CORONAVIRUS-2019 PANDEMIC, CURRENT METHODS OF DIAGNOSIS, TREATMENTS AND ENGINEERING OF THE SAFE AND EFFECTIVE MODERN VACCINES - AN OVERVIEW

MRINAL KANTI DEWANJEE*

Following the Coronavirus-2019/SARS-COV-2 attack on the front-line of epithelial cells of alveoli, the neurons in the olfactory bulb, intestinal lining and endothelial lining of blood vessels after inhalation, all organs supported by the circulatory system are affected simultaneously. Dr. Avindra Nath at NINDS identified the swelling of olfactory bulb by MRI in the acute phase resulting in multi-system organ failure. We have access to a few drugs for viral elimination like specific monoclonal antibody made by Regeneron and Lilly, anti-inflammatory drug, corticosteroids, Dexamethasone and anti-viral drug Remdesivir. The blood-thinners, heparin, low molecular weight heparin fragments and anti-platelet medication saved many lives from micro- and macro-clots and pulmonary embolism. Best approach is to avoid viral exposure before the arrival of safe and effective new generations of vaccines. In this brief review, an attempt has been made to explain the mechanism of viral entry via the ACE2 receptor and the modes of multiple interventions for both diagnosis and therapy and in rare occasions, a lung transplantation. My lifetime investigations on the diagnosis of heart muscle damage, and the mechanism of arterial thrombosis and drug development in cardiovascular diseases assisted me in identifying one of the major aspects of the blood clots, thrombi and emboli in the COVID-19 patients.

Introduction

The role of pathogens, virus, bacteria, fungus in multiple infectious diseases (1-7), viral inactivation of protective interferons (8-14), the science of immune defense, radom approaches for drug evaluations (14-24), development of preventive effective vaccines to neutralize the targeted pathogens (25-50) and the consequences of infections in the human host affecting multiple organs had been studied for almost two thousand years (51-59).

A ray of light appears at the end of a dark tunnel on November 9, 2020 after a trial on 47,000 volunteers. A new generation of COVID-19 vaccine from Pfizer and BioNTech with spike protein mRNA in lipid-droplets with an effectiveness of 90% with two consecutive intramuscular injections 21 days apart. This indicates that 90% of vaccinated persons will be spared from disease post-COVID-19 exposure and only 10% may be affected, which is more effective than that of the Flu-vaccine (~50% effective).

Pfizer is filing applications to FDA for emergency use authorization. Pfizer invested their own capital (~2 Billion dollars) for this critical vaccine to avoid interference from the unstable White House and made them in six months rather than several years. About 25 million doses will be made at the end of 2020 and 1.3 billion doses at the end of 2021. However, the vaccine must be transported in dry ice and must be stored at -84°C. Moderna and NIH are pursuing similar approach showing beneficial effect of production of antibody to the SARS-COV-2 specific spike protein and the T cell response. Vaccines will be prioritized

* Retina Genetics and Repair Laboratory, National Eye Institute, National Institutes of Health, Bethesda, MD 20892, e-mail : mrinal.dewanjee@nh.gov
Mechanism of SARS-COV-2 Infection and Its Treatment

To explain the mechanism of infection (Figure 1), viral power of rapid growth inside infected cells killing them and making multiple organs and our immune defense system dysfunctional from viral and bacterial attacks\(^1\) and sometimes paying a heavy price for hyper-inflammation and many immunoglobulins against interferons, anti-phospholipid antibodies, thrombin-activators churning fibrin-dimer\(^9\), we have now some clues but we have a long way to go to find out the intensity of inflammation. Hence, it needs on an emergency basis the use under specific pathophysiological conditions, the various drugs which include corticosteroids to suppress hyper-active immune response (Dexamethasone: 6 mg/day for 10 days, IV or oral), the anti-viral drug Remdesivir (loading intravenous 200 mg dose on day 1 and 100 mg/day for 10 days) to restrict viral replication, interferon-beta inhalation for 14 days (Synairgen) or the antibody containing plasma from recuperating COVID-19 patients to reduce the viral population and finally, we will have to eagerly wait for the success of 35 billion dollar effort of making the safe and effective vaccines!

Virology, immunology and vaccinology have advanced significantly and the timeframe of making vaccines has been shortened from 6-10 years to 9 months now. Ms. Gertrude Elion made the first anti-viral drug, acyclovir, against herpes virus 50 years ago against all odds and was awarded the Nobel Prize (1988). FDA recently approved the anti-viral drug, Remdesivir, which reduces the period of hospitalization from 14 to 10 days. With the current advanced tools and technologies, success in making vaccines is achieved easily; but testing them in a large population is more time-consuming and labor-intensive due to significant variations in different factors like the degree of immune response, gender and age, especially the elderly patients having chronic diseases like obesity, diabetes, high blood pressure and compromised organ functions.

Many questions haunt us as we are trying to keep social distance of ~6 feet for droplets > 5 micrometer and ~26 feet for floating virus aerosol particles < 5 micrometer and wear aerosol-filtering masks in the asymptomatic crowds (> 45-55%) without fever and difficult breathing response and the symptomatic ones as well. Everybody in any population appears to be a suspect in this regard, unless proven healthy by various tests that check the virus specific proteins like the Spike and Nucleocapsid proteins of virus (also called antigens), were detected by ELIZA assay or the level of antibody made by the B cells due to host-immune response. Ultimate test is made by amplifying the SARS-COV-2 specific RNA in the nasal swabs or saliva to millions of copies of DNA by the polymerase chain reactions (reverse transcriptase PCR) with costly reagents, which takes much longer time than that taken for detecting viral proteins and host-antibodies, a few hours vs days\(^4\). The SARS-COV-2 infection has also exposed the level of ignorance of the people overseeing management of science and technology, who are
denigrating our best scientists at various organizations like NIH, CDC and WHO, and spreading the misinformation of using wrong drugs5,24.

India is in an unenviable second position with more than 8.5 million cases and Brazil is in third position. There has been an ongoing intense competition of evolution between emerging pathogens and their human host over millions of years. We must make a focused unified global effort (Coalition of Pandemic Effectiveness: CEPI), supported with global resources to make effective "vaccines" continuously to win over the emerging deadly enemies. The cost is too high to ignore the world-wide economic collapse, immense miseries of patients and caregivers and thousands of lonely deaths!

How did this bat virus with its small RNA genome of 29,919 nucleotides, jumped from bats, civets, minks, etc. to human in Wuhan province in China, how it latches to the membrane of human epithelial cells of lungs, heart, intestine, endothelial cells lining the wall of blood vessels, neurons and other organs, causing the collapse of lung alveoli, shortness of breath, diarrhea, loss of sense of smell and micro-clots in the deep veins and arteries inducing heart attacks and strokes1-12. This virus infection of endothelial lining of both the arteries and veins causes deep vein clots, micro-clots and arterial thrombus. SARS-COV-2 infection adversely affected the care of chronic obese and diabetic patients with more ACE2 protein killing more men than women. Significant genetic mutations in immune response, specifically the interferon-1 and its autoantibody, make a subsets of male patients very vulnerable with multi-system organ failure13,14. The patients are afraid of visiting the emergency hospital service and are dying at home in large numbers.

About 60% of infections occur from asymptomatic patients and 30% of these elderly COVID-19 patients die from stroke, heart attack and deep vein thrombosis caused by the micro-clots formed due to the loss of endothelial function and activation of the clotting system. Unlike heart attack, where the cholesterol-plaque ruptures and a rapid platelet thrombus forms blocking the blood supply to the heart muscles, the dysfunctional endothelial cells in the COVID-19 patients stop making the vasodilator, nitric oxide, anti-platelet molecule, prostacyclin and other beneficial products51-59. In 1989 while working at Mayo Clinic, an experiment-based algebraic equation was developed by me to calculate the number of platelets required to block the arteries using radioactive platelets. Using that equation and other relevant parameters, I found that about 180-250 million platelets could block a 2-3 mm artery in 60 to 90 minutes. This needs rapid intervention with a clot-buster, called tPA to break-down the fibrin-fiber holding the platelet thrombus, followed by angioplasty for a focal stenosis, stenting and dual-platelet-inhibitors or a bypass graft for a longer segment of blocked artery37,51-59. Low molecular weight heparin fragments (LMWHs) after subcutaneous or intravenous injections and a phospho-diesterase inhibitor, Dipyridamole, save some of these patients from thrombo-embolic complications of micro and macro-clots, thereby avoiding the use of ventilator and preventing death25,29-33,34. Use of aspirin in combination with dipyridamole helped in preventing occlusion of coronary artery bypass graft which was established first by me in 1970 and unique biomarker of normalized value of the number of adherent platelets to injured artery52. As a token of appreciation, Behringer-Ingelheim, Inc., Germany, sent me a drum of 10 kg and I turned them into capsules with the help of Mayo Clinic pharmacists for oral administration in dogs, cows and pigs.

Results and Discussion

Although most of the younger patients recuperate, they suffer from multiple chronic diseases for a long time. Table1 shows the ongoing world-wide clinical trials of multiple vaccines and Table 2 shows the current modes of limited therapy. Certain Federal laws in USA discourage the use of fetal tissue in medical research; however, the

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<th>Funding in millions</th>
<th>Dose in millions</th>
<th>Trial phase</th>
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*NP=Lipid Nano-particle, BARDA: Biologic Advanced Research And Development Authority
fetal kidney cells could be used for making viral vectors on a large scale in stain-steel bioreactors (fermentors). These cells have the right assembly of groups of sugar, e.g. glucose, mannose, ribose, etc. covalently associated with the membrane proteins for viral recognition or hiding by the immune system. Many questions arose about the SARS-COV-2 virus regarding its mode of infection and host cell killing mechanisms, and the scientists are working hard to understand the modes of intervention and therapy aiming at its control.

Severe antiphospholipid syndrome involves the derangements of both inflammatory and thrombotic pathways and impacts multiple organs in the body simultaneously.

Neutrophil extracellular traps (NETs) are clusters of chromatin, microbicidal proteins and oxidant enzymes that are released into extracellular space by neutrophils to contain infections. Unregulated NETs propagate inflammation and microvascular thrombosis in the lungs of COVID-19 patients with acute respiratory distress syndrome39,40. Table 2. Targeted Drug Selection for Covid-19 Patients: Anti-inflammatory, Anti-viral and Anticoagulants (Selection is very limited).

1. Dexamethasone for reducing severe inflammation to vascular lining and all organs
2. Remdesivir (gilead Sciences, Inc.) anti-viral pro-drugs for inhibiting viral RNA synthesis; $3410. Generic drug, Covifor by Hetero, India, Rs. 5400 for a dose of 200 mg Injection for 5 days. https://www.gilead.com/-media/fils/pdfs/remdesivir/eua-fact-sheet-for-hcps.pdf
4. Convalescent plasma containing the immunoglobulin neutralizing the SARS-COV-2 particles.
5. B cells extracted from the infected patients for higher IgG titer: Monoclonal antibody Dose: Adult patients (> = 40 kg and higher is a single loading dose of 200 mg on Day 1 followed by once daily maintenance doses of 100 mg from Day 2. Pediatric patients (~ 3.5 kg > 40 kg), only use Remdesivir for injection, 100 mg, lyophilized powder. A single loading dose of Remdesivir 5 mg/kg on Day 1 followed by Remdesivir 2.5 mg/kg once daily from Day 2 (FDA approval status : EUA).

Zuo et al.41 reported that sera from SARS-COV-2 infected patients under ventilation had higher levels of extracellular DNA, myeloperoxidase-DNA (MPO-DNA) and citrullinated histone H3 (Cit-H3) which strongly correlated with C- reactive protein, D-dimer, and lactate dehydrogenase, as well as absolute neutrophil count inducing endothelialitis and micro- and macro-vascular fibrin-based clots.

Interventional neurologists indicated that new cerebral thrombi are continuously formed as those could be extracted by the thrombectomy device.

In addition, Zuo et al. identified the antiphospholipid syndrome associated with life-threatening thrombophilia, where patients develop serum pathogenic autoantibodies targeting phospholipids and phospholipid-binding proteins (aPL antibodies)41. These aPL antibodies included higher levels of anticardiolipin IgG, IgM and IgA; anti-β2 glycoprotein I IgG, IgM, and IgA; and anti-phosphatidylserine/prothrombin (aPS/PT) IgG and IgM, and in 30% using a more stringent cutoff (≥ 40 ELISA-specific units).

Higher titers of aPL antibodies induce the neutrophil hyperactivity, release of neutrophil extracellular traps (NETs), higher platelet counts, more severe respiratory disease and lower clinical estimated glomerular filtration rate. Dipyridamole increases the extracellular concentrations of adenosine and interferes with the breakdown of cAMP, also suppresses aPL antibody mediated NETosis and mitigates venous thrombosis43.

Adeno-associated viruses (AAVs) are the main viral vectors used for gene therapy and have been successfully applied in treating inherited retinal diseases and spinal muscular atrophy. An AAV is composed of an icosahedral protein shell with a single-stranded genome of approximately 4.7 kb. The intact AAVs act as a vehicle to protect and deliver oligonucleotide therapeutics.

The Janssen vaccine candidate is a recombinant vector vaccine that uses a human adenovirus to express the SARS-CoV-2 spike protein in animal cells in culture. Adenoviruses are a group of viruses that cause the common cold. However, the adenovirus vector used in the vaccine candidate has been modified so that it can no longer replicate in humans and cause disease. Janssen uses the same vector in the first dose of its prime-boost vaccine regimen against Ebola virus disease (Ad26.ZEBOV and MVA-BN-Filo) that was recently granted marketing authorization by the European Commission60.

Like MARS and SARS, SARS-COV-2 infection starts by binding of Spike protein with ACE2 receptor on cardiomyocyte surface followed by entry into the cell in cooperation with serine transmembrane protease (TMPRSS2). Recently deaths of SARS-COV-2 infected young athletes from arrhythmia, myocarditis, myocardial infarcts and cardiomyopathy were reported (20) and MRI and echocardiography identified several cardiac abnormalities in these cases27,34,51.
Interruption of conduction system via the cardiomyocytes could induce ventricular blockade and malignant arrhythmia. Incubation of SARS-COV-2 with iPSC derived cardiomyocytes results in loss of contractility and causing fragmentation in 72 hours. There also occurred the release of troponin, C-reactive proteins, lactic dehydrogenase (LDH), ferritin, interleukin-6 in blood as a result of cardiac injury.

About 40% of COVID-19 patients are asymptomatic and are protected by type I interferon-interferon receptor system. Bastard et al. observed that the presence of genetic mutation in any of the components of this defense system causes high mortality. The inborn errors of Toll-like receptor 3 (TLR3)– and interferon regulatory factor 7 (IRF7)– dependent type I interferon (IFN) immunity affect both the life-threatening influenza pneumonia and COVID-19 pneumonia. Zhang et al. identified three mutated loci in patients with life-threatening influenza: TLR3, IRF7 and IRF9.

The neurologic manifestations were observed in about 83% of SARS-COV-2 infected patients and were independent of respiratory disease severity with myalgias (44.8%), headaches (37.7%), encephalopathy (31.8%), dizziness (29.7%), dysgeusia (15.9%) and anosmia (loss of sense of smell, 11.4%). Strokes, movement disorders, motor and sensory deficits, ataxia, and seizures were very rare (0.2 to 1.4% of patients each).

Consecutive two injections of vaccine, 21-days apart, resulted in Nab responses like that of the convalescent serum obtained from SARS-COV-2 infected patients. When mice and rhesus macaques were injected with this mRNA-1273 vaccine mRNA-1273 were challenged with high-dose intranasal SARS-COV-2 rapidly cleared the virus from the upper and lower airways. This vaccine encodes the SARS-COV-2 full-length spike glycoprotein trimer, S-2P, modified to include two proline substitutions at the top of the central helix in the S2 subunit. The mRNA is encapsulated in lipid nanoparticles at 0.5 mg per milliliter and diluted with normal saline to the final target vaccine concentrations.

In COVID-19 patients some antiphospholipid and anti-interferon antibodies cause the development of micro- and macro-clots and must be tested and avoided. Vaccines trigger the human immune system (antigen presenting cells: APC, B and T cells) to produce antibody which could recognize and kill invading viruses or bacteria in future attack. The vaccines specific for SARS-COV-2 virus prime our body to seek out the target proteins present on
The biotechnology of designer monoclonal antibodies (MoAbs) developed in 1970s could target the specific viral surface protein and neutralize and eliminate the viral load in blood and tissues. About 50 companies and academic teams including Regeneron Pharmaceuticals and Eli Lilly have been pursuing this procedure. The two-antibody cocktail churned out by Regeneron Pharmaceuticals’ from hamster cells in Rensselaer, NY, saved the life of SARS-CoV-2 infected US President. In designing the MoAbs, immunologists must expose the mice/rabbits to a related virus to develop the immune systems triggering the B cells to make the antibodies. The cells producing specific antibody are then grown in pure culture followed by the purification of antibody for its subsequent use. Patients recuperated from COVID19 also made several immunoglobins to neutralize the viral loads. High-throughput microfluidic screening of antigen-specific B-cells led to LY-CoV555, a potent anti-spike neutralizing antibody from a convalescent COVID-19 patient. Biochemical, structural, and functional characterization of that antibody revealed its high-affinity binding to the receptor-binding domain of Spike protein preventing its interaction with ACE2 protein on the host cell surface. The interim analysis of a Phase-II trial data by Chen et al, with 700, 2800 and 7,000 mg of neutralizing antibody with LY-CoV555 (Eli Lilly, Indianapolis, IN), the viral load declined over time and the hospitalization or visit to an emergency department of Covid-19 patients was 1.6% in the LY-CoV555 group and 6.3% in the placebo group. In general, on days 2 to 6, the patients who received LY-CoV555 had a lower severity of symptoms than those who received placebo.

Multiple Phase III clinical evaluations, currently carried by OAZ, Moderna, Pfizer-BionTech, Johnson & Johnson, Merck, Sanofi, SINOvac and other corporations with several variants of attenuated subunit of Spike protein or novel viral DNA/RNA vaccines (Table 3) are showing higher antibody titer by B cells, the killing of infected cell and protective effects by the following mechanisms of memory T cells (Table 3).

About 30-35% of Americans refuse vaccination preventing the buildup of herd immunity, which need ~70% of the population immunized. At higher doses, more adverse effects may appear, as happened with the OAZ vaccine causing spinal inflammation/paralysis. This caused a temporary pause on the ongoing trial. Anyway, the vaccine was then pushed with the Operation Warp Speed program for rapid delivery of 300 million doses in USA at a cost of about 12 billion dollars before the election. The poorly processed polio virus used by a manufacturer in the 1950s

Table 3. Mechanism of Activation of Complex Immune Response by Multiple COVID-19 Vaccines, DNA/RNA Vaccines, Subunit (Spike Protein), Viral Vaccines and downstream Common Virus Killing Pathways via the Antigen Presenting Cell (APC), T-helper cell, Viral-neutralizing Antibody by B-cell and Killer T-cells. 

| IA. DNA Vaccine (Spike Protein) Injection → Host Cell Replication → Spike Protein → APC |
| IB. RNA Vaccine (Spike Protein) in Lipid Shell → Host Cell Replication → Spike Protein → APC |
| IIA. Replicating Viral Vector → ACE2-Host Cell Replication → Vectors/Antigens → APC → Viral Peptides |
| IIIB. Non-Replicating Viral Vector → Host Cell Replication → Antigens → APC → Viral Peptides |
| IIIA. Virus-like Particles (No genetic material) → Host Cell Replication & Vectors/Antigens → APC → Viral Peptides |
| IIIB. Protein Subunits (SARS-CoV-2 Virus) → Host Cell Replication → Vectors/Antigens → APC → Viral Peptides |
| IVA. Weakened Virus (No genetic material) → ACE2-Host Cells → Vectors/Antigens → APC → Viral Peptides |
| IVB. Inactivated Dead Virus (No genetic material) → Host Cells → Vectors/antigens → APC → Viral Peptides |
| → Common Pathway: Viral Particle → T-Helper Cell → Cytotoxic T-Cell → Kill Virus-infected Cells |
| → Common Pathway: Viral particle T-Helper Cell → B-Cell → antibody → Virus Killing |

About 10% of SARS-CoV-2 attack is from an autoimmune response (12, 15, 24, 26, 27, 30-33).
caused infection of more than 40,000 children with the same virus. So, the intended COVID-19 vaccines must be proven safe, effective and credible for FDA approval and related legal clearance for mass use in USA and abroad, probably around the early 2021.

The Poonawalla family-owned Serum Institute, Pune, India, was contracted by OAZ and Novavax teams for manufacturing stockpile of more than 300 million doses by November 2020 for world-wide commercial use. They normally provide pediatric vaccines and the antivenom-antibody for snake-bites world-wide at a low cost and will do the same for COVID-19 vaccines. Dr. HH Thorp recently pointed out that “shortcuts in testing for vaccine safety and efficacy endanger millions of lives and will damage public confidence in vaccines and in science for a long time”. About 120,000 victims die from snakebites annually. The Poonawalla family of horse-breeder by making the antivenoms with the retired old horses has been a major savior from snakebites and they could now be a major SARS-COV-2 defender, if the vaccine promise holds up!

All cells in our body make the type I interferons which are vital antiviral defense molecules acting against all types of viral infections. They trigger the infected cells to produce interleukins that attack the infected cells. About 94% of the COVID-19 patients with interferon attacking antibodies were male.

This explains the higher risk of males from this severe disease. About 10% SARS-COV-2 attack is from an autoimmune response.

Although the recent generations of novel vaccines bring a sigh of partial relief, the SARS-COV-2 mutations, specifically nine mutations in the targeted spike protein, are enhancing the anxiety level among the scientists and clinicians. Rota et al characterized the 1258 amino acids of spike proteins. The B.1.1.7 variant identified in England and the one with asparagine to tyrosine mutation (N501Y) in the receptor binding domain of the spike protein S, isolated from a patient in South Africa may become the dominant global variants with their higher transmission (~70%), and it may drive another surge of infected cases world-wide. About 15% of the contacts of people infected with B.1.1.7 in England went on to test positive themselves, compared with 10% of contacts of those infected with other variants. B.1.1.7's second mutation, a deletion named 69-70del- resulting in the loss of two amino acids in the spike protein makes it twice as infective. The mRNA vaccines are designed to recognize multiple parts of the mutated spike protein, making it unlikely that a single mutation will make it ineffective. Antibodies from blood samples of recent vaccine recipients from England and S. Africa successfully killed the mutated virus in lab dishes in the UT Galveston laboratory. More tests of patients with multiple mutations must be carried out to confirm the validity. Only a few rich countries have the whole genome sequencing ability to follow the spontaneous viral evolution via mutations with time.

Recently, mink-farmers were found to be infected with SARS-COV-2 virus in several European countries, e.g. Holland, Spain and Denmark and China—the major breeder. Thousands of minks in infected farms were culled to prevent spreading and some countries are totally banning

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**Figure 3.** Simplified Cartoons of Conventional Inactivated Vaccines (Left) and Modern Novel DNA and mRNA Vaccines (Right). Park A. “When will we get a vaccine”. Time. Modified by Dewanjee MK and Ayan Sengupta.
the mink-fir firms. In addition to infection, there is an awareness and resentment among the citizens about the cruel mass killing of minks using a mixture of carbon mono- and di-oxide gases. Furry animals, mink and civet found in China may be an intermediate virus carrier of SARS-COV-2 family. The World Health Organization (WHO) stated that multiple mutations in spike protein in minks has a lower sensitivity to neutralizing antibodies and may not be protected by the current vaccines.49

Bhattacharya proposed the preventive/prophylactic or alternative antiviral approach to COVID-19 treatment with azithromycin (AZ) along with the antiallergic medications. Until and unless the proposed bitter plant extracts or di-/tri-/polyherbal formulations are separated, purified and evaluated with the SARS-COV-2 virus-infected human cell culture and infected rodents and monkeys, all these studies on modelling are speculations and should not be used in patients. If the pharmacological properties are like chloroquine or analogs, they must be avoided for human toxicity.48,49

Hydroxychloroquine, chloroquine and azithromycin are not approved by the US Food and Drug Administration (FDA) for the treatment of COVID-19. They are only approved by the FDA for the treatment of malaria, lupus erythematosus and rheumatoid arthritis. They might kill patients from QTc interval prolongation in EKG pattern, torsade de pointes, ventricular arrhythmia, and cardiac deaths. Despite demonstrating antiviral activity in some in vitro systems, hydroxychloroquine with or without azithromycin did not reduce upper or lower respiratory tract viral loads or improve the clinical efficacy in a rhesus macaque model. However, based on certain experimental evidences, it has been hypothesized that chloroquine and hydroxychloroquine have the potential of being effective in inhibiting the SARS-COV-2 virus growth in presence of Zinc.55

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