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Global impact and clinical management of severe respiratory syndrome coronavirus-2 (COVID-19)

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Abstract

Coronaviruses are enveloped non-segmented positive-sense RNA viruses belonging to the family Coronaviridae and the order Nidovirales and broadly distributed in humans and other mammals. The recommendations for the management of COVID-19 are mentioned in a lot of Updated Literature such as in The "L. Spallanzani" National Institute for the Infectious Diseases. These recommendations are considered as expert's opinions, which may be modified according to newly produced literature data. In addition, Chloroquine and its derivative, hydroxychloroquine, have a long history as safe and inexpensive drugs for use in malaria-endemic regions and as daily treatments for autoimmune diseases, with the most common side effect being eye damage after long-term use. Although previous studies have revealed that chloroquine has therapeutic activity against viruses, including human corona virus OC43 in animal models and SARS-CoV in cell culture studies. we proposed that from natural Medicine the polyphenol compounds in olive leaf extracts were responsible for the stimulation of probiotic Microbes growth and metabolism and that olive leaf extracts ingested in human diet might have the same effect on desirable components of the intestinal microflora, Herbal medicines, plant products, and phototherapeutic have been widely used all over the world since ancient times. Such as Orange, garlic, Bananas, and lemon have an effect on increasing the immune component Microbes growth and metabolism and that olive leaf extracts ingested in human diet might have the same effect on desirable components of the intestinal microflora, Herbal medicines, plant products, and phototherapeutic have been widely used all over the world since ancient times. Such as Orange, garlic, Bananas, and lemon have an effect on increasing the immune components of the intestinal flora. Different types of fruits and vegetables, such as Green leaves, berries, and nuts, have been used for their health benefits. In addition, fruits and vegetables are rich in vitamins, minerals, and antioxidants. They are essential for a healthy diet and provide a wide range of health benefits. The recommendations are considered as expert's opinions, which may be modified according to newly produced literature data.

Key words: Medication, Covid-19, Corona virus, Nanomaterials, Phytochemicals, Natural product, Nanocapsulation, Phytotherapeutics

Introduction

The lockdown has started in late 2019, many researchers started racing to learn more about SARS-CoV-2, which is one of a family of viruses known as coronavirus for their crown-like shape (Acter et al., 2020). Northeastern University, Boston, USA, chemical engineer Thomas J. Webster, who specializes in developing nano-scale Medicine and technology to treat diseases, is part of a contingency of scientists that are contributing ideas and technology to the Centers for Disease Control and Prevention to fight the COVID-19 outbreak. The concept of using nanoparticles, Webster says, is that the virus behind COVID-19 mainly constructed of a similar scale as his nanoparticles. At that scale, the matter is ultra-small, about ten thousand times smaller than the width of a single strand of hair(Hu, Frieman, and Wolfram 2020; Liu, Zhou, et al., 2020).

Webster is proposing particles are similar in sizes that could attach to SARS-CoV-2 viruses, concerning their structure with a combination of infrared light treatment that structural change would then sustained the ability of the virus to survive and reproduce in the body. "You have to think in this size range," says Webster, Art Zafiropoulo Chair of chemical engineering at Northeastern. "In the nano-scale size range, if you want to detect viruses, you have to destroy them." Finding and neutralizing viruses with nanomedicine is at the core of what Webster and other researchers call theranostics, which focuses on combining therapy and diagnosis. Using that approach, his lab has specialized in nanoparticles to fight the microbes that cause many diseases like influenza and tuberculosis. "It's not just having one approach to detect whether you have a virus and another approach to use it as a therapy," he says, "but having the same particle, the same approach, for both your detection..."
and therapy."

In December 2019, a lot of pneumonia cases of unknown causes emerged in Wuhan, Hubei, China. Following the pneumonia cases were reported in Wuhan and shared history of exposure to sea food stores for all COVID-19 Patient an epidemiological alert and warning was released by the local health authority on Dec 2019, more than 50 -suspected cases with fever and dry cough were transferred to hospitals starting from December 31st, 2019(Zhu et al., 2020). An expert team consists of physicians, Nurses, pharmacist epidemiologists, virologists, and government officials who were soon formed after the alert. Moreover, according to the National Health Commission of China and Ethics Commission of Jin Yin-tan Hospital(Yang et al., 2020). The Ethics Commission of the designated hospital for prominent infectious diseases. In January 2020, the "World Health Organization" (WHO) defined SARS-CoV-2 responsible for the disease (COVID-19), some of the cases asymptomatic cases to severe respiratory involvement(Lai et al., 2020). On March 9th, 2020, WHO considers that COVID-19 is a global pandemic(Downing 2020). Besides, Italy is regarded as the second most affected country by COVID-19 infection after China. The "L. Spallanzani" National Institute for the Infectious Diseases, IRCCS, has been the first Italian hospital to admit and manage patients affected by COVID-19 (Nicastro et al., 2020). The recommendations for the management of COVID-19, as mentioned in the "L. Spallanzani" National Institute for the Infectious Diseases. These recommendations must be considered as expert opinions, which may be modified according to newly produced literature data(Nicastro et al., 2020).

Treatment and Management

Pharmaceutical Treatments

According to National Institutes for Infectious Diseases "L. Spallanzani", IRCCS. Recommendations for COVID-19 clinical management of anti-viral therapy as the following: Remdesivir once per day by intravenous route of Administration the loading Dose 200 mg, followed by the maintenance dose of 100 mg daily within days, or if Remdesivir isnot available the suggested Alternative Lopinavir/ritonavir* 200/50 mg tablets, two tablets q12h within 28 days (Sun 2020), Also Hydroxychloroquine phosphate 400 mg tablets loading Dose taken as one tablet q12, followed by 200 mg tablets regular Dose 1 tablet q12 within days or we can use Chloroquine phosphate instead of Hydroxychloroquine phosphate 250 mg tablets, two tablets q12 within ten days (Capalbo et al., 2020). Before Do not co-administrate Remdesivir with lopinavir/ritonavir, due to possible drug interactions, steroids administration as oral or intravenous rehydration and shall be Considered systemic in case of clinical signs suggesting an incipient worsening of respiratory functions, the steroids are mandatory if Tocilizumab is used with regimen above such as methylprednisolone 1 mg/Kg daily intravenously for 5 days, followed by 40 mg daily for 3 days and, lastly, 10 mg daily for 2 days, or dexamethasone 20 mg daily intravenously for 5 days, followed by 10 mg daily for 3 days and lastly 5 mg daily for 2 days(Bowen et al., 2012). Also, an article was published regarding the Artificial intelligence predicts that drugs Baricitinib that connected with AP2-related to protein kinase 1 (AAK1) affecting and destroying these, proteins may inhibit viral entry into the target cells, this Medication usually used in the treatment of rheumatoid arthritis, is a kinase inhibitor and indicated for controlling viral replication. Moreover, the remdesivir, also one in vitro clinical study specified that an adenosine analog, which acts as a viral protein inhibitor, has improved the condition in one patient(Zhang et al., 2020).

Chloroquine mechanism of action by rising the endosomal pH required for virus-cell fusion has the potential of blocking viral infection and was shown to affect activation of p38 mitogen-activated protein kinase (MAPK), which is involved in the replication of HCoV-229E (García et al., 2018). When the patient uses a combination of the antiretroviral drugs lopinavir and ritonavir, it shows significantly improving in the clinical condition of SARS-CoV patient(González de Requena et al., 2003). This might be an option in COVID-19 infections. Further possibilities include leronlimab, a humanized monoclonal antibody, and galidesivir, a nucleoside RNA polymerase inhibitor, and there may be included as potential treatment candidates(Philippidis 2020). Now almost the Clinical Trials focus on the efficacy of remdesivir immunoglobulins, arboid hydrochloride oseltamivir, mesenchymal stem cell treatment, hydroxychloroquine, ritonavir plus oseltamivir, lopinavir plus ritonavir methylprednisolone and washed microbiota transplantation (Velavan and Meyer 2020). Another study showed that remdesivir had an excellent therapeutic effect (Wu et al., 2020). Now China has carried out preliminary clinical trials on this drug. Currently, the clinical treatment mainly includes empirical antibacterial drugs, intravenous injection of ribavirin for anti-viral and appropriate Dose of methylprednisolone to relieve the shortness of breath U.S (Jin et al., 2020). In addition, there is a suggestion to use traditional Chinese Medicine. This property improves the physical signs of patients, as there was no critical case: no patient used an invasive ventilator, and no death was reported (Wu et al., 2020).

According to recent reports, more than 85% of patients received anti-viral Medication. For example; oseltamivir at a dose of 75 mg every 12 h oral route of administration, ganciclovir is given 0.25 g every 12 h intravenous route of administration and lopinavir/ritonavir tablets was given with Dose of 400 mg lopinavir and 100 mg ritonavir twice a day orally in combined of the addition of antibiotics that used empirically for 90% of patients. Even though using intravenous immunoglobulin and systemic steroids have been used in several reports in a particular situation (Lai et al., 2020; Gorbalenya et al., 2020; Chen et al., 2020; Huang et al., 2020). Also in other reports, several potential drug candidates including anti-viral Medication which include the following lopinavir and ritonavir, tenofovir disoproxil and lamivudine, remdesivir, umifenovir, and chloroquine has been well described, including HIV (Lu 2020) (Wang et al., 2020; Liu, Morse, et al., 2020; Rolain, Colson, and Raoult 2007).

In the current situation, lack of an approved and effective vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19, it is essential to evaluate potential prophylactic and therapeutic effects of drugs that are clinically approved for other indications (Gao, Tian, and Yang 2020). Chloroquine and its derivative, hydroxychloroquine, have a long history as safe and inexpensive drugs for use in malaria-endemic
regions and as daily treatments for autoimmune diseases, with the most common side effect being eye damage after long-term use (Kapoor and Kapoor 2020). Although previous studies have revealed that chloroquine has therapeutic activity against viruses, including human coronavirus OC43 in animal models and SARS-CoV in cell culture studies, anti-viral mechanisms of chloroquine remain speculative (Hu, Frieman, and Wolfram 2020; Paragauasu et al., 2020; Salata et al., 2017; SHIQIN 2015). Chloroquine has been used in the field of nanomedicine for the investigation of nanoparticle uptake in cells, and, therefore, insights from synthetic nanoparticle interactions with cells in the presence of chloroquine may reveal mechanisms that are active at early stages before viral replication. Specifically, nanomedicine studies may provide clues on chloroquine-induced alterations of SARS-CoV-2 cellular uptake (Hu, Frieman, and Wolfram 2020).

**Probiotics Treatment**

The best supplement to improve the immune system is to take probiotics and prebiotic about one capsule after breakfast. This type of supplement will produce compounds called immunomodulators to supply the immune system cells (Oyetayo and Oyetayo 2005). These compounds work to enhance the immune system efficiency against pathogens like viruses. It is a supplement that contains microbiota: *Lactobacillus acidophilus* and other species of *Lactobacillus* with *Bifidum* species. They will be located on colon tissues. This treatment not affected directly but enhances the immune system to attack the viruses like anyexternal bodies inside the human body (Candela et al., 2008).

Olive leaves implicate high quantities of phenol substances very similar to those present in olives and their derived products (Ghidan et al., 2018). There is compelling scientific evidence that olive leaf polyphenols are bioactive compounds. Olive leaves or their specific organic constituents have significant antimicrobial (Bisignano et al., 1999), antioxidant (Ruiz-Gutiérrez et al., 1999) and anti-inflammatory properties (Briante et al., 2002), atherosclerosis inhibition and hypotensive action (Lee et al., 2009; Omar 2010) and anticarcinogenic properties that lead to the prevention of some cancers (Owen et al., 2004). Beneficial properties of olive leaf extracts are further consolidated by the bioavailability of their polyphenolic constituents, which are readily absorbed through the gastrointestinal tract, resulting in significant levels in the circulation system (Visioli et al., 2000; Vissers et al., 2002).

In relation to humans, much concern have been focused on phenolic compounds from plants and foods that may adjust microbiota in the intestine by selectively increasing that growth of and lactobacilli and decreasing that harmful bacteria such as clostridial (Haddadin 2010). The olive leaf polyphenol composition is alike to that of olive oil. Oleuropein and other secoiridoids are the concept combination while simple phenols, enclosed hydroxytyrosol, are shown but in lower amounts (Tuck and Hayball 2002). Olive leaves consist of flavonoids such as rutin, flavonol, Luteolin-7-glucoside (Pereira et al., 2007). The olive leaf extract was shown to have an antioxidant capacity 400% higher than vitamin C and almost double that of green tea or grape seed extracts (Ryan, Robards, and Lavee 1999).

As signification of the high incidence of civilization, diseases, Science, and industry direct their interests toward the production of food products, which are beyond the normal nutritional function, deliver health benefits. These products are called functional foods, and the probiotics are an example (Fuller 1991; Roberfroid 2000). Recently, the developed countries have arrived at a new food formulation, originated from the combination of nutraceutical compounds and probiotic microorganisms, and formulations are mounting quite a trend (De Leonards et al., 2008).

The growing popularity of functional food causes increasing interest in raw materials, which can raise the value of food when supplemented (Duda-Chodak, Tarko, and Statek 2008). Different results were obtained regarding the effects of plant extracts rich in polyphenolic compounds on the growth of probiotic bacteria and other microorganisms. It was proved that plant extracts could inhibit the growth of food associated with pathogens and microbes.

**Nanotechnology Treatments**

Nonmaterial's (N.M.s) have unique physicochemical properties in providing versatile scaffolds for functionalization with biomolecules. Moreover, certain N.M.s such as gold and magnetic nanoparticles as well as polymeric hybrid N.M.s have shown a respond to external stimuli achieving a spatiotemporal controlled release of macromolecules (Mout et al., 2012; Sapsford et al., 2013). For these reasons, over the last two decades, engineered nanomaterials have been successfully tested and applied in Medicine and pharmacology. Gold nanoparticles (AuNPs) are a piece of evidence to treat the harmful responses arising from reactive oxygen species (ROS). Silver nanoparticles (AgNPs) are microbial agents which could be potentially used as an alternative to anti-viral to treat human infectious disease, especially influenza. Virus infections were unsuccessfully treated by anti-viral (Ghidan et al., 2017; Al and Ghidan, 2018; Mariadoss et al., 2019).

However, many concerns about the use of AgNPs on humans arise from their potential toxicity, although mechanisms are not well-understood. We represent here, in the context of influenza virus infection of lung epithelial cells, that AgNPs down-regulated influenza induced CCL-5 and -IFN-β release (two cytokines important in anti-viral immunity) through RIG-I inhibition, while enhancing IL-8 production, a cytokine important for mobilizing host antibacterial responses (Rezvani et al., 2019). AgNPs activity was independent of coating, and it was not observed with gold nanoparticles.

Down-stream analysis indicated that AgNPs disorganized the mitochondrial network. It prevented the anti-viral IRF-7 transcription factor influx into the nucleus. Importantly, we represent that the modulation of the RIG-I-IRF-7 pathway was concomitant with inhibition of either classical or alternative autophagy (ATG-5- and Rab-9 dependent) depending on the epithelial cell type used (Villeret et al., 2018). Altogether, this demonstration of AgNPs-mediated functional dichotomy (down-regulation of IFN-dependent anti-viral responses and up-regulation of IL-8-dependent antibacterial responses) may have practical implications for their use in the clinic (Villeret et al., 2018). Chloroquine, an approved malaria drug, is known in
nanomedicine research for the investigation of nanoparticle uptake in cells, and it may have the potential for the treatment of COVID-19 (Shukla et al., 2020). Gold, silver, zinc, and copper nanoparticles can be affected by this virus, as well as Magnette nanoparticles (Patient as nano capsulation).

Natural products and biochemicals

Eclipta prostrata and known for its therapeutic values in the cure of viral infections, human bronchial epithelial cell injury. It has many pharmacological properties such as anti-inflammatory, anti-cancer, and antioxidant activities (Feng et al., 2019; Li and Kan 2017).

Immunomodulatory activity of some monoterpenes limonene and carvone

The action of the immunomodulatory activity of some monoterpenes was studied on animals like mice—administration of carvone and limonene like other various monoterpenes. The researches indicate the increase of the total count of white blood cells (WBC) in mice. The maximum total of WBC count in carvone treated mice appeared on the 12th day while in limonene was on the 9th day after the combined administration of carvone and limonene increased the total antibody production. Antibody producing cells in the spleen, bone marrow cellularity (figure 1), and alpha-esterase positive cells significantly compared to the healthy animals indicating its potentiating effect on the immune system (De Carvalho and Da Fonseca 2006; Andrade and De Sousa 2013; Kalsum et al., 2017).

![Figure 1: Naturally occurring monoteroenes carvone and limonene](https://www.phoenixpub.org/journals/index.php/jaar)

Food and Some Nutritional Elements

Herbal medicines, plant products, and phototherapeutic have been widely used all over the world since ancient times. Such as Orange, garlic, Bananas, and lemon have an effect on increasing the immune system (Vanderhaeghe 2000). Anti-viral properties of garlic were shown in vitro activity against influenza A and B (Weber et al. 1992). Regarding orange, there is much literature regarding orange extracts the results of the provided anti-viral activity. These properties suggest that this orange peel could provide advantages as a topical prophylactic/therapeutic agent for some viral infection (Guo et al., 2012; Marzouk 2013; Huang et al., 2015).

Prevention and Disinfectants

The most efficient solution to destroy the coronavirus is a solution contains the following compounds: 71% ethanol, 1% hydrogen peroxide and 0.10% Sodium hypo chlorite by using as external prevention for cleaning and disinfectant (Pradhan et al., 2020)

Novel treatments

SARS-CoV-2 escalates mostly through tiny droplets of viral particles from breathing, talking, sneezing, coughing that enter the body through the eyes, mouth, and nose. Prospective role of inanimate surfaces for the spread of coronaviruses and their distraction with disinfectant agents. It suggests that those germs may survive for days when they attach themselves to countertops, handrails, and other hard surfaces (Kingsbury et al. 2020). That's one reason to make theranostics with nanoparticles the focus of the COVID-19 outbreak. Nanoparticles can damage these pathogens even before they break into the body, as they hold on to different objects and surfaces (Albrecht, Evans, and Raston 2006). His lab has developed materials that can be sputtered on objects to form nanoparticles and attack viruses.

"Even if it was on a surface, on someone's countertop, or a mobilephone," he says. "It doesn't mean anything because it's not the active form of that virus. That same technology can be fine-tuned and changed to target a wide range of viruses, bacteria, and other pathogens. Unlike other novel drugs with large molecular structures, nanoparticles are so small that they can move through the body without disrupting other functions, such as those of the immune system.

"Almost like a surveyor, they can go around your bloodstream," Webster says. "They can survey your body much easier and under much longer times and try and detect viruses." To do all that, the Centers for Disease Control and Prevention (CDC) need to know the specifics about what kind of structure is required to neutralize SARS-CoV-2, Webster says.

An alternative to nanomedicine is producing synthetic molecules. But Webster says that tactic presents some challenges (Alvarez et al., 2017). In the case of chemotherapies used to treat cancer cells, such synthetic drugs can cause severe side effects that kill cancer cells, as well as other cells in the body (Sak 2012). The same thing could be happening with synthetic chemistry to treat a virus, where molecules are killing a lot more than just that virus (Wimmer et al., 2009). Webster says. Still, Webster acknowledges that there aren't many researchers focusing on nanoparticles to kill microorganisms. One of the main reasons for the lack of those solutions is that the same benefits that make nanoparticles ideal to fight infectious diseases also make them a concern for the U.S. Federal Drug Administration. Because of their size, nanoparticles are extensive to seep through other parts of the body (Buzea, Pacheco, and Robbie 2007; Ratner and Ratner 2004). To decrease that risk, Webster's lab has focused on using iron oxide. Particles of that makeup entail chemistry that is already natural to our bodies and diets.

Even if you have a viral infection, you need more iron, because you could be anemic depending on how bad the infection is. "We're developing these nanoparticles out of chemistries that can help your health. Iron-based nanoparticles could be directed with magnetic fields to target specific organs in the body, such as lungs and other areas susceptible to respiratory complications after contracting viral infections (Ratner and Ratner 2004; Greish et al.,
2018). That too, Webster says, is something that you couldn't do with a novel synthetic molecule. What this all means is that we just have to do the studies to show those iron nanoparticles are not going into the brain or the kidney and that these nanoparticles are going exactly where you want them to go to the virus.

**Expected Medication to treat corona virus**

**First family: Antimalaria**

**Chloroquine:**
It used for the treatment of acute malaria. As chemoprophylaxis also the mod of action (MOA) binds to and inhibits DNA and RNA polymerase interferes with metabolism and hemoglobin utilization by parasites inhibits prostaglandin effects, chloroquine concentrates within parasite acid vesicles. It raises internal pH resulting in inhibition of parasite growth, and it may involve aggregates of ferrirrotoporphyrin IX acting as chloroquine receptors causing membrane damage that may also interfere with nucleoprotein synthesis (Wellem and Plowe 2001; Krogstad et al., 1987; Trape et al. 1998). The proposed mechanism involves chloroquine-induced suppression of PICALM, which prevents endocytosis-mediated uptake of SARS-CoV-2’S

**Quinine**
It was conjunction with other antimalaria, and for uncomplicated chloroquine-resistant P. falciparum malaria, MOA depresses oxygen uptake and carbohydrate metabolism, intercalates into DNA disrupting the replication and transcription of the parasites, cardiovascular effects similar to quinidine (Krishna and White 1996; Denes, Gabster, and Huang 1981).

**Second family: Antiviral**

**Amantadine**
As an anti-viral agent and anti-Parkinson's agent, the MOA as anti-viral blocks the uncoating of influenza A virus, preventing the penetration of the virus into host. As anti Parkinsoninactivity may be due to it's blocking the reuptake of dopamine into presynaptic neurons or by increasing dopamine release from presynaptic fibers (Davies et al., 1964; Staničova, Miškovsky, and Šutiak 2001).

**Rimantadine**
Prophylaxis adult and children > 1 and treatment within an adult of influenza A viral infection (45), the MOA exerts its inhibitory effect on three antigenic subtypes of influenza a virus (H1N1, H2N2, H3N2) early in the viral explicative cycle possibly inhibiting the uncoating process it has no activity against influenza B virus, 2-8fold more active than amantadine (Tominack and Hayden 1987; Jefferson et al., 2002). On the other hand, the researchers found that the molecular bond between SARS-CoV-2's spike protein and ACE2 looks fairly similar to the binding pattern of the coronavirus that caused the outbreak of SARS in 2003 (McNamara, Richt, and Glickman 2020). There are some differences, and however, in the precise amino acids used to bind SARS-CoV-2 to that ACE2 receptor compared with the virus that causes SARS (severe acute respiratory syndrome), this Medication maybe can use to treat coved 19 (Denis et al.; Prabakaran, Xiao, and Dimitrov 2004).

**Conclusion**
Chloroquine and its derivative, hydroxychloroquine, have a long history as safe and inexpensive drugs for use in malaria-endemic regions and as daily treatments for autoimmune diseases, with the most common side effect being eye damage after long-term use (Kapoor and Kapoor 2020). Although previous studies have revealed that chloroquine has therapeutic activity against viruses, including human coronavirus OC43 in animal models and SARS-CoV in cell culture studies, Herbal medicines, plant products, and phototherapeutic have been widely used all over the world since ancient times. Such as Orange, garlic, Bananas, and lemon have an effect on increasing the immune system. Silver nanoparticles (AgNPs) are microbial agents which could be potentially used as an alternative to anti-viral to treat human infectious disease, especially influenza; there is a novel treatment by using magnetite nanoparticles as nanomedicine drug for Covid-19.

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