of the pandemic. The idea of using hydroxychloroquine came from previous experience during the initial outbreak of MERS in 2012 when physicians and other scientists conducted random observations on various approved medication to identify potential treatment for HIV, ZIKA virus-infected Ebola infected patients and MERS infection [21][22]. The uncontrolled observations suggested that in some patients chloroquine might prevent the virus from invading the human cells in vitro [22]. These observations were not confirmed with well controlled clinical trials because MERS and SARS-CoV-1 did not cause large epidemic and were under control relatively quickly, thus not enough patients in larger trials.

The interest in hydroxychloroquine emerged with the sudden rise of the cases worldwide with SARS-CoV-2 based on the above observations. It attracted disproportionate attention spurred with the endorsement from political leaders in the USA, France and India, and was amplified by news outlets and social media [23] [5]. Many regulatory agencies like the US Food and Drug Administration (FDA) and Indian regulatory agencies, out of a desperate move, provided cautious advice on its use. As a consequence many COVID-19 patients started taking hydroxychloroquine for prophylactic and treatment of symptoms [24]. The authorisations, however, were quickly revoked within a few weeks [25][26]. This unusual approach was taken with caution by many physicians and other regulators worldwide. The American College of Cardiology said in a statement that given the adverse effects of hydroxychloroquine, those taking the drug should either do so as part of a clinical trial or only after evaluating its risk and benefit [10]. The effect of the media and political pressure leads to unhealthy increase and demand hydroxychloroquine in the first half of the 2020. The uncontrolled use of this medication and some reported cases of death[27]. Furthermore, the unprecedented need for a supply of the drug lead to a real worldwide shortage and limiting dispensing quantities for patients with rheumatic diseases or lupus [1] [28][29].

The mutation of SARS-CoV-1 to SARS-CoV-2 gave the virus an advantage of bypassing many of the defence mechanisms provided opportunities for the virus to be transmitted widely, causing a current pandemic. It also enables the virus to infect cells with multiple strategies, thus provoking a challenge to manage this disease. The justification for the use of hydroxychloroquine is probably based on the experimental works on the mechanism of action (Figure 4).

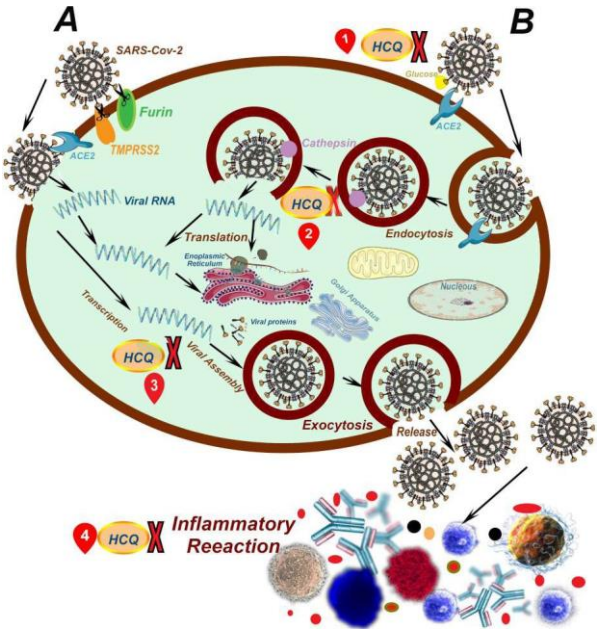

Figure 4. Schematic representation of the SARS-Cov-2 viral infection and replication, with the proposed effect of hydroxychloroquine on different stages of viral infection. For the full details see the text.

The main structure of the SARS-CoV-2 virus is its envelope. It is composed of four proteins, including spike glycoprotein (commonly labelled as S protein), small envelope glycoprotein, membrane glycoprotein, and a nucleocapsid protein component. The later attaches to the core RNA, playing part in the replication process. The spike glycoprotein is one of the most critical components of the virus. It facilitates the entry to the cells. It is a trimeric glycoprotein, comprising both functional and receptor-binding domains. Structure-function studies have also shown that the spike protein of SARS-CoV-2 is highly glycosylated[30].

Much has been learned about the current knowledge of the mechanism of SARS-CoV-2 infection during 2020 pandemic [31] [32][33][34]. The virus uses different approaches to enter the cells. The first (panel A in Figure 4) involved some membrane proteases that cleave the Spike protein, mainly transmembrane serine protease 2 (TMPRSS2) and Furin enzyme[35]. The proteolytic activities of Spike protein help in priming the virus to fuse with plasma members[36]. Some investigators believed binding to angiotensin-converting enzyme 2 (ACE2) is expected to trigger conformational changes in the spike protein facilitates cleavage by the transmembrane proteases [37]. This process results in the fusion of the viral membrane with the plasma membrane, consequently causing the cell entry of the viral RNA (the non-endosomal pathway)[36].

The second entry strategy is via the process of endocytosis (Panel B of the Figure 4). The Spike glycoprotein binds to host receptor (ACE2) [38][39], serving as a medium of cell entry[40]. Proteases mentioned above and others like, a disintegrin and metalloproteinase domain 17 (ADAM17) might promote this interaction. In this process, glycosylation of the spike and ACE2 proteins support this process. Thus, hyperglycaemia might induce potential dysregulation of glycosylation of ACE2 and the spike protein of SARS-CoV-2, which possibly augment the spike protein to bind to ACE2 enhancing the viral entry into the cell. Therefore increasing severity COVID-19 in diabetic or obese patients[41]. Quinine and in particular hydroxychloroquine may prevent the virus from binding to the ACE-2 receptor by inhibiting terminal glycosylation creating a less efficient environment for the virus entry [42][43] (Pointer 1 in Figure 4). When the virus enters the cell in the endosomal vesicles forming a highly dynamic, multifunctional cellular compartment with multiple proteolytic enzymes, mainly various forms of Cathepsins which cleave the spike protein at low pH, leading to fusion of the viral envelope and membrane the endosomes. So, uncoated the viral particle releasing of viral nucleic acid (RNA) into the cytoplasm. Chloroquine and its derivatives can modulate the acidification of endosomes and partially inhibiting this process [44] [45] (Pointer 2 in Figure 4).

In both strategies, the viral RNA is released. The life cycle subsequently takes place by RNA replication, transcription of the viral protein and final assembly. Some Investigator also suggested that hydroxychloroquine may interfere with some

process of replicase-transcriptase complex [46] (Pointer 3 in Figure 4).

The assembled virus will be released from the infected cell by the process of exocytosis. The new viral loads will further provoke an intense inflamematory reaction. Some investigators believe that hydrochloric acid may also contribute in modulating the inflammatory responses [47] [48][32] (Pointer 4 in Figure 4).

The potential Clinical Benefits of hydroxychloroquine in COVID-19

During the early days of the pandemic, many are observational studies and small uncontrolled studies supported the benefits of hydroxychloroquine. These were based on the experimental findings and early observations with previous coronaviruses epidemics. In February 2020, a report of clinical trials on patients with COVID-19 in ten hospitals in China suggested that chloroquine treatment might shorten the duration of the disease[49]. French microbiologist Didier Raoult and colleagues published a randomised study of hydroxychloroquine in 20 COVID-19 patients and concluded that this group of drugs had reduced viral load in the nasal swab but didn't report clinical outcomes such as deaths[50,51]. Thought hydroxychloroquine and other quinine were recommended the former is toxic derivative[22,52]. It was found to be more potent than chloroquine to inhibit SARS-CoV-2 in vitro[53].

It was estimated that hydroxychloroquine dosing regimens for COVID-19 prophylactic to maintain half-maximal effective concentration (EC_{50}) is higher than the dose needed for antimalarial management. Thus, the suggestion was to use 800 mg loading dose followed by 400 mg twice or 3 times weekly for pre-exposure prophylaxis setting and 800 mg loading dose followed in 6 hours by 600 mg, then 600 mg daily for 4 more days for post exposure prophylaxis setting[53]. The complexity of virus pathogenicity as explained above, lead many to advocate combined therapy. Hydroxychloroquine, combined with azithromycin (an antibacterial drug), was clinically noticed to be better to stop the spread of the infection than hydroxychloroquine alone, in addition to significant viral load reduction[50].

These findings fuel the media and political interest despite that many physicians and scientists start to show doubts, in particular due to the serious side effects like the one on cardiovascular that been descrybed above.

Randomised controlled trial with hydroxychloroquine

The interest mixed scepticisms in the use of hydroxychloroquine have necessitated more studies and proper Randomised controlled trial with more in-depth analysis. It is not surprising that by the end of 2020 there are more than 4300 studies recorded (clinicaltrials.gov) of which 265 clinical trials on hydroxychloroquine. Eighty-six of these studies were already completed and reported. Another 84 studies were terminated either early, withdrawn or suspended for various reasons such as the non-recruitment or inadequate sample size[55]. Even more studies (currently about 87 studies) which are still active. These studies were done through the various stages of COVID-19 infection such as pre-or post-exposure prophylaxis, out-patients or symptomatic hospitalised patients or an intensive care unit management [56]. Some studies included the efficacy of hydroxychloroquine in combination with other antibiotics or antiviral drugs or some minerals like zinc [57] or even using lower doses of hydroxychloroquine [58].

The two large randomised trials in hospitalised patients or in the acute intensive care period were WHO SOLIDARITY trial and RECOVERY trial Bother were launched around March 2020 to assess hydroxychloroquine and other potential COVID-19 treatment against the standard care.

Recovery Collaborative Group in the UK run The RECOVERY trial[59]. It was randomised, controlled, open-label platform trial comparing a range of possible treatments with usual care in patients hospitalised with COVID-19. Randomly assigned 1561 patients received hydroxychloroquine and 3155 to receive standard care. The primary outcome was 28-day mortality. It was completed on the 5th of June 2020[59]. The results suggested that patients in the hydroxychloroquine group were less likely to be discharged from the hospital alive within 28 days than those in the usual-care group (59.6% vs. 62.9%; rate ratio, 0.90; 95% CI, 0.83 to 0.98) [59]This study provided an extra finding that a moderate dose of dexamethasone (6 mg daily for 10 days) in patients with COVID-19 and respiratory failure who required therapy with supplemental oxygen or mechanical ventilation a can reduce mortality[60].

The WHO SOLIDARITY Trial was a large multicentre study involving 405 hospitals in 30 countries. It was reported recently (December 2020)[61]. The study randomly assigned 11,330 adults in patients with COVID-19. They were assigned to one of the five options (four active and the local standard of care).

1. 2750 were assigned to receive remdesivir,
2. 954 to hydroxychloroquine,
3. 1411 to lopinavir (without interferon),

4. 2063 to interferon (including 651 to interferon plus lopinavir), and

5. 4088 to no trial drug.

The major finding that neither remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalised patients with COVID-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay[61].

ORCHID (Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic disease) trial. It was a multicentre, blinded, Randomised trial of hydroxychloroquine versus placebo for the treatment of adults hospitalised with COVID-19[62]. ORCHID trial was halted as it did not show any benefit for hydroxychloroquine based on its seven-point ordinal scale outcome [63][64].

The randomised controlled trial in China involved 16 government-designated COVID-19 treatment centres in China, in the first weeks of February 2020. It recruited 150 laboratory confirmed COVID-19 hospitalised patients. The study reported that the administration of hydroxychloroquine did not result in any benefit than the standard of care. Adverse events were higher in hydroxychloroquine recipients than in non-recipients[65].

Furthermore, few studies assessed the pre-exposure prophylaxis to COVID-19. Skipper et al. [66] reported multisite, randomised, double-blind, placebo-controlled trial enrolling 491 participants from the United States and Canada. They found hydroxychloroquine did not substantially reduce symptom, severity or prevalence over time in no hospitalised persons with early COVID-19.

The Coalition of COVID-19 Brazil Investigators used hydroxychloroquine and azithromycin to treat patients in a multicentre, randomised, open-label, three-group, controlled trial involving 504 hospitalised patients with suspected or confirmed COVID-19 who were receiving either no supplemental oxygen or a maximum of 4 litres per minute of supplemental oxygen. The study found that the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical status in 15 days as compared with standard care[67].

Other clinical trials showed hydroxychloroquine did not prevent illness compatible with COVID-19 or confirmed infection when used as post-exposure prophylaxis within 4 days after exposure[68][69]. Other regional trials in many countries provided further confirmation that the use of hydroxychloroquine, whether alone or with combination with other treatment is not warranted for the treatment at any stages of COVID-19.

Lessons from the history of hydroxychloroquine.

We have learned a lot from the history of hydroxychloroquine over the past 500 years. Using hydroxychloroquine for the prevention and treatment of COVID-19 has received significant attention in 2020. Most notably, the enthusiasm for hydroxychloroquine has been one of politicisation rather than science[55], confirming that science and politics are not intertwined. By definition, science but not politics require diligence and honest assessment of the findings[70]. This public enthusiasm prompted for continuing scientific investigations and more rigorous evaluations that provide sufficient evidence to exclude any benefit for hydroxychloroquine with or without azithromycin in all stages of COVID-19 [71] [55][72].

Despite earlier encouraging findings from in vitro and early observational studies, randomised clinical trials showed the opposite. Thus, a need to reflect our interpretation of all the scientific findings at differ stages and settings. For example, is the the dosing estimate using the conventional pharmacokinetics for a drug that works at both extracellular and intracellular level appropriate? Is dosing used for one condition like rheumatoid arthritis or as antimalarial medication applied to the drug to be used as antiviral medication[73]. Is the contradiction between our investigational and clinical findings related to dosage? Is our existing knowledge of in vitro and in vivo viral replication mechanisms the same? The experience with hydroxychloroquine also showed that using data from a similar viral infection may not be sufficient for a learned conclusion. For example, studies identify functional differences between SARS-CoV-1 and -2 entry processes and mechanistically explain the limitation of in vivo utility of hydroxychloroquine as a treatment for COVID-19[44]. Most of the early knowledge of the other coronavirus effects may not be used because of the sophisticated mutations induces by SARS-CoV-2 in the pattern that produced COVID-19 pandemics. It is a somewhat tricky questions of our future approach to research and interpreting the finding as we apply it to our medical practice. It shows us that mutations and natural selection are a powerful tool that can affect our medical management.

The other lesson we learned is that viral pathobiology can differ in different cells. Thus, using studies with cells from specific organ or species cannot be extrapolated to other organs. We have still used the concept in our modern science communities, although we have often claimed that this is not the case. For example, Hoffmann et al.

have shown that hydroxychloroquine can block the entry of coronavirus in the African green monkey kidney cells, but not human lung cells[74]. It shows that extrapolation of the mechanism from different species of the species cannot be generalised. Thus, many of the mechanism we described above in hydroxychloroquine may prove inaccurate in human-specific cells. Thus, hydroxychloroquine history was illuminating in many aspects of its early day of discovery 500 years ago. Today, the interaction of science with political and social factors and how evolution and biology work may influence our medical judgment. These lessons can help in our pursuit of knowledge and its application.

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