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Review Article

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## SARS-CoV-2: Recent Past and Present: An Unusual Review

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### Abstract

Since SARS epidemic arose in 2002-2003, followed by the present SARS-CoV-2 pandemic, the World has been hit in every aspect of his life. Learning from our recent past is important and questions, quite a lot of questions are to be answered. The knowledge gathered about SARSs as a whole is growing and should be used to avoid similar situations. Our present is complex and real solution does not exist up to now. This unusual review is intended to describe existing solution, and suggests some intuitions of solutions by asking right questions to be answered. Not only chemistry as a science is concerned, but other aspects of life could be interested by this review.

**Keywords:** *Coronavirus, SARS-CoV-2, virus, Comorbidity, Pneumonia, Wuhan, DNA, m-RNA*

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### 1. Introduction

Severe Acute Respiratory Syndrome (SARS) was known since the 2002-2003 epidemic when infection caused more than 800 deaths. Those were the result of infection caused by a novel human coronavirus, SARS-CoV (Pillaiyar *et al.*, 2016). Last December 21, 2019, another pandemic broke out in Wuhan (China), and then rapidly spread over the World, so that by March 2020, almost every country was affected (Worldometer daily). This novel coronavirus was labeled SARS-CoV-2 or Covid-19 by the WHO (WHO, 2020).

The symptoms of SARS-CoV-2 infection disease are not specific, but they are so different each from other that it is difficult to tell them from those caused by influenza, MERS infection, and other respiratory infections as well as those related to zinc deficiency (Larsen, 2020; Prasad, 1961; Prasad, 1963; Prasad, 2007; Sardi, 2020).

In order to identify people with SARS-CoV-2 contaminations and infections, many tools have been implementing for testing. One among the most used is RT-PCR technology, but it does not always provide actual positive cases but many times false positive ones, so that the contamination numbers should be considered with caution and checked by complementary means (Feng *et al.*, 2020). To the best of my knowledge,

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PCR results are obtained after cycles of amplifications of the initial nucleic acid sample weight, so that the actual use of this technique is to facilitate the identification of a weighable material.

Then the final observed molecular weight does not represent the actual mass of the initial nucleic acid or its fragment. This was confirmed by Dr. Fauci (Fauci, 2020) of National Health Institutes in a July release in a podcast: "July 16, 2020, podcast, "This Week in Virology": Tony Fauci makes a point of saying the PCR Covid test is useless and misleading when the test is run at "35 cycles or higher." A positive result, indicating infection, cannot be accepted or believed" and published November 7, 2020 in Principia Scientific International, and written by Jon Rappoport. Moreover it would be very important to add that when testing people for Covid-19, the virus and its mutations should be identified in the most reliable way possible. Obviously, this topic is far beyond the scope of this review.

The answer to the question about the origin of the pandemic is crucial in order to be in a position to find out ways of preventing forthcoming pandemics. Instead of answering such a key question, controversies are not the solution, and do not give clues about the emergence of SARS-CoV-2. Therefore, there is an actual everlasting battle between the laboratory-made virus theory and the natural origin of the virus. According to the natural evolution theory, the virus jumped from animals to humans, through zoonotic transfer from bats to pangolin, then from pangolin to humans, because the SARS-CoV-2 genome is close to that of this animal (Andersen, 2020; Zhang et al., 2020; Xiao et al., 2020).

This theory is also supported by the WHO through releasing a report on February 2020: "Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (Covid-19) February 16-24, 2020, p. 34: "Since the Covid-19 virus has a genome identity of 96% to a bat SARS-like coronavirus and 86%-92% to a pangolin SARS-like coronavirus, an animal source for Covid-19 is highly likely. This was corroborated by the high number of RT-PCR positive environmental samples taken from the Huanan Seafood Market in Wuhan" (WHO, 2020).

By contrast and according to the man-made theory, SARS-CoV-2 virus was prepared through an international scientific collaboration coming from "Gain-of-Function" experiments (GOF) in 2015 (Menachery et al., 2015). In this paper, the authors reported that "they made a chimeric virus using the SARS-CoV reverse genetics system". The resulting chimera expressed the spike of bat coronavirus SHC014 in a mouse-adapted SARS-CoV backbone. Besides, French Nobel Prize, Montagnier (2020a and 2020b) reported that the presence of genome segments of HIV-1 and *Psalmidium falcifarum*, responsible for the malaria in the SARS-CoV-2 genome could not be the result of a natural mutation, but the result of human manipulation. What is more, it is of interest to know that two of the four so called "Pangolin papers" that were heavily used to orient global opinion toward a natural origin of SARS-CoV-2 are under investigation by Editors for serious questions and problems, raised by the US Right to Know (Suryanarayanan, 2020).

Despite the emergency of knowing where SARS-CoV-2 came from in order to take steps for avoiding future plagues of such a kind, for us it is also beyond the scope of this review to give details about this situation. In the meantime, an actual panic has spread over the officials, academics and populations in the World since no country was spared, with the result of many deaths. These deaths do not likely overcome those caused annually by seasonal influenza, according to several mainstream media. In a US CDC's weekly release about Provisional Death Counts for Coronavirus Disease 2019 (Covid-19) and Excess Deaths Associated with Covid-19, it was reported that many people who had died during the Covid-19 pandemic in the US died "with" the virus, but not "from" it (CDC, November 2020). That is to say that those deaths originated from other causes than from Covid-19.

Many reviews have been published to this respect and updates are available in the literature. Many others are published regularly updating the knowledge about this topic and they describe their various aspects. However, these reviews focus mainly on drugs developments and pharmacological treatments of the Covid-19 infections (Pani et al., 2020; Lam et al., 2020). Unfortunately, no nutritional indications are provided to people in order to boost everyone's immunity, and mitigate the pandemic impact the best way possible. There are no descriptions about alternative and holistic tools in the mainstream scientific literature that could be used safely by a general audience to fight the pandemic. Interestingly, Mercola (2020. daily updates) provides every day much nutritional information within everybody's means.

At a time when no efficient drug, and no efficient and safe vaccine is found on the market to cope with the virus and the disease, the emergency should be saving lives and explore every way that could be implemented to achieve this goal: this is the aim of this review of which content can be obsolete in view of growing knowledge that could be gathered and because of emerging potential therapies or vaccines that could be developed. However, this review is not intended to push people to self-medication at all, but induce everyone to be aware of existing tools and their alternatives that could be used wisely.

## 2. Existing Strategies

After the outbreak of the pandemic hit the World, every country took a number of steps to protect his population going from bearing masks, lockdowns, and/or social distancing in order to curb the curve of infection and deaths. The only European country that took no such measures was and is still Sweden; this country relies on herd immunity to curb positive tests curves according to European main stream press ([Euronews.com](https://www.euronews.com), 2020). Besides, Taiwan a non-WHO member, close off the boarder of China, imposed neither lockdown, nor businesses closures and remained relatively unaffected by the pandemic ([Wang et al., 2020](#)).

In the beginning, the WHO (2020) made very dark predictions about Africa because of his poor health system and multifactorial considerations that could undermine containment strategies of the pandemic. However, comparing the scores between Continents towards the pandemic, Africa as a whole is showing a good resilience with lower contaminations, lower infections and reduced number of deaths ([Worldometer, 2020](#)). During this year, a study performed showed that African better resilience than other Continents towards SARS-CoV-2 might likely be the result of healthy people's pre-existing SARS-CoV-2-cross-immunity ([Grifoni et al., 2020](#)). This cross-immunity is a broad natural immunity acquired by people who had been exposed to various viruses included some coronavirus strains. Other arguments mentioned in the mainstream press about African resilience were heat, youth, nutrition, but taken together those cannot be backed up.

## 3. Physical Strategies

Since the pandemic broke out people were plunged in an actual panic and many measures were implemented such as masks, washing hands, social distancing and lockdowns in order to limit contaminations and infections. One of the measures that have been broadly accepted by public is washing hands for hygiene considerations. Except the latter, the remaining measures were and continue to be compulsory and they are generally disputed all around the World.

After implementing physical barriers everywhere, some observations can be made as a result of a brief analysis of the global situation. First, masks are devoted mainly to limit the propagation of the virus through its emission by coughing or sneezing. However, taking into account the virus size, to what extend any mask could stop it and get through the holes of the fabric of the mask? As a rule, only surgical masks are believed to be the best suited to achieve this goal. Nevertheless, Chughtai, and then Bae gave evidence that surgical masks, the most performing of the kind, cannot filter adequately virus present in aerosols ([Chughtai et al., 2019](#); [Bae et al., 2020](#)). Now, after about 8 or 9 months of masks use, the latter are of both hygienic and environmental serious concerns, because they are found everywhere thrown on the ground.

Second, lockdowns that were designed to limit crowds, a number of economic, health, social and psychological problems have arisen: job losses, anxiety, increasing stress, depression, cardiovascular issues, suicides, irritability, divorces and domestic violence are observed in many countries ([Brooks et al., 2020](#)). It is likely that strict lockdown could lead to worsen the situation respect to results that were expected for. As a matter of fact stress is largely documented for its implication into chronic inflammation which causes corresponding chronic diseases. Besides, comorbidity has been singled out as a major factor of deaths of patients with Covid-19. It is obvious that any measure that generates stress could be considered as a death-booster. This could be derived from the above-mentioned study and another Clemens' ([Clemens et al., 2015](#)). Putting together the results of those studies, it might be presumed that during this pandemic lockdowns, especially those which are not thoroughly explained and not well understood by people might have contributed to some extent to comorbidities and their corresponding deaths.

Many and diverse healing strategies have been implemented through the World in order to cope with the disease. A global coordinated strategy would ease this situation, but obviously a global agreement does not

exist since countries specificities are set forth. It is worth mention that many compulsory measures are questioned and even lawyers are against them as human rights and freedom are at stake, according to Langlois (2020).

The US Centers for Disease Control & Prevention (CDC, 2020) was aware that measures implemented in order to protect people were sometimes difficult to maintain. Even the World Health Organization (WHO, 2020) released a notice about the efficiency of masks saying that "Currently there is not enough evidence for or against the use of masks (medical or other) for healthy individuals in the wider community. WHO continues to recommend that medical masks be worn by individuals who are sick or those caring for them." Another paper deserves mention about personal protection (Xiao *et al.*, 2020). It is noteworthy to single out that these days both CDC and the WHO recommend the use of this device, inducing some countries to implement mandatory masks.

As regards social distancing, the only European country who took no such measures was and still is Sweden. According to Euronews (2020), a European mainstream press, Sweden relies on herd immunity to curb positive tests curves. It is also interesting to mention that Taiwan, a non-WHO member, located close off the boarder of China, imposed neither lockdowns nor businesses closures and remained relatively unaffected by the pandemic (Wang *et al.*, 2020). Then, what did Taiwan since the beginning of the pandemic to be so preserved from a major damage?

#### 4. Affordable Strategies to Mitigate SARS-CoV-2 Infections

It is worth to mention that there is no existing drug, nor vaccine that is available in the World. As a consequence, everybody should be aware that the viral risk should be included in every aspect of our life so that available means to mitigate the impact of viral infections would be wisely used since the biodiversity is an actual wealth for people around the World.

##### 4.1. Hydrogen Peroxide, $H_2O_2$

Hydrogen peroxide has been known around the 1900s and was used since 1920 for its antibacterial and antiviral activities. In fact, hydrogen peroxide is a metabolite that is produced through catalase enzyme and vitamin C, leading to its decomposition into water and native oxygen atom. Then immune system uses this natural chemical to oxidize pathogen germs and viruses, and then wipes them off (Aronoff, 1964; Urschel, 1967; Finney, 1966). Any healthy immune system is able to produce its own hydrogen peroxide to kill pathogens and viruses. This reagent breaks down the virus membrane or destructs infected cells that are used by the virus to replicate and multiply. Controlling a viral infection does not mean to kill the virus as the latter is not a living being *per se*. The virus becomes a problem when it infects cells that it converts into its factories. That is why it is important to get rid of infected cells and deprive the virus of a support which enables it to reproduce and disseminate. Therefore killing infected cells with hydrogen peroxide might be a safe, cost-effective, and affordable approach to deprive virus of crucial factories that otherwise would be used for its reproduction.

In 1986, Farr (1987), the founder of Alternative medicine, reported the intravenous use of hydrogen peroxide in order to improve chronic degenerative diseases micro-circulation. His significant achievement was the update Tummicliffe and Stebbing's initial 1916 use, injecting intravenously oxygen without causing gaseous embolism (Tummicliffe, 1987). This therapy was successfully efficient in taking care of patients with many diseases through bio oxidative strategy (Farr, 1992). After long years of successful use of hydrogen peroxide in treating many patients, Farr (1992) went to declare "no longer is the double-blind study the gold standard in medicine," because "alternative treatment protocols can significantly improve the health status of a group of chronically ill patients, compared to a normal population, regardless of their diagnosis, in a time span of only six months." ... Therefore he recommended it for several diseases such as influenza, bronchitis, herpes zoster, asthmatic reactions, Epstein-Barr virus, CMV, HIV, type II diabetes, COPD, vascular disease, arthritis, chronic pain, Alzheimer's disease, toxic dementia, Parkinsonism, migraine headaches, and immune regulation.

According to work performed some eight years ago, some researchers found out hydrogen peroxide could be useful for ischemia (Armogida *et al.*, 2012). Their work showed that despite hydrogen peroxide was considered a toxic chemical it is a ubiquitous endogenous metabolite that is endowed with a number of health

beneficial properties in many physiological and neurological processes. Significant properties are many such as the modification or the expression of activity of the Superoxide dismutase (SOD), glutathione peroxidase (GPx) and CAT enzymes, which are key regulators of  $H_2O_2$  metabolism.

According to David Brownstein, hydrogen peroxide could treat coronavirus as well. When used intravenously injection of a pure solution of the chemical, hydrogen peroxide could save 107 patients. In fact, out of 107 patients who were treated with the chemical solution, only one was hospitalized, but no one deceased (Brownstein *et al.*, 2020). Later on the author suggested the use of hydrogen peroxide through nebulizing it with a respiratory face mask. According to recommendations, this process could avoid hospitalizations, collapse of hospitals and be a cost-effective treatment as Joseph Mercola (2020) commented. What is more, the solution of pure chemical could be considered as a safe and affordable at-home-prevention and therapy available to everyone. Besides, 0.5% solution hydrogen peroxide is a cheap and available chemical that can inactivate SARS, MERS and endemic HCov within a minute (Kampf *et al.*, 2020).

In a report, Sies and Jones made an understanding explanation about the interaction of reactive oxygen species, endogenous hydrogen peroxide, and antioxidants. It is worth reprint this statement: "At the low physiological levels in the nanomolar range,  $H_2O_2$  is the major agent signaling through specific protein targets, which engage in metabolic regulation and stress responses to support cellular adaptation to a changing environment and stress ... Recent methodological advances permit the assessment of molecular interactions of specific ROS reactive oxygen species molecules with specific targets in redox signaling pathways.

Accordingly, major advances have occurred in understanding the role of these oxidants in physiology and disease, including the nervous, cardiovascular and immune systems, skeletal muscle and metabolic regulation as well as ageing and cancer. In the past, unspecific elimination of ROS by use of low molecular mass antioxidant compounds was not successful in counteracting disease initiation and progression in clinical trials. However, controlling specific ROS-mediated signaling pathways by selective targeting, offers a perspective for a future of more refined redox medicine" (Sies and Jones, 2020).

#### **4.2. Ozone Therapy, $O_3$**

Many viruses and their hard-to-treat infections need cysteine to fuse with host cells. Coronaviruses are rich of cysteinyl moieties both on their spike and within their membrane; this makes them very sensitive to oxidation. Then they cannot withstand oxidative processes especially when they are exposed to native oxygen, should it be produced by human neutrophils or by decomposition of pure hydrogen peroxide or ozone. Oxygen gas was found to be produced by human neutrophils as a tool to destroy viruses (Babior *et al.*, 2003). This induced researchers to use medical ozone, a mixture of 95% pure oxygen and 5% ozone, as an efficient tool to combat viral diseases because blood treated with ozone enabled human body to resist and cope with viral infections (Rowen and Robins, 2020; Bocci and Paulescu, 1990; Zamora *et al.*, 2005; Liu *et al.*, 2016). A number of reports gave evidence that ozone proved its efficacy against viruses such as hepatitis A virus (Herbold *et al.*, 1989), poliovirus (Shin and Sobsey, 2003), vaccinia virus, cytomegalovirus (Roy *et al.*, 1981; Mirazimi *et al.*, 1999), Ebola virus (Lee and Sapphire, 2009), HIV virus (Ryser *et al.*, (1994) were inactivated by ozone through the oxidation of their cysteinyl moieties. Therefore, because cysteine moieties are crucial for coronavirus to fuse with host-cells membranes, ozone could be a safe, inexpensive and affordable means of treating SARS-CoV-2 disease (Lopez *et al.*, 2008; Schoeman and Fielding, 2019; Madu *et al.*, 2009).

It could be assumed that only corporate interests impair the dissemination and use of such a natural and powerful anti-viral tool. This treatment was reported to be exceptionally safe (complication rate of only 0.7 per 100,000 treatments) as compared with usual treatments. Moreover, the treatment with ozone took about 15 min (Brownstein *et al.*, 2020). It was used successfully by intramuscular or intravenous injections, resulting in improving of all symptoms of SARS-CoV-patients (Brownstein *et al.*, 2020).

#### **4.3. Hyperbaric Oxygen Therapy (HBOT)**

One among the dreadful symptoms that almost lead patients to death is hypoxemia. Fundamentals of respiration teaches that a safe lung absorbs air by a diffusion process and when breath difficulties are observed, ventilators are used to push oxygen into the lungs alveoli, which are already damaged and compromised. Therefore, some researchers reported that ventilation could be more harmful than beneficial, often increasing

the risk of patients' death (Marini and Gattinoni, 2020). By contrast to mechanical ventilation, hyperbaric oxygen provides the patient with oxygen in a pressurized cabinet and allows the body to suck this air by a natural way and injecting the needed flow directly in the blood (Zhou *et al.*, 2020; and International Hyperbaric Association, 2020). However it is useful to know that the broad use of HBOT is impaired by the cost of the equipment.

#### 4.4. Zinc ion ( $Zn^{+2}$ )

Zinc was known for many years as an immunity booster and enhancer. It has been used to accelerate healing against common cold and other viral diseases, including ARN-virus diseases infections, through the inhibition of the replication of the virus. Zinc is so important for the immune system that the US National Institutes of Health (2019, December 10) disseminated nutritional information sheets about zinc, providing the recommended contents for each age and sex.

Zinc plays important roles in the maintenance of a proper health. Its deficiency can lead to many poor health conditions symptoms and the supplementation with this element improves all of them (Prasad, 2004). When zinc depletion is installed in a person, many symptoms are observed such as loss of taste (Heyneman, 1996), growth retardation (Simmer and Thompson, 1985), hair loss, diarrhea (Arakawa *et al.*, 1976), weight loss, impairment of immunity affecting sexual and reproductive functions (Rink and Gabriel, 2000; Wintergerst *et al.*, 2007), poor healing of wounds, age-related diseases (van Leeuwen *et al.*, 2005) etc... However, it would be wise to be careful in consuming zinc supplementation because the symptoms observed with coronavirus infection and deficiency of zinc are widespread and might be tied to other health conditions. Besides, excess of zinc is not recommended since it is detrimental to the health so that only clinical analysis could assess zinc levels in people in need with it (Maret and Sandstead, 2006). Therefore after assessing the levels of the element in patients, restoring zinc levels is of paramount importance so that many biological functions could operate smoothly.

When it comes to respiratory diseases and Covid-19, researchers were interested in finding out factors that could determine the severity of the disease and search out to know how to mitigate it. Recently, a paper reported the results of an investigation about the relationship between health conditions of hospitalized people and their endogenous zinc content. Analyses performed showed that many among the hospitalized people were zinc-deficient as compared with the control group; what is more, the observed symptoms were likely related to zinc deficiency, thus determining the severity of symptoms that were more observed within the zinc-deficient group (Jothimani *et al.*, 2020). Any absence or deficiency of zinc led to an impairment of the immune function (te Velthuis *et al.*, 2010).

Besides, another report showed that using zinc and its ionophores during the treatment of patients with Covid-19 led to both the inhibition and the replication of SARS coronavirus within minutes *in vitro*. It was observed that increasing the levels of intracellular zinc improved the symptoms of patients with SARS-COV-1, then it was assumed that it could lead to same health beneficial results when patients are infected by SARS-COV-2. The same work showed that less than 70 mg/dL indicated a hypozincemia, a factor that could serve as indicator predicting CovidD-19 severeness of illness. Best results were obtained when the protocol associated the drug, zinc and ionophores (Yasuia *et al.*, 2020). Those associations resulted in the shortening of hospitalizations and reduction of death rates (Rahimian *et al.*, 2020). Another research showed that zinc contributed to shorten the duration of common colds and other viral diseases (Eby *et. al.* 1984); Kurugöl *et al.*, 2006; Hemilä, 2017).

As regards viral infections including coronavirus infection diseases, zinc was a crucial component that had been associated with a number of therapeutic protocols (te Velthuis *et al.*, 2010; Derwand and Scholz, 2020). According to a research, treatments with zinc were associated with reduced in-hospital mortality among patients with Covid-19 (Frontera *et al.*, 2020). It is also worth mention an early example of protocol that included ionic zinc to improve patients with Covid-19 symptoms (Scholz *et al.*, 2020). This protocol made Dr. Zelenko famous in the mainstream press in New York, at the beginning of the pandemic in the United States. Dr. Zelenko (Scholz *et al.*, 2020) reported his successful early use of zinc sulfate and hydroxychloroquine, with no heart side effects and observing a notably reduction of numbers of hospitalizations.

Moreover another work reported that ionic zinc was an anti-inflammatory and athero-protective drug. In that context, evidence was given that elderly supplemented with zinc experienced a decrease of incidence of infections (Bao *et al.*, 2010; Prasad *et al.*, 2007). According to this above-mentioned work, assumption could be made that inflammation and cytokines storm could be the result of proliferation of intestine flora imbalance, the dangerous ones overcoming the good ones. Therefore, zinc could maintain the health from inside.

## 5. Revamping Old Drugs

### 5.1. Chloroquine and Hydroxychloroquine

The protocol including zinc and other drugs was also followed and applied by Didier Raoult (2020), who successfully treated his patients with Covid-19 in IHU-Marseille (France). However he has been facing a fierce corporate opposition since the beginning of the pandemic because of his use of chloroquine (Figure 1); the controversy is far to come to an end. Moreover, a number of reports denied any benefit in using chloroquine or hydroxychloroquine (Figure 1) in the treatment of Covid-19 infections. The most cited report was published by Lancet but was later retracted after it was obvious that data were fabricated and did not rely on actual experiments (Mehra *et al.*, 2007). Because those controversies between pro- and con-users of chloroquine and its derivative, a few researchers and Medical Doctors reasonably and publicly asked whether medicine was intended to save lives or making profits.

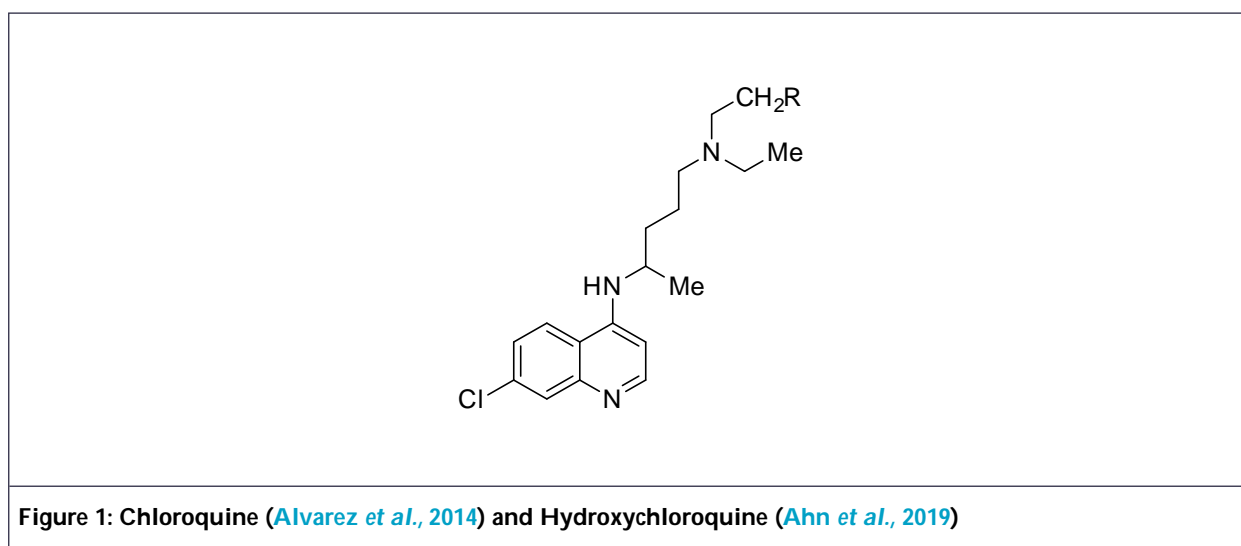


Figure 1: Chloroquine (Alvarez *et al.*, 2014) and Hydroxychloroquine (Ahn *et al.*, 2019)

Despite chloroquine has been known as an antimalarial drug and its safety is well documented for about 70 years, the drug was again targeted by additional trials questioning its efficacy and safety in the treatment of Covid-19 infections. It is worth mention that the whole of those trials used either higher chloroquine toxic doses than recommended, or conditions of use that were different from usual ones (RecoveryV7.0 2020-06-18. ISRCTN50189673). The WHO (2020) sponsored the so called "Solidarity" trial for Covid-19 treatments, concluding that remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon regimens appeared to have little or no effect on 28-day mortality or the in-hospital course of Covid-19 among hospitalized patients. As a result, some countries forbade the general use of chloroquine while maintaining other antiviral drugs such as remdesivir and lopinavir (Medrix, 2020).

Another trial, called REMAP-CAP (REMAP-CAP 2020) recommended hydroxychloroquine as a priority so that in case of success, the drug be included in antiviral treatments against Covid-19. But the randomization trials are under course and initial results are to be published December 2021. This is a good approach that could fix people on the drug efficacy or not against Covid-19 infections. In the meantime, supplementary evidence is going on providing the efficacy and safety of hydroxychloroquine in association with azithromycin (Arshad *et al.*, 2020).

An additional work was published in October 2020 and deserves to be known. Their meta-analysis found a 20% reduction of risk of contracting the disease was observed when treating patients with hydroxychloroquine

(Garcia-Albéniz *et al.*, 2020). Later, another meta-analysis singled out the beneficial effect that was observed when treating patients with reduction of mortality by a factor of 3 along with effective improvements of clinical and virological outcomes (Million *et al.*, 2020). Increasing number of papers and analyses are found in the literature, giving evidence for the efficacy of hydroxychloroquine with treatments, provided it is given early to patients. Those results were related to analyses from 139 studies and the publication was driven by data that are regularly updated. The main points of the conclusion of those papers were as summarized below (<https://hqcmeta.com>).

- HCQ is effective for Covid-19. The probability that an ineffective treatment generated results as positive as the 139 studies to date is estimated to be 1 in 17 billion ( $p = 0.00000000006$ ).
- Early treatment is most successful, with 100% of studies reporting a positive effect and an estimated reduction of 64% in the effect measured (death, hospitalization, etc.) using a random effects meta-analysis, RR 0.36 [0.29-0.46].
- 100% of Randomized Controlled Trials (RCTs) for early, PrEP, or PEP treatment report positive effects, the probability of this happening for an ineffective treatment is 0.002.
- There is evidence of bias towards publishing negative results. 89% of prospective studies report positive effects, and only 73% of retrospective studies do.
- Significantly more studies in North America report negative results compared to the rest of the world,  $p = 0.003$ .

The common point for the success of treatment with chloroquine or hydroxychloroquine is the early use as soon as symptoms are observed and clinically verified. In such a case, no worsening of the disease, and no toxic effects were observed while reduction of hospitalization and deaths were also observed (Prodromos, and Rumschlag, 2020; Ladapo *et al.*, 2020).

The big concern with trials with hydroxychloroquine is the lack of harmonization of definitions and protocols. People who are recruited for trials must be healthy people and not people at risk of contracting and dying from SARS-COV-2 such as elderly ones. What is more, there are many conflicts of interest linked to trials and scientific publications about findings and opinions on therapies against SARS-CoV-2. Then, what could guarantee that successful trials with healthy people would work on people at higher risks? It would be better going on with trials that have shown moderate beneficial effects with chloroquine or hydroxychloroquine in order to allow a much broader assessment of their safety and efficacy. REMAP-CAP (2020) will perhaps address controversies and undesirable disputes.

It is worth mention that chloroquine (CQ) and hydroxychloroquine (HCQ), a metabolite of CQ, are not potent antiviral drugs, but they ease the zinc ion to cross the cell membrane from outside into the cell, where the element inhibits the replication of the virus, thus decreasing the viral charge in the body and inhibiting some pathogens that contribute to inflammation (Chartier *et al.*, 2020). In spite of disputes and controversies, Chloroquine and its derivative, hydroxychloroquine continue to be used successfully in many countries, including China, where the pandemic started (Gao *et al.*, 2020).

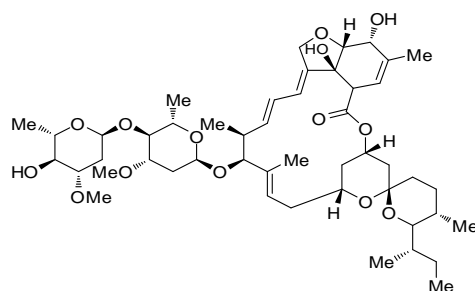


Figure 2: Ivermectin (Anderse *et al.*, 2020)



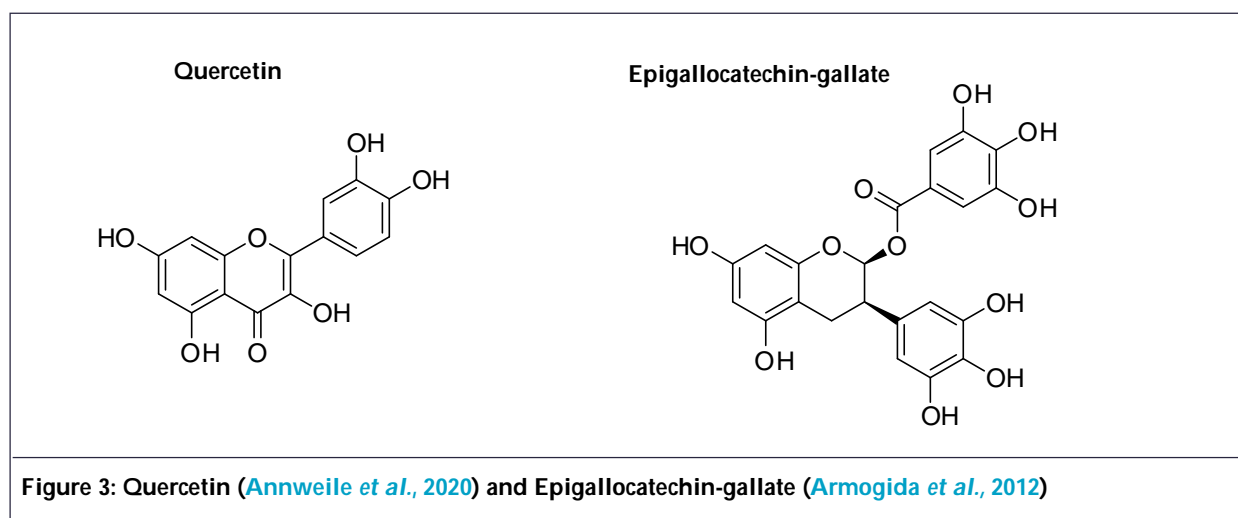
Since there is no specific drug in a position to cope with SARS-2 infections and diseases, many attempts of products association were made in order to have some solution to the pandemic. In Brazil, hydroxychloroquine alone or in association with prednisone, a corticosteroid, led to a 50-60% reduction of hospitalization but deaths were not significant. Besides, there was no heart arrhythmias observed. Ivermectin (Figure 2), azithromycin and oseltamivir did not provide substantial improvement (Fonseca *et al.*, 2020).

### 5.2. Natural Products and Respiratory Syndromes

Since remote times, people all around the world have been resorting to natural products to heal their illnesses. During these days, because of the emergency and the lack of satisfactory answers to their inquiries and the absence of efficient drugs against SARS-CoV-2 infections, traditional medicines have acquired a renewed importance. Needless to say herbs, leaves of some trees and bushes have been used in various regions of the World to heal respiratory diseases. Scientific research has shown that some of them have proved either to block the propagation of many viruses, including coronaviruses at an early stage, or/and to inhibit its replication, thus preventing them to acquire drug resistance. Below are presented a few among them with their brief descriptions.

### 5.3. Quercetin and Derivatives

As regards SARS-CoV-2 infections, known zinc ionophores of zinc are quercetin (Annweiler *et al.*, 2020) and epigallocatechin-gallate (Armogida *et al.*, 2012) (Figure 3), both natural antioxidants, the former being also an antiviral, and the latter both an antioxidant and a signaling molecule. Those natural compounds play the same role as chloroquine and hydroxychloroquine, favoring the uptake of endogenous zinc by cells and increasing the content of the element in the cell (Dabbagh-Bazarbachi *et al.*, 2014). It could be made assumption that nutritional antioxidants that can behave as zinc chelators could be used in enhancing the uptake of zinc by, and into cells, and might contribute to mitigate the severity of SARS diseases.



All the observations that were made on a cohort of people whose mean age was 63, allowed making hypotheses that people who died during the pandemic, likely died from coronavirus infections because of poorer levels of zinc, while those who had higher levels survived longer. Therefore zinc had a direct antiviral action on the replication of SARS-2 within the cell (Gonzalez *et al.*, 2020). It would be wise to assess zinc levels in people at risk or in those who have been infected before they are treated for Covid-19. Therefore nutritional recommendations could be added to available and affordable tools that people might use to prevent viral diseases and, if needed, use them as dietary supplements in order to mitigate the impact of SARS-2 on their lives.

Some years ago, when Ebola virus infection was an actual plague for African countries, quercetin showed its potency in curing the infection. At the same time, evidence was given that this compound inhibited influenza A virus entry, exhibiting antiproliferative, antioxidative, antibacterial, and antiviral activities (Qiu *et al.*, 2016; and Yi *et al.*, 2004).

Nutrients such as flavonoids, which are known for their health benefits, are attracting much interest by researchers, the medical corporation, and the public. A huge literature is available about such compounds of which relevant properties are much diversified such as inhibition of hepatitis C (Rojas *et al.*, 2016), and anti-cancer (Lin *et al.*, 2011; Chen *et al.*, 2018). The major representative of this family is quercetin and it might be made available to people in order to boost and reinforce their immunity, preventing major respiratory acute symptoms and deaths.

According to an investigation, liquorice was shown to inhibit Epstein-Barr virus because of its content of quercetin (Andersen *et al.*, 2020) and isoliquiritigenin (Armogida *et al.*, 2012), two compounds of the family of flavonoids (Figure 4). However, research indicated that the antiviral activity of the former was higher than the latter (Lee *et al.*, 2015).

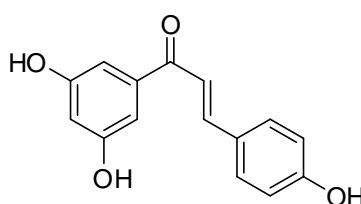


Figure 4: Isoquiritigenin (Arakawa *et al.*, 1976)

The assessment of the biological activity of quercetin showed that this compound had a broad-spectrum antiviral activity. Besides its mechanism of action includes the inhibition of lipopolysaccharide (LPS)-induced tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) production in macrophages, from which stems the cytokines storm (Li *et al.*, 2016). *In vitro*-studies have shown quercetin to exert antiviral activity against SARS-CoV (Ryu *et al.*, 2010), and preliminary findings suggest quercetin can inhibit the SARS-CoV-2 main protease as well. The good news is that researchers are in fact planning to study the use of quercetin against Covid-19.

According to a Canadian report, their researchers Michel Chrétien and Majambu Mbikay began investigating quercetin as a consequence of the beginning of the SARS epidemic that broke out across 26 countries in 2003. They developed a derivative of quercetin (Aronoff *et al.*, 1964) (Figure 5) provided with broad-spectrum protection against a wide range of viruses, including SARS (Yi *et al.*, 2004). Some years later, the Ebola outbreak in 2014 offered them another opportunity to investigate quercetin's antiviral effects and, this time too, they found it effectively prevented infection in mice, "even when administered only minutes before infection" (Qiu *et al.*, 2016).

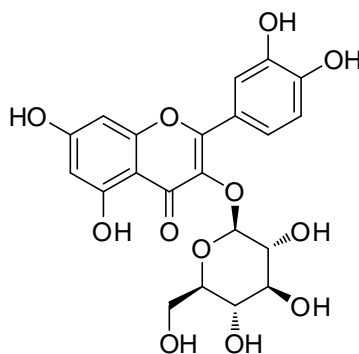


Figure 5: Quercetin 3- $\beta$ -O-D-glucopyranoside (Aronoff *et al.*, 1964)

Since the FDA has already approved quercetin as a safe nutrient, it would be assumed that it is safer than chloroquine or hydroxychloroquine. Besides, the same compound was shown to inhibit influenza A virus. It can be assumed that dietary phenols are able to inhibit the virus at each stage of its proliferation (Yi *et al.*, 2004). Taking into account the properties and biological activities of quercetin, researchers have focused on the design, synthesis, and structure-relationship of modified derivatives of quercetin. A number of papers were published and disclosed interesting structures such as glycosylated and methylated derivatives, leading to either increased or lowered activities as anti-inflammatory, antioxidant, and anti-obesity activities. Enzymatic synthesis of quercetin-family derivatives showed that the overall activity of quercetin was higher than its analogues such as tamarixetin = isorhamnetin and quercetin-3-*O*-glucuronide > isorhamnetin-3-*O*-glucoside > quercetin-3,5,7,3',4'-pentamethylether > quercetin-3,4'-di-*O*-glucoside. The whole of the results showed that quercetin 3-hydroxy group was crucial for its antioxidant activity. By contrast, methylation of quercetin resulted in higher anti-inflammatory effects. Besides, the anti-obesity activity was improved through glycosylation (Magar and Sohng, 2020).

#### 5.4. Astragalus

A work reported that the saponins from *Astragalus* inhibited the replication and proliferation of avian and bronchitis viruses (Xiaoguang and Zenjing, 2014; Zhang *et al.*, 2017; Xue *et al.*, 2017). It was also reported that the consumption of *Astragalus* prevented people to be infected by both SARS and H1N1 virus: moreover, when people were sick, severe symptoms were improved by the consumption of this herb. This could be an example of curing a sickness by nutrition.

#### 5.5. Glycyrrhizins

Glycyrrhizins are a mixture of bioactive compounds from liquorice roots. They behave as preventors of SARS infection and replication of SARS-associated coronavirus (Cinati and Morgenstern, 2003; Hoever *et al.*, 2005). The structure of glycyrrhizic acid, also named glychirrizin (Arshad *et al.*, 2020) (Figure 6), is shown below. According to personal experience in the neighborhood, the consumption of liquorice roots and/or teas resulted in increasing high blood pressure to some consumers. Therefore, care should be taken especially by people with existing hypertension so that detrimental level of blood pressure limit is not reached.

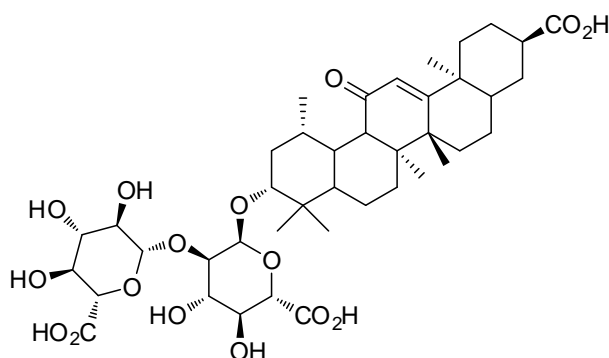
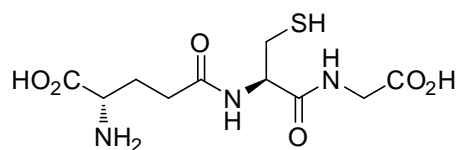


Figure 6: Glycyrrhizic Acid (Arshad *et al.*, 2020)

#### 5.6. Glutathione

Glutathione (Figure 7) is a tripeptide made of three amino acids namely glycine, cysteine, and glutamic acid. Glutathione (Babior *et al.*, 2003) is the most powerful antioxidant that human body uses to cope with Reactive Oxygen Species (ROS). The latter are known to generate chronic inflammation and blood clotting. Glutathione, an ubiquitous molecule, plays key role such as being able to recycle other antioxidants like vitamin C, E and coenzyme Q10, the latter is crucial for the proper functioning of mitochondria (Leong and Ko, 2016).



**Figure 7: Glutathione (Babior et al., 2003)**

Glutathione is also known to have anti-inflammatory properties (Morrzis et al., 2014). Coming up to SARS-CoV-2, one of the dreadful symptoms of the pandemic is excessive blood clotting. In the beginning, instead of blood clotting, the symptom was considered pneumonia. In fact excess of inflammation due to Covid-19 was the response of the body triggered by the infection (Campello et al., 2020). Breath shortness and respiratory difficulties could be both stemming from excessive blood clotting, because lung alveoli were congested by clots, stopping exchanges between lung and blood. Research has shown that Covid-19 severe symptoms were observed in patients with insufficient glutathione levels so that its deficiency may likely be the most cause of severe symptoms of SARS-2 illness. The responsiveness of everyone to SARS-2 infection mostly depends on his/her glutathione levels since low levels are found in people with chronic diseases that put them at higher risks of severe symptoms and death as quoted by Polonikov (2020).

Besides, the same severe symptoms were also observed in patients with deficit of vitamin D, namely 25-hydroxyvitamin D3 (Alvarez et al., 2014; Jain et al., 2014). What is more, it has been shown that glutathione positively interferes in the biosynthesis of vitamin D3 (Parsanathan and Jain, 2019). Moreover, glutathione has been shown to control sportsmen performance as it regulates the oxidative stress (Grucza et al., 2019). Therefore, it could be assumed that restoring the levels of glutathione in more exposed people, namely, elderly and sick people, could preserve them from severe symptoms due to SARS-2 disease by limiting the formation of detrimental ROS and inflammation.

Unfortunately, supplementation with glutathione does not provide satisfactory results since it is poor absorbed by oral consumption. Therefore the more efficient way to overcome this difficulty in order to restore optimum glutathione levels is dietary supplementation with *N*-acetyl cysteine, a precursor of glutathione.

People with diabetes are prone to hypertension and stroke; glutathione has shown to protect them against stroke by reducing cerebral thrombosis. Moreover, lung and other organs are damaged by oxidative stress because of bacteria and viruses. As back as 1997, researchers have shown that *N*-acetylcysteine long-term treatment attenuated influenza-like symptoms as well as improved cell-mediated immunity. Research reported that this affordable product was effective in reducing symptoms during winter especially in elderly and at-risk people (De Flora et al., 1997).

Recently, evidence was given for the ability of *N*-acetylcysteine to improve inflammatory response in patients with pneumonia by reducing lung damage and injury of other organs (Wang et al., 2018; Zhang et al., 2018). Moreover, intravenous *N*-acetyl cysteine treatment of people with severe symptoms of Covid-19 inhibited cytokines storm in people under mechanical respiration; it also reduced C-Reactive Protein (CRP) and ferritin, thus allowing discharge from respirators and full recovery (Ibrahim et al., 2020). Finally but not the least, *N*-acetylcysteine has been shown to inhibit virus replication and expression of pro-inflammatory molecules in cells infected with H5N1 influenza virus (Geiler et al., 2010). The whole potential of effects of *N*-acetylcysteine deserves a careful attention because restoring the levels in people means healing them from inside and with no side effects.

### 5.7. Sambucus

Another work reported that ethanol extract of Eldeberry (*Sambucus Nigra*) and other phenolic acids constituents inhibited coronavirus NL63. Caffeic acid and its derivatives are likely involved and are responsible for this

activity. (Weng *et al.*, 2019). It is of interest mention that many cinnamic acid derivatives, the skeleton of which are found in a number of natural antiviral and/or anticancer compounds that may inspire further research within the domain of SARS-2 therapies. Some among them are displayed below.

### 5.8. Chlorogenic Acid

High blood pressure is a comorbidity that endangers patients with SARS-CoV-2. It is important to keep the latter within a safe range. Research has shown that Chlorogenic acid (Bae *et al.*, 2020) (Figure 8) has shown to improve nitric oxide endothelial status and decrease hypertension (Mubarak *et al.*, 2012; Kaiser *et al.* 2013).

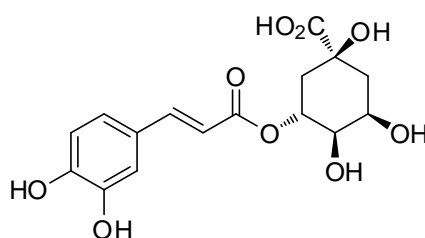


Figure 8: Chlorogenic Acid (Bae *et al.*, 2020)

### 5.9. Hispolon

Hispolon (Bao *et al.*, 2010) (Figure 9), may be considered as a natural hybrid of caffeic acid and pyruvic aldehyde. It was isolated from a mushroom *Phellinus igniarius*. Research has evidenced its activity as an antioxidant and an anticancer which induces apoptosis and activates mitochondria membranes. Those activities could be taken benefit of in controlling oxidative stress in patients with SARS-COVID-2 (Hsiao *et al.*, 2013).

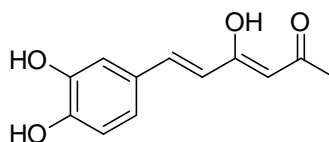
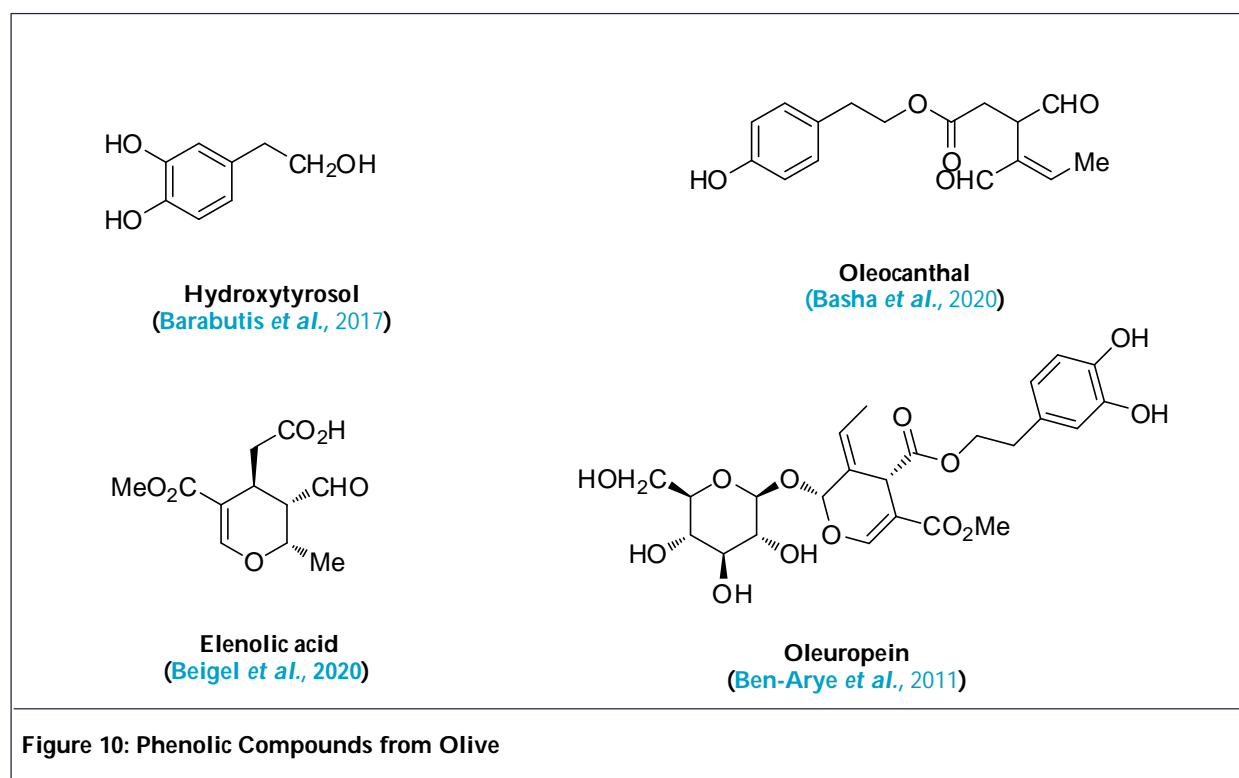


Figure 9: Hispolon (Bao *et al.*, 2010)

Bromopyruvic acid and *p*-hydroxyphenyl lactic acid were found to inhibit glycolysis in cancer cells, thus destroying only cancer cells, but not affecting normal ones. Bromopyruvic acid behaves like a “Trojan horse” whereas *p*-hydroxyphenyllactic acid behaves like a “Blackdoor block” as Pedersen (2007) quoted. In the search for specific drugs to destroy only infected cells by Coronavirus, it would be challenging to develop drugs on this basis.

### 5.10. Olive Leaf Compounds

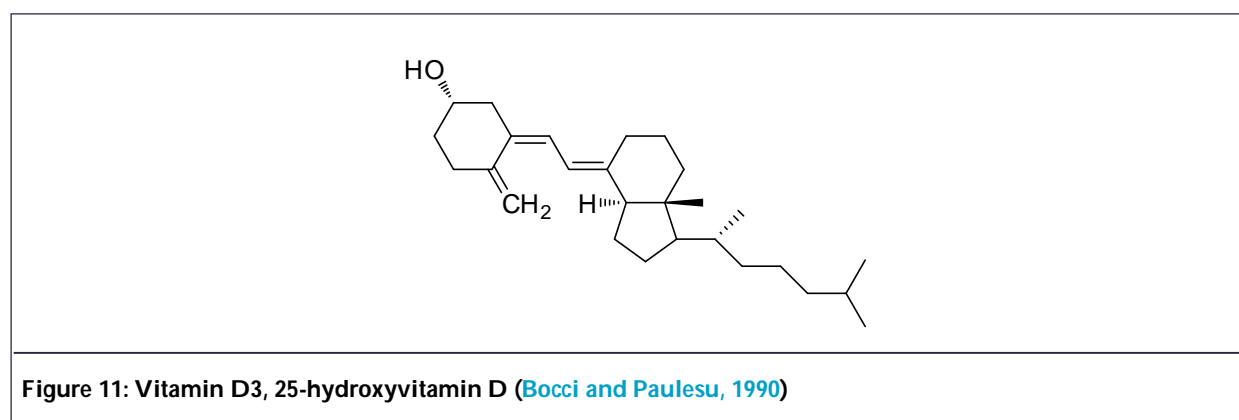
Olive leaf extracts and components are claimed to possess many beneficial effects. In the Mediterranean regions, traditional medicine uses olive leaves tea to treat high blood pressure. Scientific research identified many phenolic compounds in olive leaf and nuts and it is believed that those compounds are responsible for this activity. Among them are hydroxytyrosol, oleuropein, oleocanthal and elenolic acid (Figure 10). Those components may also be found in other species (Ma *et al.*, 2001).



Besides, evidence was given for the anti-inflammatory activity, anti-cancer and anti-viral activity of olive leaves, likely acting by synergism. Coming up to coronavirus infection, it is now well known that the virus targets the host cells ACE 2 receptor, the same which is activated in HIV-1 infections. That is why some successful treatments of HIV-1 and SARS-2 infections were made with olive leaves extracts (Lee-Huang et al., 2003; and Boss et al., 2016).

### 5.11. Vitamin D3, Cholecalciferol

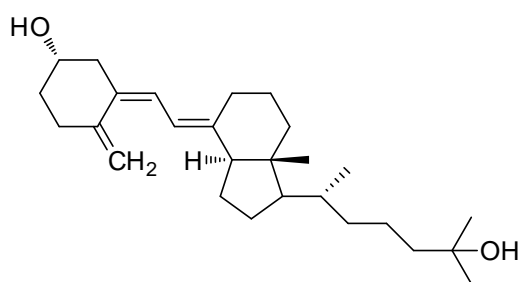
Along with zinc, vitamin D plays a crucial role in regulating immune function so that it would be advisable to associate zinc and vitamin D in the prevention and the cure of SARS diseases (Wintergerst et al., 2007). Vitamin D (Figure 11) (Bocci and Paulesu, 1990) is naturally produced by humans after exposition to the sun. People living in countries where enough sun is not shining are generally deficient of vitamin D and must be supplemented.



Research has shown that the deficiency of vitamin D is tied to health concerns such as increase of infectivity of people towards viral infections including SARS-CoV-2. By contrast, when optimal levels of vitamin D are maintained, it was observed a reduction of the risk of respiratory distress syndrome. Research determined that 40-60 ng/mL of vitamin D are considered the best levels to maintain and to be restored (Grant et al., 2020).

Moreover vitamin D is safe, cheap, and affordable to anyone in order to prevent and protect the whole respiratory tract against acute respiratory illness (Martineau *et al.*, 2017).

Coming up to SARS-COV-2, it has been shown that supplementing preventively people at risk of SARS-COV-2 or restoring protective levels of vitamin D in everyone could shield people against severe symptoms of the pandemic. What is more, with shielding levels of vitamin D, patients' survival is improved (Annweiler *et al.*, 2020). According to Basha *et al.* (2020), prevention and protection of people against SARS-2 illness have been successfully covered by a supplementation of vitamin D. In Spain, one of the European countries that was most hit by Covid-19 and deaths, supplementation with calcifediol (Figure 12) (Brooks *et al.*, 2020) doses (a vitamin D3 analog) in addition to standard of care—With the inclusion of the use of hydroxychloroquine and azithromycin—had significantly lowered intensive care unit admissions (Castillo *et al.*, 2020).

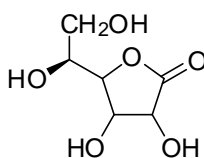


**Figure 12: Calcifediol (Brooks *et al.*, 2020)**

Results and observations about this vitamin induce people to consider vitamin D as a crucial element in the prevention of many diseases including respiratory problems and viral infections. Evidence was given even at the personal level that almost every one could avail the opportunity of protecting himself (herself) against viral diseases and chronic diseases such as heart diseases, high blood pressure, diabetes etc... after just checking his/her vitamin D levels and restore them when necessary.

### 5.12. Vitamin C

The importance of vitamins and especially the deficiency of vitamin C were acknowledged since 1932 by Diet (1932), who described the growing status and the relationship between nutrition and vitamins A, C and D. Of particular importance, the deficiency of vitamin C caused scurvy.



**Figure 13: Vitamin C, Ascorbic acid (Brownstein *et al.*, 2020)**

Since 1940, F.R. Klenner successfully treated both orally and intravenously influenza and pneumonia with high doses of vitamin C while Hunt *et al.* (1994) obtained remarkable results in the treatment of influenza and pneumonia leading to an 80% decrease in deaths (Chakravorty *et al.*, 1994). A couple of years ago, an excellent review updated the topic and described investigations that set forth activities and efficacies of vitamin C. It is noteworthy that vitamin C, of which deficiency is associated with scurvy, was also associated to susceptibility to infections both in infants and in adults, the latter likely caused by increased oxidative stress because of both by cold and heat (Hemilä, 2017).

Recalling Klenner's work, "a hidden pioneer of vitamin C" (Figure 13) (Brownstein *et al.*, 2020), Saul (2007) set forth the achievements of treatment of viral infections such as pneumonia, poliomyelitis and multiple sclerosis with vitamin C.

An interesting 2013 paper gave strong evidence that the *in vivo* antiviral activity of vitamin C was effective at the early stages of the infections (Kim *et al.*, 2013). As a matter of fact, macrophages are our first line of defense and they produce hydrogen peroxide to fight virus and bacteria. In this context, vitamin C is crucial in the production of hydrogen peroxide by macrophages. Since sepsis is one of symptoms associated with SARS-2 infections, intravenous injection of vitamin C was used to mitigate and might improve the symptoms (Walker *et al.*, 2019). Moreover, in a research experiment, investigators treated pneumonia in infants lower than 5 years old and scheduled investigations according to different ages of people groups. They found out that vitamin C was efficient in reducing the duration of severe pneumonia in children in a way that morbidity and mortality were cost effectively reduced (Khan *et al.*, 2014).

The big concern about vitamin C use is that there is no homogeneity in therapeutic doses to be used according to the illness, so that a sound comparison between studies is rather difficult. However, vitamin C is found in many meta-analyses with its associations with other drugs, almost reporting much more benefits than detrimental effects to patients (Moskowitz *et al.*, 2018; Carr, 2019; Barabutis *et al.*, 2017; Marik 2018; Ahn *et al.*, 2019).

### 5.13. Essential Oils

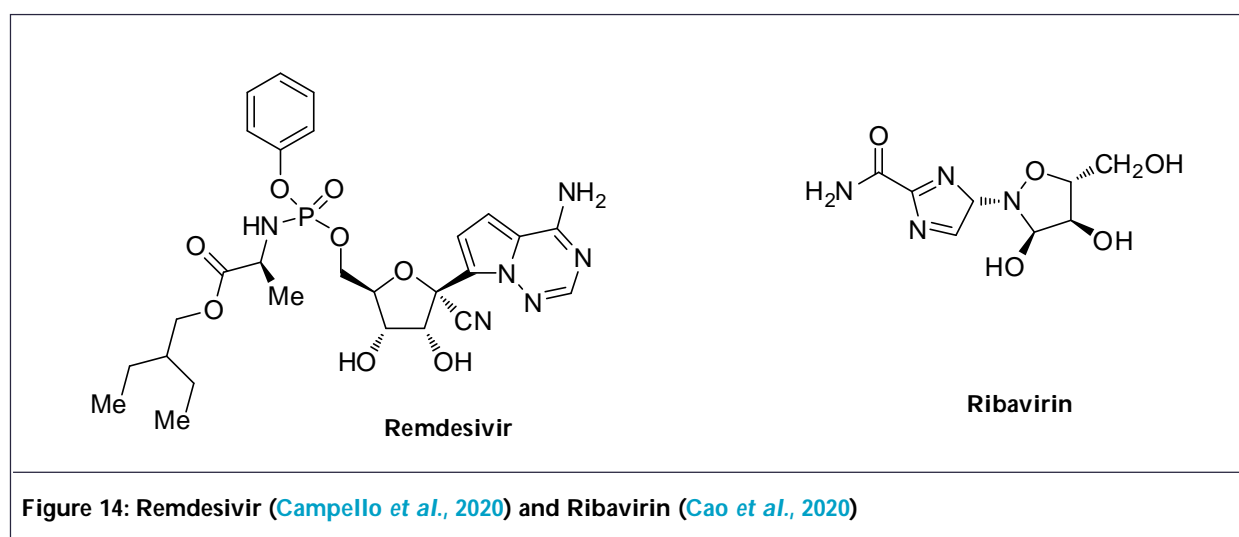
A few essential oils were examined for their inhibition or their inhibition or for prevention of respiratory infections. Oregano was studied and the results were enough relevant so that oregano oil was tested in a number of experiment with success, mainly in Alternative Medicine (Wu *et al.*, 2010; Gilling, 2014; Ben-Arye *et al.*, 2011).

### 5.14. Synthetic Antiviral Compounds

Many papers and reviews were already devoted to the development of anti-SARS-2 drugs around the World. Some synthetic drugs that are spoken of are displayed below. In the absence of reliable data about the efficacy of candidates, the developers could describe and discuss about this topic much more competence than I can do it. However, no drug is available to combat efficiently coronavirus disease till now. Nevertheless, some candidates are found in the literature and a few ones are discussed about below. It is important that many of the papers available about this topic disclose conflicts of interest and it is interesting to be aware of the scope and limitations of each publication.

### 5.15. Remdesivir® (GS-5734)

As the trend was set up in the search for nucleosides, nucleotides, and their analogs to treat HIV infections, the same trend is observed when CoV-19 broke out. Existing retroviral compounds such as ribavirin and





fluorouracil showed no efficacy against Coronavirus infections. Ribavirin needed higher doses than Remdesivir to achieve significant inhibition of SARS-CoV virus (Pruijssers and Denison, 2019) (Figure 14). Despite this difficulty, there is a need to develop wide-broad spectrum antiviral nucleosides or nucleotides to target any stage of the virus replication and/or decrease its charge (Lo et al., 2017).

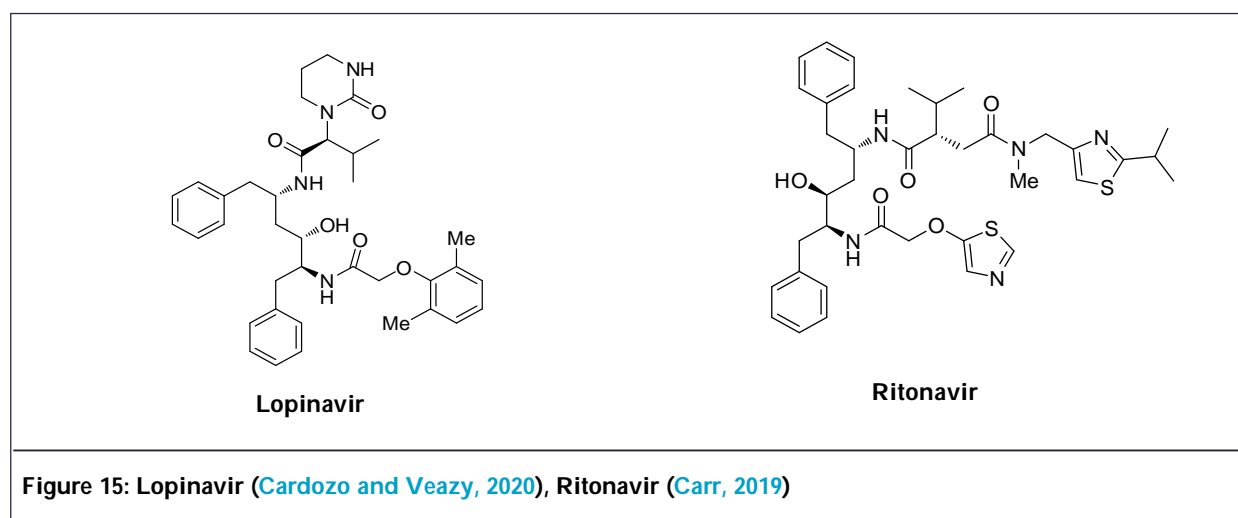
Remdesivir is this kind of analogue of nucleotides that was developed by Gilead Company (USA) in an attempt to fight a number of retroviruses infections such as Ebola virus, MERS-CoV, SARS-CoV, and SARS-CoV-2. The drug showed promises on animal models but failed to show its efficacy on Ebola virus infection (Malin et al., 2020). When tested on patients with SARS-CoV-2, the drug shortened the time of recovery and hospitalization even on patients who were under mechanical ventilation (Grein et al., 2020). It is worth mention that this drug along with other was used in a complex protocol to take care of President Trump during his hospitalization according to a Science Magazine release (Cohen, 2020).

According to research, the drug was generally associated with a more rapid improvement of the patients' health than those receiving placebo, but did not shorten the time of healing. In this study, because 66% of patients involved in the study showed side effects, the treatment with the drug was early stopped (Wang et al., 2020). The same results were observed by a different group, and another one mentioned the common side effects linked to the use of remdevisir such as nausea, worsening respiratory failure, alanine aminotransferase and constipation (Beigel et al., 2020; Goldman et al., 2020).

A recent study also showed that Remdesivir® decreased the viral load in upper respiratory tract, but active replication was maintained in the lower tract bringing about two patients to die. This time, the treatment was stopped because additional undesirable effects were observed such as increase of alanine aminotransferase, renal failure, respiratory distress (Dubert et al., 2020). Those side effects were also acknowledged by the WHO (2000) according to a 26 August report.

### 5.16. Lopinavir®

Lopinavir (Figure 15) (Cardozo and Veazy, 2020) is a protease inhibitor which was developed initially to treat HIV infections and immunodeficiency syndrome (AIDS). It was generally used in association with ritonavir® (Carr, 2019) (Figure 15). The observed side effect was amplification of underlying hepatitis B and C. However and according to research this drugs association was tested on severe patients with SARS-CoV infection and it provided no health benefit at all (Cao et al., 2020).

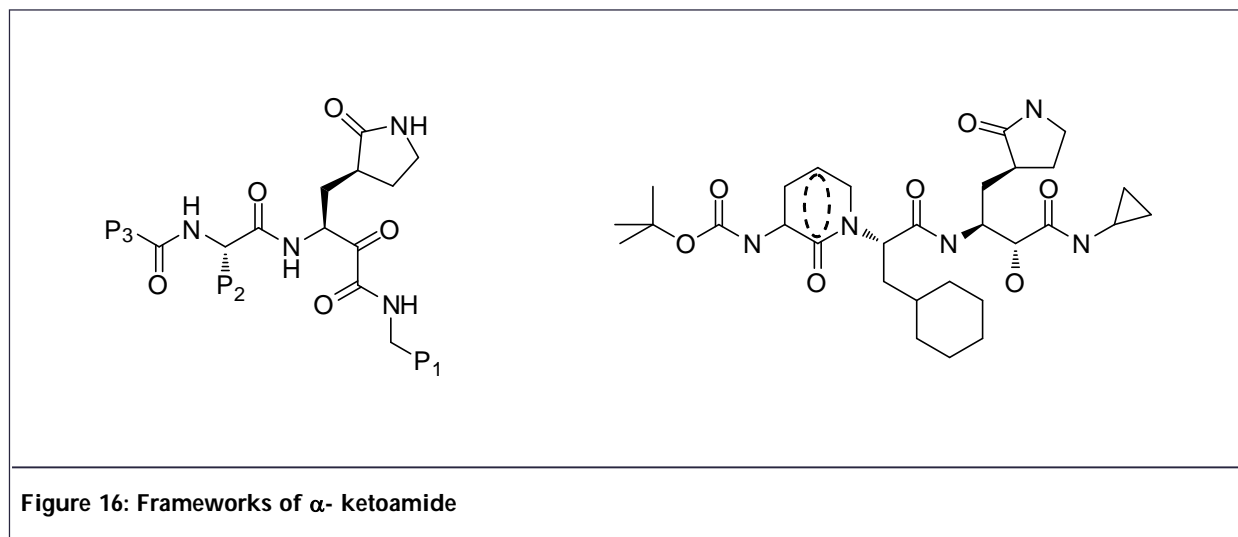


According to a 2004 paper, this association was used during the 2002-2003 SARS epidemic and it provided interesting results such as lower mortality, reduction of nosocomial infections after reduction of steroid treatment (Chu et al., 2004).

### 5.17. Alpha-Ketoamides

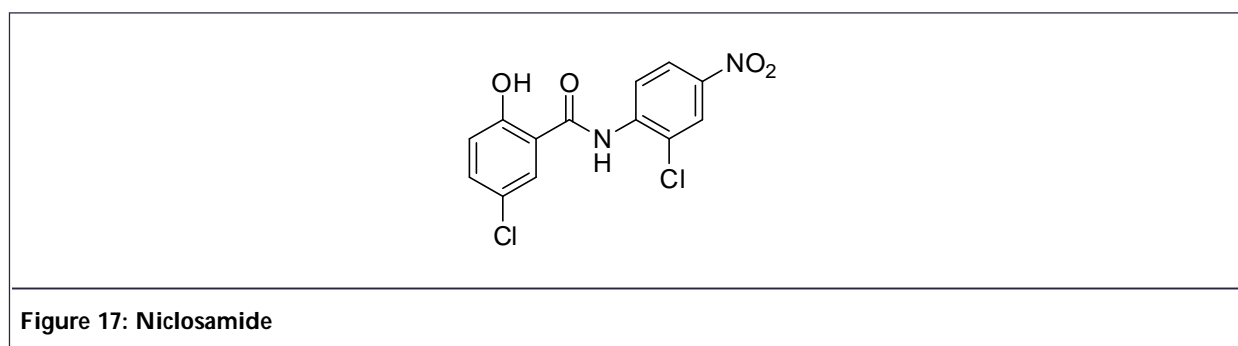
Many virus need proteases to infect cells and ensure their replication. The identification of the structures of proteases allows design and synthesis of therapeutic targets that could be used as protease inhibitors. One

among successful attempts to achieve this goal was made by Zhang and coworkers in 2019. They obtained a series of novel ketoamides that revealed broad-spectrum inhibitors of Coronavirus and Enterovirus proteases (Zhang *et al.*, 2020). The main framework of those protected  $\alpha$ -ketoamides is displayed below (Figure 16, left).  $P_1$  was a protecting group that was almost a phenyl group, while  $P_2$  included various groups such as benzyl, 4-fluorobenzyl, alkyl and cycloalkyl groups and others.  $P_3$  was mainly a cinnamyl group. All derivatives were found non cytotoxic but on the counterpart, their  $IC_{50}$  was in the range of mM.



Efforts towards the development of ketoamides have been maintained by other investigators through 2020 and led to further  $\alpha$ -ketoamides with longer plasma half-lives (Mengist *et al.*, 2020). The main asset of the resulting potent protease inhibitor  $\alpha$ -ketoamide (Figure 16) was a marked tropism to the lung and easy administration by inhalation avoiding invasive means such as injection.

Because of the great impact on people life, FDA has repurposed a number of drugs and a simple amide, Niclosamide<sup>®</sup>, an anthelmintic drug, was shown to be active against a series of viruses such as SARS-CoV-2 syndrome, Middle East respiratory syndrome (MERS-CoV), Zika virus (ZIKV), Japanese encephalitis (JEV), hepatitis C virus (HCV), Ebola virus (EBOV), human rhinoviruses (HRVs), Chikungunya virus (CHIKV), human adenovirus (HAdV) and Epstein-Barr virus (EBV) (Xu *et al.*, 2020). These effects are to be compared with those observed with quercetin. Because quercetin showed no side effects, it would be wise to investigate possible side effects of Niclosamide<sup>®</sup> (Castello *et al.*, 2020) (Figure 17) and compare the magnitude of the inhibitory effects of both drugs against SARS-CoV-2 and, maybe, both compounds might be tested together.

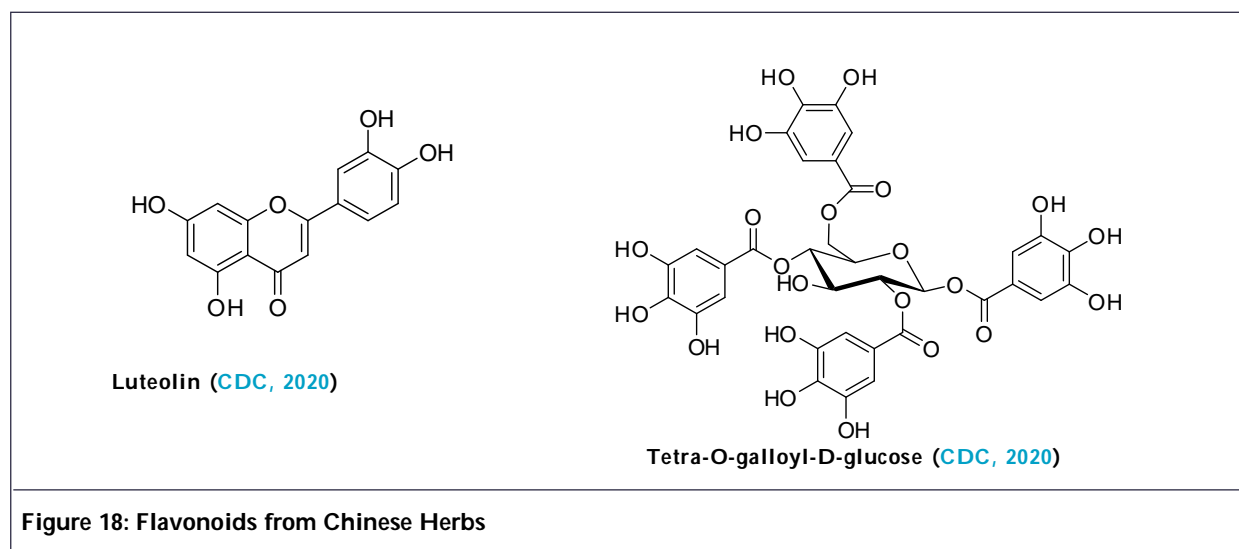


Niclosamide<sup>®</sup> gives evidence for an emergency for revamping old drugs to get a breakthrough in a challenging domain where much is still to be understood and to be done.

### 5.18. Small Molecules

A screening of Chinese herbal medicine allowed the researchers to identify two small molecules that could be used to develop drugs that inhibit the entry of various viruses into the cells. Those compounds were tetra-*O*-

galloyl-D-glucose (CDC, 2020, April) and luteolin (CDC, 2020) (Figure 18), the latter is a flavonoid with a structure related to quercetin. Both these compounds showed broad-spectrum antiviral activity against the entry of HIV, hepatitis C virus, and other viruses (Yi *et al.*, 2004).



It is known that quercetin is a compound with antioxidant effects as well as is gallic acid. Since many antioxidant compounds show anti-inflammatory and anti-cancer properties, it could be assumed that the antioxidant activity is related to anti-inflammatory and anti-cancer activities provided that this relationship is verified. Therefore research could focus on compounds with these activities to assess their potential inhibitory effect against SARS-CoV-2 virus in order to quench either inflammation or hyper blood clotting.

## 6. Immunological Approaches

### 6.1. Traditional Vaccines

A traditional vaccine, whose development and assessment of efficacy and safety, needs at least 10 to 12 years research and control. For safety and security, investigators have to stand back in order to make up a reliable assessment of its efficacy and safety. To the best of our knowledge, a vaccine is a preventive tool but not a healing one but it is devoted to boost natural immunity. The latter would be in a position to fight safely and efficiently a targeted invader through the recognition of its antigens. Then the immune system produces either specific killer cells or antibodies to cope with the invader (Peeples, 2020). As it is well established, diseases such as diphtheria, measles, mumps, and poliomyelitis were eradicated through vaccination. Then they were developed according known, traditional, and established protocols. First of all a bacterium or a virus is weakened or killed. Then it is injected in a healthy people so that her/his body identifies this pathogen, produces specific antibodies and wipes it off.

Afterwards relying on immunity cells or antibodies, the body will remind this germ and antigens for a long time and, when a future infection occurs, the immunized body is in a position to fight it without the need of a new vaccination. Besides, natural immunity coming from exposition of various pathogens provides people with much more broad protection than targeted vaccination. A few years ago, Research showed that artificial immunity enhanced people's susceptibility to other infections than unvaccinated people. For example, influenza vaccination led to virus respiratory interference (Cowling *et al.*, 2012). On another side, Wolff (2020) showed that vaccine derived virus interference was significantly associated with coronavirus and human meta-pneumovirus; moreover, significant protection with vaccination was associated not only with most influenza viruses, but also para-influenza, RSV, and non-influenza virus co-infections virus interference.

### 6.2. m-RNA Vaccine Candidates Against Coronaviruses

With the events of HIV, dengue, Ebola, Chikungunya, SARS, MERS diseases and infections, many attempts were made to develop efficient vaccines. To the best of my knowledge and unfortunately, none satisfactory

was found out so far, nor approved. The left most valued pharmacological alternative was and is still developing a drug or associations of drugs to relieve the patients. The biggest concern with vaccines is that vaccines against dengue fever, SARS-CoV, MERS-CoV whichever their composition showed an ADE, i.e., antibody-dependent enhancement. Put into other words, vaccinated people or animals submitted to vaccinations and later exposed to the virus developed more severe diseases than those who had not been vaccinated (Peeples, 2020; and Cardozo and Veazey, 2020). This would mean that the presence of virus-specific proteins in a vaccine, of which the role is to be antiviral, might boost the entry of virus into the host cells and sometimes enhance its replication (Tirado and Yoon, 2003).

The outbreak of SARS-2 was an opportunity to launch many investigations to develop efficient vaccines, and the hope was that one among them could be ready for about early next 2021 year at the soonest. The first thing of importance to mention is that coronaviruses produce two kinds of S-glycoproteins that are located in their spikes. Those glycoproteins are targeted by current under-development vaccines, since the virus uses them to bind, get into the host cells, and infect them (Du *et al.*, 2009). Two kinds of antibodies can inhibit those S-glycoproteins, i.e., the binding antibodies and the neutralizing antibodies. The former does not fight the infection but instead triggers the paradoxical immunologic system response, resulting in an excessive response whose symptom is an excessive blood blotting.

According to Haseltine (2020), those antibodies bind to the virus and are responsible for the fight against the infection. The race towards vaccines under development for SARS-CoV-2 is concerned by 180 vaccine candidates and many are relying on m-RNA vaccines according to a paper published by Krammer (2020). The m-RNA vaccines are made through a novel technology which has never been implemented before for developing vaccines. The fundamentals of this technology is that the vaccine will instruct normal cells to make the SARS-CoV-2 spike protein, which is used by the virus to fix itself to the ACE2 receptors of the cell.

After production of viral proteins, the body will be instructed to produce specific antibodies *in vivo* then an immunological response will be triggered. It is expected that in-body made antibodies will not harm the vaccinated people and not make them sick. The concern is that because coronavirus, being retrovirus, their m-RNA might hijack the host's cell genetic machinery and instruct him to make viral proteins. Another question is which kind of the spike protein will be made by the host cell?

Anyway, if an efficient vaccine could be made and protect people all around the World, it would be an actual breakthrough in this field. Nevertheless, there are still many questions to ask and answers to provide, because those vaccines under development are fast-tracked products for which many aspects are yet unknown.

For honesty, it is worth mention different opinions against and favorable about m-RNA vaccines. First of all, Gates (April 30, 2020) mentioned in his notes that "Human kind has never had a more urgent task than creating broad immunity for coronavirus. ... We'd need a miracle treatment that was at least 95% effective to stop the outbreak. Most of the drug candidates right now are nowhere near that powerful. They could save a lot of lives, but they are not enough to get us back to normal. ... Realistically, if we are going to return to normal, we need to develop a safe, effective vaccine.

We need to make billions of doses, we need to get them out to every part of the world, and we need all of this to happen as quickly as possible. That sounds daunting, because it is. Our foundation is the biggest funder of vaccines in the world, and this effort dwarfs anything we have ever worked on before. It is going to require a global cooperative effort like the world has never seen. But I know it will get done. There is simply no alternative. Here is what you need to know about the race to create a Covid-19 vaccine.

According to Haseltine (2020), former Harvard medical professor and Gregory Poland of the Mayo Clinic the new technology of making new experimental vaccines arises many questions to be answered before the efficacy and safety of m-RNA vaccines could be definitely known. For William Haseltine, trials should be done in another way to be faithful: "These companies have published their vaccine trial protocols. This unusually transparent action during a major drug trial deserves praise, close inspection of the protocols raises surprising concerns. These trials seem designed to prove their vaccines work, even if the measured effects are minimal.... Prevention of infection is not a criterion for success for any of these vaccines. In fact, their endpoints all require confirmed infections and all those they will include in the analysis for success, the only difference being the severity of symptoms between the vaccinated and unvaccinated. Measuring differences

amongst only those infected by SARS-CoV-2 underscores the implicit conclusion that the vaccines are not expected to prevent infection, only modify symptoms of those infected.

According to Gregory Poland, and reported by Edwards (2020) "We do not know anything about groups they did not study, like children, pregnant women, highly immunocompromised people and the eldest of the elderly". According to Peeples (2020), almost twenty years ago, Peter Hotez, dean of the National School of Tropical Medicine and professor of pediatrics and molecular virology and microbiology at Baylor College of Medicine, was shaken and concerned by trials about a vaccine against another coronavirus. In fact "he witnessed how immune cells of vaccinated animals attacked lung tissue, in much the same way that the RSV vaccine had resulted in immune cells attacking kids' lungs".

Very recently, a former Pfizer's Official, Michael Yeadon (Mercola, 2020), sees no emergency at all for large vaccination campaign, because "very few people will need the Covid-19 vaccine as the mortality rate is so low and the illness is clearly not causing excess deaths."

The summary of this story is as follows:

- Pfizer, in a joint venture with BioNTech, announced that their mRNA-based Covid-19 vaccine candidate, BNT162b2, was "more than 90% effective" in a Phase 3 trial.
- While Pfizer did release a clinical protocol of its trial, it only issued a press release; data for the interim analysis has not been peer reviewed or published.
- Infectious disease expert William Haseltine criticized Covid-19 vaccine trials, including Pfizer's, saying their protocols reveal that they are "designed to prove their vaccines work, even if the measured effects are minimal".
- Asymptomatic infections are not regularly being tested for in Pfizer's trial, so it's possible that those who have been vaccinated could still be asymptomatic carriers of Covid-19, spreading the disease to others.
- Also missing from Pfizer's press release is how the vaccine fared in different age groups, a key data point since older people are those most at risk of serious disease outcomes.
- There is concern that Covid-19 vaccines could cause antibody-dependent enhancement, or ADE, in which the vaccine enhances the virus' ability to enter and infect your cells, resulting in more severe disease than had you not been vaccinated.
- It is far too soon to know whether the vaccine is safe, as, on average, it can take 10 to 12 years for a vaccine to be developed and go through the normal licensing process.

According to Mercola (2020), the main feature of all those investigations related to mRNA fast-tracked vaccines, skipping some steps of the usual assessment of a vaccine, whereas traditional vaccines needed 10 to 12 years to be developed and delivered to public.

Eventually, if pharmaceutical companies are not liable at all for any damage or death incurred by vaccinated people in the next future, this is not fair at all because they will be shielded by lawsuits removal while people would not be protected by any shield at all. Manufacturers' shield would be made by amendments to existing laws such as National Childhood Vaccine Injury Act of 1986, and the Declaration under the Public readiness and emergency preparedness Act for Medical counter measurements against Covid-19 (US Health Resources and Public Administration, 1986; Health of Human Services, 2020).

## 7. Conclusion

In my opinion, it is likely more and more obvious that the World will live with a permanent infectious risk, threatening health, economy and well-being of people, wherever they will be. The World does not need anxiety, insomnia, fear and shock to be happy. We need a World where everyone can be happy, safe and sound. Sustained development would mean provide every living being with opportunities to fully develop his/her genetic potential. It would also mean that nobody should lose self-confidence and altruism. No drug or vaccine could make anyone happy. Therefore, some questions are to be asked, and the answers to are doors we progressively open to get through, but they should never be closed behind.

Searching the best tools and therapies to cope with infectious diseases is of a paramount importance, provided that people be thoroughly informed about health matters and make them participants. Then, efforts should be maintained to provide sets of anti-infectious diseases therapies, revamping also old medicines that could serve as well, should another emergency occurs. Information about those matters should not be left exclusively to “experts” and to mainstream press. Very often, the latter behaves like the actual experts in the field, while a few Medical Doctors contribute to spread fear and panic through mainstream press, leaving people disoriented and confused with contradictory news. Without reliable information, people will continue their lives plunged into smog. Since the beginning of the pandemic, it seems like that someone or groups of people are pulling strings from behind the scene and people are losing self-confidence, altruism and all the fundamentals of a human society.

During this pandemic, countries have progressively closed their borders and global trade exchanges have depleted putting many at risk of food starvation. Therefore, the lesson would be every country should take steps to effectively safeguard the environment avoiding conflicts between people, inhabitants and animals, at the same time preserving enough green lands for agriculture and biodiversity. They could also ensure a sound balance between development, economy, health and well-being. Biodiversity would perhaps mean that local solutions could be better than imported ones. Hippocrates said: “Let your food be your first medicine”.

### Conflicts of Interests

The author has no conflict of interests to disclose.

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