

# Novel Corona Virus (COVID-19): Current Strategies and Future Aspects

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**Abstract:** Novel coronavirus (COVID-19) recently emerged as a new pandemic disease that affects millions of people worldwide. This disease considers as a potential threat to human society. Researchers are continuously working to identify virus structure, the pathophysiology of the disease, and possible treatment of the disease. Currently, to fight against the coronavirus, two major strategies have been adopted throughout the world; one is to target virus-cell machinery, and the second is to improve patient immunity. In this review, we have described detailed information about the structure and life cycle of the novel coronavirus, current therapy, and future strategies to fight against this pandemic disease. Computational methods are useful for understanding virus structure, disease pathology, and discovering novel anti-COVID agents. These methods can provide fast and efficient solutions to fight against this disease. We also highlighted the potential role of robotic technology and its importance in various clinical aspects. These robotic technologies may also play an important role in fighting COVID-19.

**Keywords:** COVID-19; FDA-approved drugs; vaccines; antibodies; natural products; artificial intelligence.

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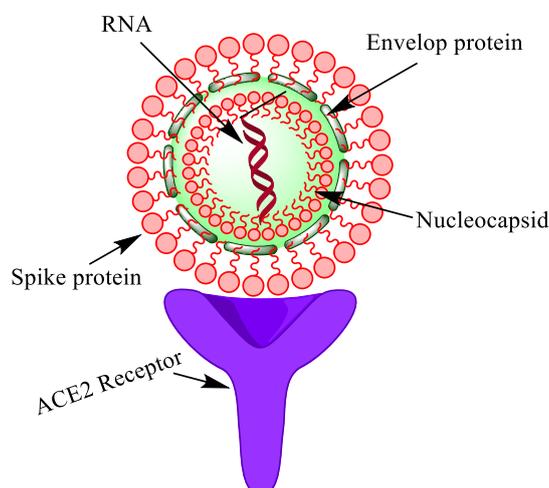
## 1. Introduction

Coronavirus (2019-nCoV) or the severe acute respiratory syndrome coronavirus 2 (Covid-19-2) is quickly transmitting, which commenced in Wuhan city of Hubei province of China later to several parts of the world[1]. Coronaviruses (Subfamily- Coronavirinae) are enveloped, single positive stranded RNA virus. There are six CoVs known to cause human diseases categorized into low pathogenic and highly pathogenic CoVs. Severe Acute Respiratory Syndrome (SARS) CoV is highly pathogenic which mainly infects lower airways causing fatal pneumonia[2]. Two events had occurred in the past due to beta coronavirus. In 2002– 2003, a coronavirus of bat origin with palm civet cats as intermediate hosts in China's Guangdong province affected 8422 persons and caused 916 deaths (mortality rate 11%)[3]. In 2012, MERS-CoV of bat origin emerged in Saudi Arabia with dromedary camels as intermediate host affected 2494 persons and causing 858 deaths (fatality rate 34%)[4]. In December 2019, adults in Wuhan were admitted to the hospital with an unknown cause considered as severe pneumonia [1]. Samples were tested positive, which were accumulated from the market, denoting the origin of the outbreak[5].

In initial cases, the epidemic initiated from the Hunan Seafood market, but the increase in the number of cases and the evidence of human-human transmission was confirmed when healthcare practitioners contacted an infected patient. On 7<sup>th</sup> January 2020, the virus was identified and characterized with Real-time reverse transcription-polymerase chain reaction (RT-PCR) and next-generation sequencing as coronavirus having > 95% homology with bat coronavirus and >70% similarity with the SARS-CoV[6]. SARS-CoV is Betacoronavirus likely occurring in Chrysanthemum bats with pangolins and snakes as intermediate hosts[7]. The virus is present in huge amounts in infected people with approx a billion RNA copies per ml of sputum and can stay on contaminated surfaces longer than a week [8]. The incubation period is 2-14 days [6]. Classes of all ages are at risk of the virus, especially children and elderly persons with co-morbidities are more prone to infection. In the incubation period, persons who are asymptomatic are the main sources of infection and serve an important role in epidemic prevention and control[9]—respiratory droplets transmitted through inhalation or contact are the major source of transmission. The initial symptoms involved are fever, cough, dyspnea, myalgia or fatigue, sputum production, headache, hemoptysis, and diarrhea. Some cases progressed to acute respiratory distress syndrome (ARDS), acute cardiac injury, acute kidney injury (AKI), and shock[6]. Diagnosis comprises of patients having moderate or severe symptoms featured low lymphocyte counts, systemic inflammation and bilateral infiltrates from Chest X-ray and chest computed tomography which is more specific shows ground glass infiltrates. On January 30, 2020, the World Health Organization (WHO) declared COVID-19 to be a Public Health Emergency of International Concern (PHEIC) and considered as pandemic disease[10].

## 2. Corona Virus Structure and Life Cycle

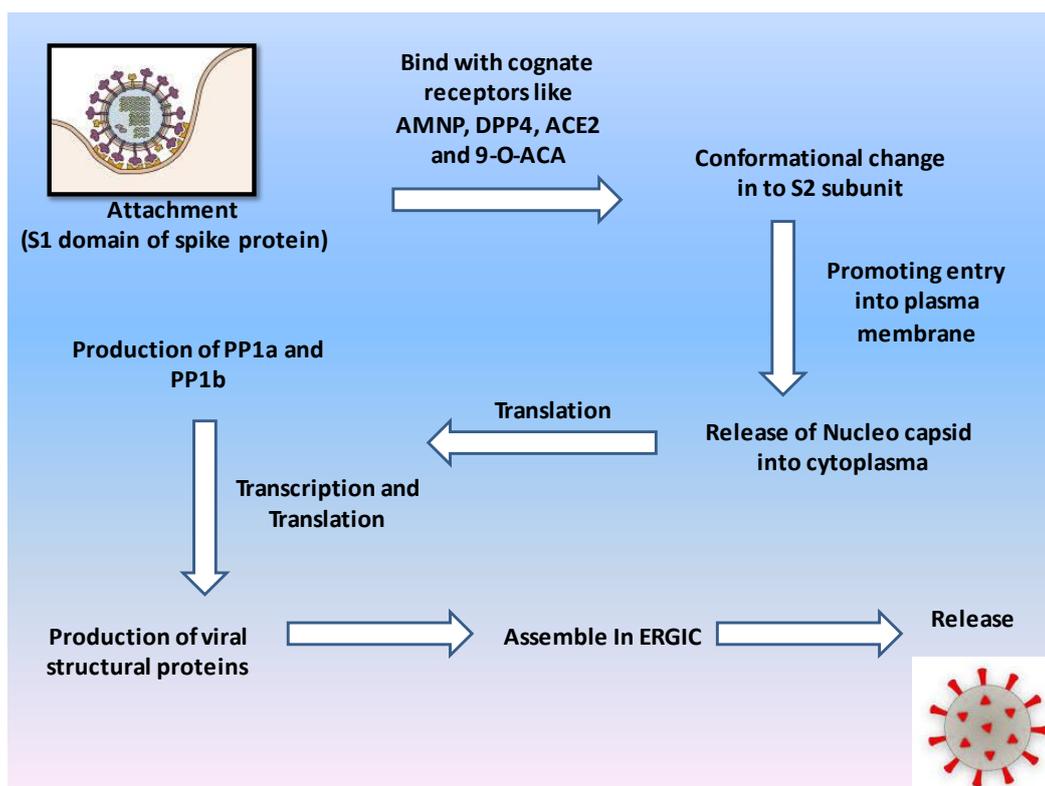
Coronavirus (CoV) is a type of large enveloped RNA virus that belongs to the family of coronaviruses. As per the international committee for the taxonomy of viruses, CoV is divided into four categories: alpha, beta, gamma, and delta, based on the viral genome sequence. The shape of the Cov looks spherical or moderately pleomorphic under an electron microscope. The average number of genomes is about 26-30kilobase [11,12]. Two-thirds of CoV contains viral polymerase, RNA synthetic materials, and two nonstructural polyproteins. The other one-third of the genome portion is divided into different structural units like protein spike (S), envelope (E), membrane (M), Nucleocapsid, and other helping proteins [13,14] (Figure1).



**Figure 1.** Structure of novel coronavirus.

The viral life cycle stages of Cov are nearby similar to the normal viral cycle stages like attachment with the host cell, penetration, transcription, translation, assembly, and release. The life cycle of CoV starts with the attachment of the S1 domain of spike protein (S) with the host. This process makes a conformational change in the S2 subunit of S and ultimately promotes entry into the cell plasma membrane [15]. The virus utilized host cell receptors include different receptors like N-amino peptidase [16] angiotensin-converting enzyme-2 (ACE2) [17], Dipeptidase-4 (DPP4) [18], and 9-O-acetylated sialic acid [19]. Different types of CoVs utilize different sites. After entering the cytoplasm, viral RNA is transferred through ribosomal frame-shifting and produces PP1a and PP1ab polyproteins. This protein will assemble and replicate the polymerase enzyme, which is involved in replicating the coronavirus. The next step is an assembly of viral products and release from the plasma membrane via exocytosis (Figure2).

It is believed that novel coronavirus is a type of beta coronavirus. This beta coronavirus contains spike protein (S) which plays an important role in binding. This protein binds with host cell surface membrane protein called angiotensin-converting enzyme-2 (ACE2) protein. This virus also contains several nonstructural proteins like RNA-dependent RNA polymerase (RdRp), coronavirus main protease (3CLpro), and papain-like protease (PLpro). The interaction between viral S protein and host cell surface protein ACE2 can be the major target Anti-CoVtherapy. It was reported in a cryo-EM structure that the binding affinity of SARS-CoV-2 S protein is 10-20 times more than SARS-CoV [20].



**Figure 2.** Life cycle of novel coronavirus.

### 3. Current Strategies and future aspects to fight against COVID-19.

#### 3.1. Use of existing drugs.

Government authorities of the healthcare division are trying to identify the drugs which having target specificity towards Covid-19. In a virus, RNA synthesis occurs due to RNA-dependent RNA polymerase (RdRp), several antiviral drugs that can block viral RdRp RNA

polymerase. The major target includes inhibition of spike protein(s), RNA-dependent RNA polymerase (RdRp), coronavirus main protease (3CLpro), and papain-like protease (PLpro) [21,22]. Current therapy against COVID-19 includes using existing drugs like remdesivir, chloroquine, hydroxychloroquine, arbidol, etc., and fixing dose of anti-HIV drugs in combination lopinavir-ritonavir, which is currently in clinical trials[23].

The drug chloroquine and its derivative hydroxychloroquine might be effective against this disease due to its ability to block the replication of RNA synthesis [24,25]. The mechanism of chloroquine against COVID-19 is to boost basic pH in the virus compartment containing acidic pH through endosomes into the cell membrane and block the m-RNA replication. It can also inhibit nucleic acid replication, glycosylation of virus proteins, virus assembly, additional virus particle transport, virus release, and further processes from achieving its antiviral influence[26]. Another benefits of this drug are to inhibit COVID-19 origination at the site of receptor angiotensin-converting enzyme-2 or ACE-2 in the treatment of Covid-19[25].

Gilead Sciences, Inc. discovered Remdesivir to treat Ebola virus infection, and presently it is in Phase-III of clinical trials for the treatment of COVID-19 [22]. Remdesivir is preferred in the prevention of COVID-19 infection due to the most promising and powerful antiviral activity. The drug remdesivir targets the receptor RdRp and inhibits the RNA-dependent RNA polymerase for replication of the viral genome. This drug is most significant than other antiviral drugs because of two advantages. The first one is the drug safety profile as it is already used in the treatment of Ebola infection, and the second is the number of clinical evidence which shows the potency of the drug.

The Australian researchers have found that Ivermectin is an inhibitor of Covid-19 causative virus (SARS-CoV-2) in vitro. Also added that a single treatment was able to affect an about 5000-fold reduction in COVID-19 virus at 2 days in cell culture. The latest advancement may lead to the improvement and trial of a novel clinical therapy for the pandemic. Combination therapy of drugs like sofosbuvir with ribavirin is useful for the Covid-19 infection. This combination therapy can inhibit RNA synthesis as both drugs are closely bound to the receptor and block the RNA-dependent RNA polymerase [27].

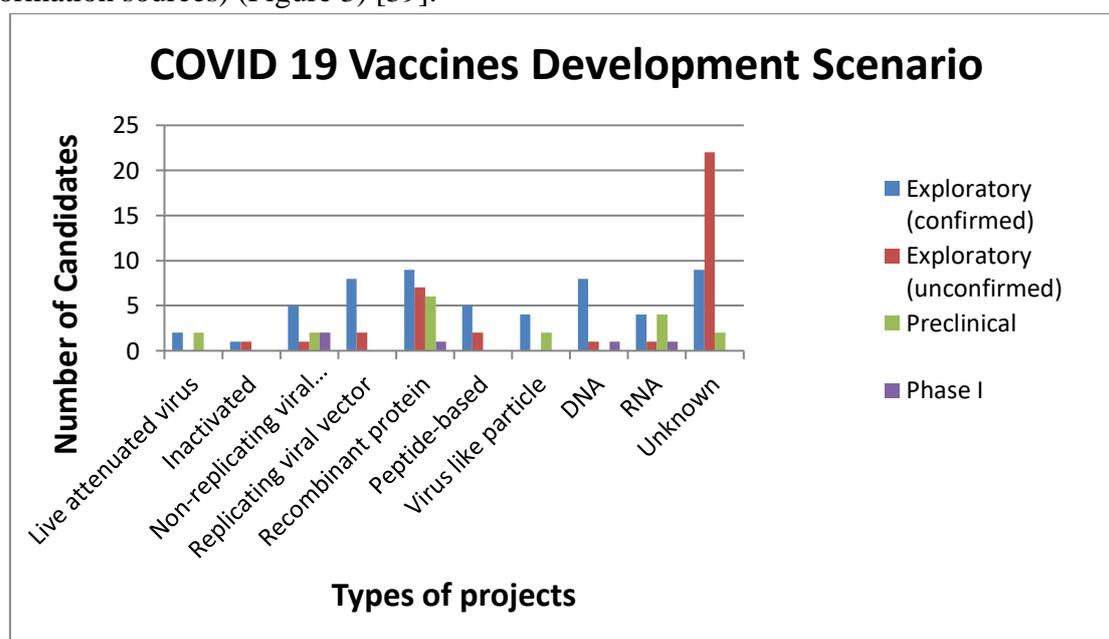
**Table 1.** Repurposing of drugs to treat COVID-19.

Sr. No.	Name of Drug	Category	Target candidate/Receptor
01	Chloroquine/ Hydroxychloroquine [28]	Antimalarial	ACE-2 (angiotensin-converting enzyme-2), AT-2 (angiotensin-2)
02	Azithromycin [2]	Macrolide Antibiotics	Ribosomal target
03	Sofosbuvir [27]	Antiviral	HCV-encoded proteins NS5B polymerase
04	Ribavirin[29]	Antiviral	RdRp(RNA-dependent RNA Polymerase)
05	Penciclovir [30]	Antiviral	HSV DNA polymerase
06	Umifenovir / Arbidol [5]	Antiviral	ACE-2 (angiotensin-converting enzyme-2)
07	Favipiravir[31]	Antiviral	RdRp (RNA dependent RNA polymerase)
08	Interferon Beta [7]	Interferon	Interferes with viral replication by several mechanisms
09	Lopinavir [32]	Antiviral	PLpro (papain-like protease) , 3CLpro (corona virus main protease)
10	Ritonavir [32]	Antiviral	RpRd(RNA-dependent RNA Polymerase)
11	Galidesivir [33]	Antiviral	RpRd(RNA-dependent RNA Polymerase)
12	Triazavirin[34]	Antiviral	Nucleoside analogue, influenza virus
13	Darunavir [35]	Antiviral	Type HIV-1 protease
14	TMC-310911[35]	Antiviral	Protease inhibitor
15	Remdesivir[36]	Antiviral	RdRp (RNA-dependent RNA Polymerase)

Currently, there are few drugs that are used, either single or with the combination of other drugs mentioned in Table 1.

### 3.2. Antibodies and vaccines.

Polyclonal and monoclonal antibodies have specificity for different viral proteins like SARS-CoV-2 spike, envelope, and nucleo-capsidprotein. Researchers focus more on developing antibodies against the S-protein of novel coronavirus than other target proteins because of their ability to elicit an immune response. Various cytokines like chemokines, interferons, interleukins, lymphokines, etc., were produced and interfered with viral replication during the infection.[37]Cytokines storm has been reported to correlate with disease severity in SARS-CoV-2 infection due to its ability to act as a chemical signal in the immune system to pathogen invasion. ProSci Inc. has developed COVID-19 (SARS-CoV-2, 2019-nCoV) antibodies against the virus, and it is also effective on the virus receptor ACE-2 binding domain.[38]. To control, eradicate and prevent the occurrence, it is critical to develop safe and efficacious vaccines. As SARS and MERS viruses have nearby homology with SARS COV-2, it helps design COVID-19 vaccines. Antiviral vaccines are of the following types: 1) Inactive or live attenuated viruses 2) Virus-like Particle (VLP) 3) Viral vectors 4) Protein-based 5) DNA based 6) mRNA based. There are 363 patents in CAS related to vaccine development which contains 175 patents for non-coronaviruses, and 188 patents of Anti-SARS and Anti-MERS, which shows immune response[37]. Till 8 April 2020, the worldwide COVID-19 vaccine R&D scenario consists of 115 vaccine candidates. 78- Confirmed active (73 projects are under exploratory or preclinical phase) and 37- not confirmed (status cannot be determined from information sources) (Figure 3) [39].



**Figure 3.** Different types of vaccines under development to fight against COVID-19.

### 3.3. Natural Products Reported of Anti-SARS activity.

Herbal medicines are a rich source of antiviral properties, and several mechanisms were identified to fight against the virus, which provides new wings for researchers to work on this area [40]. The natural products have the ability to interact with various stages of the viral life cycle, such as viral entry, replication, assembly, and release, to inhibit or reduce the activity of the virus [41]. They also have the capability for targeting virus-host-specific interactions against the receptors in the host cell. Several plant extracts were reported as anti-SARS activity

in the past [42]. The active research on these plant extracts or phytoconstituents may provide an effective solution to fight against this pandemic disease (Table 2).

**Table 2.** Some examples of the plants reported for antiviral activity against the coronavirus.

Sr no	Plant/Phytoconstituents	Family	Fraction used	Extract used	Mechanism/ Targeted part
01	Lycoris radiata [40]	Amaryllis	Stem cortex	Ethanol	Unknown
02	Artemisia annua[40]	Compositae	Full plant	Ethanol	Unknown
03	Pyrossia lingua[40]	Polypodiaceae	Leaf of plant	Chloroform	Unknown
04	Lindera aggregata[40]	Lauraceae	Root of plant	Ethanol	Unknown
05	Isatisindigotica[43]	Brassicaceae	Phenolic compound	Methanol	SARS-Cov 3CL protease inhibitor
06	Torreyanucifera[44]	Taxaceae	Amentoflavone from plant	Ethanol	SARS-Cov 3CL protease inhibitor
07	Myricetin and scutellarein[45,46]	Resedaceae	Polyphenolic compound	--	SARS-Cov helicase inhibitor, nsP13, main protease
08	Houttuynia cordata [47]	Saururaceae	Leaf	Water extract	SARS-CoV 3CL protease inhibitor; viral polymerase inhibitor
09	Saikosaponins (A,B <sub>2</sub> ,C,D) [48]	--	Oleanane derivatives	--	Inhibits viral attachment and penetration stages

### 3.4. Home remedies as an immunity booster.

Common symptoms of Covid-19 are cold, fever, weakness, irritation in the neck, shortness in breathing, etc. This may occur due to the lower immunity level of the patient. As a part of precaution in COVID-19, some natural products are useful for improving immunity level and health [49]. Immunity is a major factor here we can have considered as per signs/symptoms of COVID-19. There are a few natural products; suggested to use as home remedies to improve immunity level [50,51] listed in Table 3.

**Table 3.** Natural home remedies to boost immunity level.

<p><b>1. Giloy</b></p> 	<p>Its ability to reduce the symptoms of common flu and is effective against chronic fever. It is an expert as an immunity booster as compared with other home remedies also effective in digestion and diabetes [52]. It can be used as by made juice of Giloy stem with a combination of clove &amp; ginger for same.</p>
<p><b>2. Elderberry</b></p> 	<p>Elderberry extracts have several properties like antiviral, anticancer, anti-inflammatory. It is very much useful for the covid-19 as a part of improvements in the immune system. It contains a major section of flavonoids that are responsible for biological activity. Thus can be useful as the best home remedy in any viral and bacterial infection disease [53].</p>
<p><b>3. Neem</b></p> 	<p>It is an effective immunity booster that helps to fight against covid-19 and any kinds of infection caused by the virus. Also, neem is a very good home remedy used in several diseases [54].</p>
<p><b>4. Amla</b></p>	

	Amla contains vitamin C and has the ability to improve the immune system [4] during flu, cold, and cough; besides existence a rich source of vitamin C, it is helpful to increase the absorption of iron and calcium from nutrition. Also, it is an alkaline food that is very useful to balance the stomach acid level [55].
<b>5. Shilajit</b>	
	It contains more than eighty-four minerals with fulvic acid. It has numerous health benefits with several properties, including an antioxidant to improve immunity level and memory and an energy booster for the diseased patient associated with a viral infection like covid-19 [56].
<b>6. Chyavanpras</b>	
	It is a mixture of ayurvedic species like sugar, honey, ghee, amla, sesame oil, berries, various herbs, and other useful species. It is widely sold in India as a dietary supplement that effectively boosts the immune system and the ability to fight illness, infections, and disease. Potent immune booster as compared to other, thus very much useful against to improve health and immunity towards covid-19 [57].

### *3.5. Importance of artificial intelligence in CoVID-19 research.*

Artificial intelligence is the simulation of human intelligence by computers. It contains a subfield which is known as machine learning methods. Various computational tools can be useful for discovering new drugs and may provide important clues to researchers[58]. The technique called computer-aided drug design can be very useful for the discovery of new molecules against this disease. CADD is divided mainly into structure-based drug design (SBDD) and Ligand-based drug design (LBDD). SBDD uses the information of the 3D structure of disease protein, while LBDD applies when 3d structure of disease protein is not available. It uses knowledge of existing molecules to design a new molecule, believing that new molecules may have higher potency and fewer side effects than previous ones. The SBDD can be performed using Docking and De-novo drug design methods. LBDD can be performed using QSAR, virtual screening using pharmacophore[59]. These computational techniques provide a fast and efficient way for the discovery of new Anti-COVID therapy. Using Bioinformatics tools, scientists are evaluating the biological structure of COVID-19, and already they succeeded. The structure of the spike protein and its binding mechanism with host identified. Another target called coronavirus main protease (3CLpro) was also identified. These targets have already been proved as potential Anti- COVID therapy. Apart from this, several nonstructural proteins were also identified. Researchers are discovering new potential agents using these targets by applying structure-based drug design methods. Day by day, research papers are increasing about establishing targets and finding novel agents using different computational methods[37,60].

### *3.6. The role of robotics to combat CoVID-19.*

There is a number of examples reported especially in the case of infectious disease were medical, paramedical, or cleaning staff gets infected as they are directly or indirectly involved with patients. After the outbreak of Ebola 2015, it was discussed in the workshop organized by the White House Office of Science and Technology Policy and the National Science

Foundation that there are three major areas where robotics technology can provide efficient solutions in pandemic disease, including clinical care logistics and quarantines. The development of robotic technology in the above area may provide benefits in the current situation of CoVID-19. To control disease, disinfection of non-contact ultraviolet surfaces by robotic technology [61] can be very useful because COVID-19 spreads from person to person via close contact or respiratory droplets and via contaminated surfaces. The contaminated surface includes metals, glass, or plastic, where this pathogen can survive up to some days. New robotic technology can be useful for identifying high-risk areas and sterilizing surfaces where contamination may occur. For the diagnosis purpose like temperature measurement in public areas, in-out hospital patient development of the thermal robotic system can be useful[62]. For the diagnosis of COVID-19, sample collection is done by nasopharyngeal and oropharyngeal swabs. This test requires skilled staff for the collection of samples, handling, and testing. In this whole procedure, robotic technology may speed up the process and reduce the risk of infection. Some people don't have symptoms, but they are vectors to spread this infection. In this case, the blood test is important to identify infection. Automated blood collection and testing can reduce the risk of infection. In a nutshell, COVID-19 disease can be the catalyst for the development of robotic technology. However, this task is challenging as robotic system development requires the social gathering of experts to develop such complex models[63].

### *3.7. Convalescent plasma as a potential therapy for COVID-19.*

Convalescent plasma (CP) therapy can be useful technique for the prevention and treatment of various infectious diseases. This therapy was used successfully in the treatment 2009 H1N1 pandemic, SARS, and MERS infection. This therapy gave satisfactory results in terms of safety and efficacy [64-66]. In 2014, it was recommended by World Health Organization (WHO) to use convalescent plasma of patients who had recovered from Ebola virus disease. However, this therapy is unable to improve the survival rate because of o the absence of data of neutralizing antibody titration for stratified analysis[64,66]. The novel coronavirus has structural similarities with SARS and MERS, and clinical symptoms are also similar. Due to this, CP therapy might be a promising treatment option for COVID-19 treatment. Patients who are recovered from this disease may be valuable donor sources for CP therapy. The antibodies obtained from the recovered patient may have the ability to suppress viral growth. Therefore, it is advisable to test the safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients.

## **4. Conclusion**

Currently, almost all countries are fighting against this deadly disease. Researchers from all around the world are engaged to find specific therapy against novel coronavirus. To date, there is no specific drug/vaccine/antibodies that are clinically approved to treat this disease. To fight against novel coronavirus, approaches are adopted; one is to target the virus, and the second is to improve immunity. Currently, various FDA-approved drugs are used to treat patients. In addition, various vaccines and antibodies are under clinical trial. In this scenario use of artificial intelligence, techniques may provide a fast and innovative solution. Scientists are already using this kind of machine learning method to boost the research process. Applications of robotics technology are also useful to support the health care system. Finally,

we want to add that in the absence of specific therapies, social distancing, immunity maintenance, primary precautions (like sanitization, wearing a mask, etc.) are helpful to break the chain of infection.

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## Conflicts of Interest

There is no conflict of interest.

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