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# Therapeutic and Preventive Approaches against COVID-19: A Review

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***Abstract***

*Several vaccines are found for the novel coronavirus SARS-CoV-2, responsible for the Coronavirus Disease 'COVID-19' but with a no clear, unified and effective treatment plan, nor definitive therapies for it, but only a variety of potential approaches. The objective of this work was to present, an overview of a variety of therapeutic and preventive approaches that have been applied instead, in a matter to calm the fatal viral pneumonia and developing safe, effective, anti-coronavirus therapeutic agents from naturally derived compounds would make a hopeful solution to end this pandemic. A number of experimental therapies have been rushed into clinical trials for COVID-19 patients, and with medical journals publishing new COVID-19 research studies at breakneck speed, it can be difficult to keep up with the latest news and guidelines. Potential anti-coronavirus therapies can be divided into two categories depending on the target, one acting on the human immune system or human cells, and another, on the virus itself.*

**Keywords:** SARS-CoV-2, COVID-19, mask, therapy, vaccine.

## INTRODUCTION

There are hundreds of coronaviruses, most of which circulate in animals. Only seven of these viruses infect humans and four of them cause symptoms of the common cold. But, three times in the last 20 years, a coronavirus has jumped from animals to humans to cause severe disease, this end of 2019 novel coronavirus (nCoV/ β-coronavirus) scientifically named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for the similarity of its structure to severe acute respiratory syndrome related coronaviruses [1–5], previously known by the provisional name of 2019 novel coronavirus (2019-nCoV), causes the Coronavirus Disease COVID-19, a highly contagious and progressive infectious disease [6–13].

The novel coronavirus infections were at first associated with travel from Wuhan, but the virus has now established itself around the world in a rapidly expanding pandemic, with flu season fast approaching, health officials are urging the public to help contain the spread of influenza and avoid another outbreak amid the ongoing COVID-19 (coronavirus) pandemic. "The two viruses are very similar, and it's going to make this flu season very challenging", said infectious disease specialist Rekha Murthy, MD, vice president of Medical Affairs and associate chief medical officer at Cedars-Sinai.

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## PREVENTION

Mathematical Models, suggest that public mask wearing is most effective at reducing the spread of the virus, since the most common droplet size threshold has a minimum of 5–10 μm, that's why a mask may be instrumental in preventing a second wave of infections. In fact, there is currently a

 

global shortage of N95/FFP2 respirators and surgical masks for use in hospitals, that's why, simple cloth masks, present a pragmatic solution for use by the public although the high difference of protection [14]. The use of face masks has become ubiquitous in Asian countries and the WHO currently recommends that people should wear face masks if they have respiratory symptoms or are vulnerable to the disease [15].

Precautions that include increased ventilation rate, using natural ventilation, avoiding air recirculation, avoiding staying in another person's direct air flow, and minimizing the number of people sharing the same environment, may help avoid the infection [16]. In addition to, home stay obligation, avoiding crowdedness, social distancing by maintaining a distance of at least 1 meters or more outdoors and 1.5 to 2 meters indoors and even between family members, as well as hand hygiene practice, either by soap or hand sanitizers, covering coughs and sneezes with disposable tissues and no face-hand contact [16–19], because it has been reported that SARS-CoV-2 is sensitive to 75% ethanol, ether, chloroform, chlorine-containing disinfectant, peracetic acid, and other fatty solvents [20], some studies also concluded that higher temperature at 56°C 30 minutes, pressure, and UV may be associated with less SARS-CoV-2 prevalence [21].

## THERAPEUTIC APPROACHES

Current approaches to COVID-19 therapies generally fall into two categories: antivirals — which prevent the virus from multiplying — and immune modulators — which help the immune system to fight the virus or stop it from overreacting dangerously. Some potential therapies act in a different way or via multiple mechanisms.

The major druggable targets of SARS-CoV-2 include the 3-chymotrypsin-like protease (3CLpro), papain like protease (PLpro), RNA polymerase ARN dependant (RdRp), and spike (S) proteins [22]. Effective antiviral therapy and measures to modulate the innate immune response and restore the adaptive immune response are essential for breaking the vicious cycle of the disease and improving the outcomes [23].

### Drugs

Structure-based rational design of binders with enhanced affinities to either ACE2 or the S protein of the coronaviruses may facilitate the development of decoy ligands or neutralizing antibodies (NAbs) for suppression of viral infection [24]. Also, TMPRSS2 is indispensable for the development and homeostasis and thus constitutes an attractive drug target [25]. There are several potential synthetic anti-viral, antibiotic or anti-inflammatory candidates [2].

#### *Anti-virals*

Lopinavir/Ritonavir (Kaletra), nucleoside analogues, neuraminidase inhibitors, Remdesivir, Umifenovir (Arbidol), RNA synthesis inhibitors (such as Tenofovir Disoproxil and Lamivudine), [17, 22]. Another promising drug candidate for the treatment of patients with COVID-19 is molnupiravir (or EIDD-2801), which targets the RdRp of SARS-CoV-2 currently in phase III trials for the treatment of patients with COVID-19 [26].

#### *Antibiotics*

Azithromycin has been used for the treatment of infectious diseases with a few side effects, it acts as an inhibitor of red blood cells (RBC) invasion, besides of the antibiotic and immunomodulatory effects too [27].

#### *Anti-parasitics*

Ivermectin used for parasitic infections, also showed an anti-viral action against the SARS-CoV-2 [28]. Chloroquine/hydroxychloroquine used for malaria treatment, with its effects on inhibition of uncoating or alteration of post-translational modifications of newly synthesized proteins and aiding zinc uptake into cells have, been proposed and showed an increase rate of recovery [17, 22, 29].

 

***Anti-inflammatories***

Anti-inflammatory drugs especially Janus kinase-signal transducer and activator of transcription (JAK-STAT) inhibitors, used against rheumatoid arthritis, may be effective against elevated levels of cytokines and useful in inhibiting viral entry [30, 31]. The three best candidates are, Baricitinib, Fedratinib, and Ruxolitinib [32], especially, Baricitinib in combination with direct-acting antivirals like Remidesivir may help fight off the infection [33].

*Corticoids*

Using corticoids as an anti-viral therapy can be a bit risky, but Dexamethasone, showed promising results in the early clinical trials against COVID-19, decreasing lung water and reducing its inflammation [34].

***Immunosuppressive Drugs***

Developing neutralizing antibodies against the ACE2 or other receptors, comes with a high possibility for reducing the severity of the disease [31]. These drugs, help in reducing the cytokine storm, like Tocilizumab or Sarilumab, which are inhibitors of the Interleukin-6 Receptor (IL-6R) (also known as CD126), that could improve and represses the deterioration of severe COVID-19 patients inflammatory symptoms [13, 35]. Also, Monalizumab, an inhibitor antibody against NKG2A (also known as CD159, receptors that stimulate or inhibit cytotoxic activity of NK cells), that has been developed and has shown promise to restore the function of CD8+ T and NK cells [36].

A study about a humanized Llama antibody against SARS-CoV-2 was conducted, where they found that, these molecules or nano-bodies, would potentially protect against the virus by blocking S-ACE2 interaction and induce antiviral functions, these multi-specific antibodies would be easier to manufacture than polyclonal antibodies, due to the production needs of only one molecule [37].

**Convalescent Plasma Therapy**

On 24/03/2020 Food and Drug Administration (FDA) has given small basis trial for giving plasma therapy, collected from a recovered patient after proper procedure [11], some reports indicated the use of convalescent serum for therapy of patients with COVID-19 in China, still, it hasn't been widely used, in absence of definitive management protocols [38].

Convalescent plasma (CP) therapy, is a classic adaptive immunotherapy, representing the administration of antibodies against a given agent, it has been applied to the prevention and treatment of many infectious diseases, notably for COVID-19, where it might be a promising therapeutic option [39–41]. It can be used for either prophylaxis of infection, with higher effectiveness or treatment of the disease, which would mostly be effective shortly after the onset of symptoms [39].

It was revealed that one appropriate dose of CP, improved the increase of oxyhemoglobin saturation accompanied by rapid neutralization of viremia and all enrolled COVID-19 patients achieved primary and secondary outcomes [40], with results suggesting that it can even help stop viral shedding [42].

CP therapy can be easily accessible, promising, and safe, but comes with risks too, like the transfusion of a potential pathogen and doses at sub-neutralizing concentrations that could suppress innate antiviral systems, another risk lies within the possibility of attenuating the immune response leaving an individual vulnerable to subsequent re-infection [39, 40].

**Mesenchymal Stem Cells Therapy**

Mesenchymal Stem Cells (MSCs) therapy demonstrates a successful harnessing of natural endogenous pathways with protective immunomodulatory properties in opposing viral infection due to the presence of specific cytokines improved qualities. These cells are ACE2-, easily accessible and

 

can be isolated from various tissues such as bone marrow and adipose tissues, including umbilical cord, dental pulp, menstrual-blood, buccal fat pad and fetal liver [43, 44]. But immunogenicity, low invasive procedure, limited cell source and ethical issue are the main limitations of this therapeutic approach [43]. However, there's also, synthetic stem cells "LIFNano", in which leukaemia inhibitory factor (LIF) oppose the cytokine storm in the lungs during viral pneumonia [44].

China have announced the use of MSCs in severe cases with COVID-19 infection [45], in addition to USA, Jordan, Iran, and several other countries [43], after therapy, all of the patients had significantly improved pulmonary function [44].

**Therapeutic BoNTs**

Botulinum toxins (BoNTs) are bacterial protein toxins of *Clostridium botulinum*, that naturally induce paralysis of muscle and sudden respiratory failure leading to death in humans. However, there is a therapeutic BoNT with highly diluted injection portions, that appear to elevate immune cell counts and platelet counts in the blood, which might help fight off the SARS-CoV-2, as it can enhance the antigen presentation and the macrophages-mediated phagocytosis to eliminate the virulent factors, improve blood circulation and oxygen supply, adding to those, a neuro-protection against cerebral ischaemic insults with a capacity to migrate from intramuscular injection site to the brain and other organs. It is a relatively safe, beneficial and effective therapy that could easily be neutralized using available antibodies [46].

**New Technologies**

New technologies have been utilized preemptively to counter the symptoms of SARS-CoV-2 [47].

***Small interfering RNA therapy***

Small interfering RNA (siRNA) are a class of double-stranded non-coding RNA molecules, siRNA-based therapy can be developed against the novel coronavirus, where the siRNAs can hit the highly conserved regions of SARS-CoV-2 RNA like, RdRp, helicase, proteolytic enzymes, and the nucleoprotein and also can act as an inhibitor to suppress the genetic disorders of the lungs [48].

***CRISPR***

CRISPR-Cas13 has been utilized to target essential parts of the SARS-CoV-2 virus, through an approach called PACMAN (Prophylactic Antiviral CRISPR in huMAN cells), which has an RNAse activity that can be either used for both the detection as previously mentioned chapter and the destruction of SARS-CoV-2 [47].

**Natural Medicine**

Developing safe, effective, anti-coronavirus therapeutic agents from naturally derived compounds is a hopeful solution [22]. That's why, the search for new molecules with a preservative power of natural origin has an importance, notably by the use of medicinal plants [49]. Besides, naturally occurring phytochemicals provide a valuable and powerful resource of chemical compounds displaying antiviral properties [22].

In Chinese culture, Traditional Chinese Medicine (TCM) played a unique role in the prevention and treatment of emerging infectious diseases, it has also been widely used for the treatment of the novel coronavirus pneumonia, mainly by preventing infection for healthy persons and improving symptoms for patients with mild symptoms, owing to its ability to activate immune cells, improve phagocytosis and induce the production of cytokines [50].

"Qing Fei Pai Du Tang" (QFPDT) is screened out by the National Administration of Traditional Chinese Medicine (NATCM) and widely recommended nationwide [50]. Other TCM (such as ShuFeng JieDu or Lianhua Qingwen capsules) were also proposed [17].

 

In India, a different matter was the aim to develop an efficient viral inactivation system that has a high preventive potential, by exploiting active compounds from natural Indian medicinal plants renowned for their antiviral and pulmonary protective potentials and infusing them into a nano-fiber-based respiratory masks [51]. There's also the Traditional Indian Medicinal Practices like Ayurveda, Siddha and Unani, not to forget, their plants/herbs, that have been widely used as a treatment and as a preventive strategy for several diseases, including respiratory viral infections, to create immune-boosting and inflammation-modulating effects to manage the immune system [31].

An Egyptian study showed that the Heat Shock Protein A5 (HSPA5) cell-surface is up regulated upon infection, then translocated to the cell membrane where it's subjected to be recognized by the SARS-CoV-2 spike. The author tried to illuminate that some natural product active compounds, may utilize this human cell-surface receptor, having an impact on the virus attachment, like the phytoestrogens and estrogens that showed high affinity through his molecular docking study [52].

Natural products are known historically for their pharmaceutical properties, especially for the Moroccan medicinal plants, where three molecules of which had a significant antiviral power, B–Eudesmol from *Laurus Nobilis* L, Digitoxigenin from *Nerium Oleander* and Crocin from *Crocus Sativus L.* These compounds were interesting as inhibitors of SARS-CoV-2 main protease (3CLpro) [49], which is one of the best-characterized drug targets among coronaviruses that blocks viral replication [53].

In Algeria, an *In silico* study showed that multiple compounds from the *Ammoides verticillata* plant harvested from western Algeria targeted the ACE2 receptor, notably, by the Isothymol ligand with high affinity [54]. Along with a molecular docking study that demonstrated how glycosylated flavonoids from natural sources could inhibit the 3CLpro, mainly, the Quercetin-3-O-rhamnoside molecule, which is found in some fruits and vegetables and also in tea infusions [55].

**Boosting Immunity**

Immunity might be stimulated using vitamin D, C and B3 or low doses of IL-2 [56]. Moreover, Vitamin D appears to have similar modulating effects on IL-6 as Tocilzcumab, as it could offer a realistic alternative treatment [57].

**Vaccines**

Obviously, the ultimate solution is producing a SARS-CoV-2 vaccine [58], since there isn't any effective eradicative treatment for COVID-19 at present [33]. One of the key components in developing virus neutralizing antibodies or a vaccine design is the CoVs S protein [59, 60].

Research institutions and pharmaceutical companies worldwide are stepping up research and development for a coronavirus vaccine. Most of these vaccine would be either as inactivated vaccines, subunit vaccines or viral vectored vaccines (VVV) and should pass the 3 phases of trials before approval and licensing [60], including the mRNA-based vaccines, that were granted the first historic authorization for emergency use [61], but even once a vaccine is approved for human use, high virus mutation rates, would mean that a new vaccine may be need to be developed for each outbreak [58]. A particularly effective vaccine would show results earlier as the difference with the control group would be greater but, most trials would not expect results before the first half of 2021 [62]. COVID-19 vaccines are needed, even if they have minimal impact on transmission and despite the challenges of vaccine allocation, such vaccines are likely to achieve the herd immunity. Furthermore, challenges in distributing a vaccine logistical or political will mean a longer wait for a global end to the pandemic.

## CONCLUSION

Health officials around the world are working to contain the spread of the virus through public health measures such as social distancing, contact tracing, testing, quarantines and travel restrictions.

 

Scientists are always working to find medications to treat the disease and to develop a 100% safe vaccine for this infectious disease, that is still posing a massive challenge to the global health. Besides, instead of concentrating efforts on "unlikely" therapies, it would be better to know how the immune response to this virus develops and how previous exposures to "old" coronavirus can influence the immunity of the population against COVID-19 virus. Viruses tend to mutate, so we can never be confident that vaccines will work. Therefore, relying on preventive measures such as frequent hand washing, use of masks, restricted traveling, personal hygiene, and healthy eating may keep us safe from COVID-19, in hopes that a proper and a specific definitive treatment would be available.

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