ISSN (O): 2349-5332
CODEN: IRJPHY

POSSIBLE POTENTIAL THERAPY FOR COVID-19: A REVIEW

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Submitted on: 25.05.2020;	Revised on: 04.06.2020;	Accepted on: 10.06.2020

ABSTRACT:

Several Wuhan, China patients were admitted into hospitals with pneumonia symptoms in December 2019. As the number of patients with similar symptoms started to increase, the causative agent gradually was isolated from the samples. It was initially called the 2019 novel coronavirus (2019-nCoV) and has recently been re-rebelled as coronavirus 2 (SARS-CoV-2) severe acute respiratory syndrome; the disease it causes has been named coronavirus disease 2019 (COVID-19). Given the rapid pace of scientific discovery and clinical data generated by the large number of people swiftly infected with SARS-CoV-2, clinicians need accurate evidence of effective medical treatment for this infection. Scientists are striving to find antivirals and other drug categories specific to the virus. Several drugs, such as chloroquine, arbidol, remdesivir, and favipiravir, are currently undergoing clinical trials to test their effectiveness and safety in treating corona virus disease in the world in 2019 (COVID-19); some promising results have been achieved so far. This analysis will help to understand the current corona virus and the medicine that is available for its treatment.

KEYWORD: Corona virus, SARS-CoV-2, Treatment, Antiviral drug, Antimicrobial drug,

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Indian Research Journal of Pharmacy and Science; 25(2020)2251-2257;
Journal Home Page: https://www.irjps.in
DOI: 10.21276/irjps.2020.7.2.16

INTRODUCTION:

The world has seen the existence of new viruses over the last few decades which posed serious threats to global health. Several patients in Wuhan, China began reporting symptoms that resembled pneumonia in late December 2019. A new virus was found, and the 2019 novel coronavirus (2019-nCoV) was first named. The World Health Organization (WHO) eventually changed the virus name to coronavirus 2 (SARS-CoV-2) of severe acute respiratory syndrome (1). The disease it causes was named 2019 coronavirus disease (COVID-19). The SARS-CoV is a positive-stranded RNA virus from the family Coronaviridae. Other viruses from the same family include the severe acute respiratory syndrome coronavirus (SARS-CoV), which appeared in 2002, and Middle East respiratory syndrome coronavirus (MERS-CoV), which was reported in 2012 (2).

Coronaviruses (CoVs), a large family of single-stranded RNA viruses, can infect both animals and humans and cause respiratory, gastrointestinal, hepatic, and neurological diseases (3). CoVs are further divided into four genera, being the largest known RNA viruses: alpha-coronavirus, beta-coronavirus, gamma-coronavirus, and delta-coronavirus (4). Six human coronaviruses (HCoVs) have been identified to date, including alpha-CoVs HCoVs-NL63 and HCoVs-229E and beta-CoVs HCoVs-OC43, HCoVs-HKU1, severe acute respiratory syndrome-CoV (SARS-CoV) (5), and respiratory syndrome-CoV in the Middle East (MERS-CoV) (6).

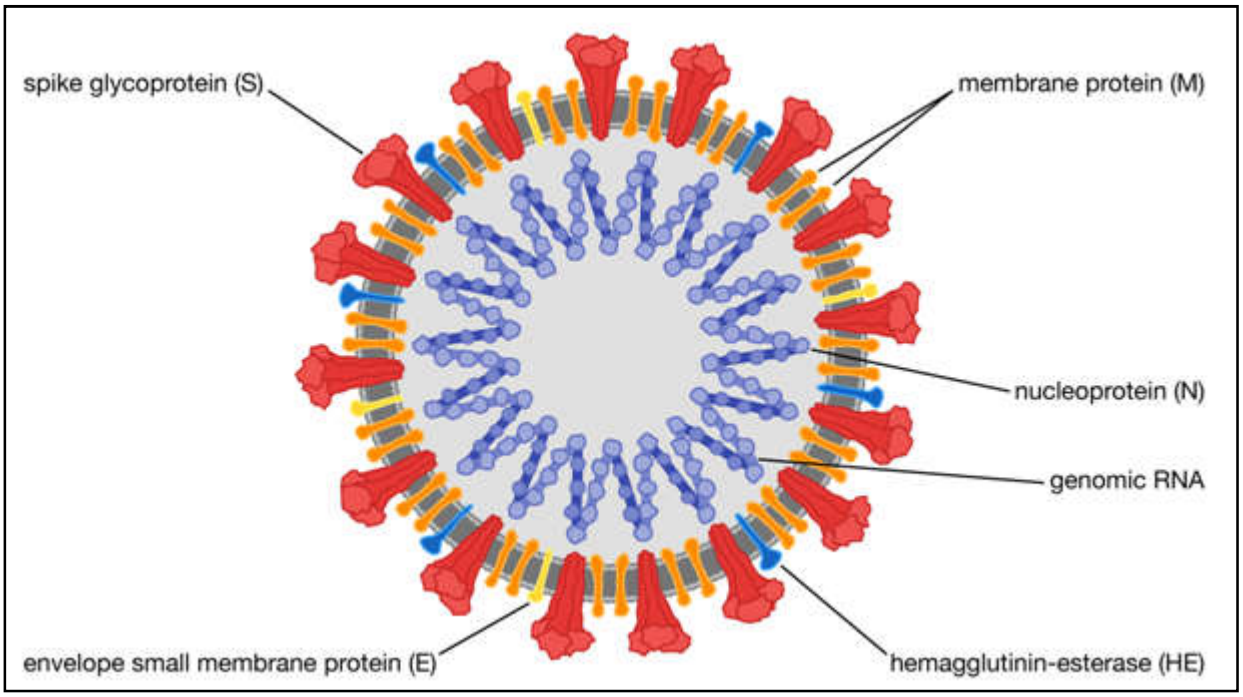

Figure 1: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

SARS-CoV-2: Virology and Drug Targets:

SARS-CoV-2, a single-stranded RNA enveloped virus, targets cells through the angiotensin-converting enzyme 2 (ACE2) receptor-binding viral structural spike (S) protein. The virus particle uses host-cell receptors and endosomes to join cells following binding of the receptor. A host type 2 serine protease transmembrane, TMPRSS2, facilitates the entry of cells via the S protein (7). Viral polyproteins which encode for the complex replicase-transcriptase are synthesized once inside the cell. The virus then synthesizes RNA via its polymerase-dependent RNA. Structural proteins are synthesized with the result that viral particles are assembled and released (8, 9, 10). These steps along the viral lifecycle provide potential drug therapy targets (Figure 2). Promising targets for drugs include non-structural proteins (e.g. 3-

chymotrypsin-like protease, papain-like protease, RNA-dependent polymerase RNA), which share homology with other novel coronaviruses (nCoV). Additional drug targets include the pathways to viral entry and immune regulation (11, 12).

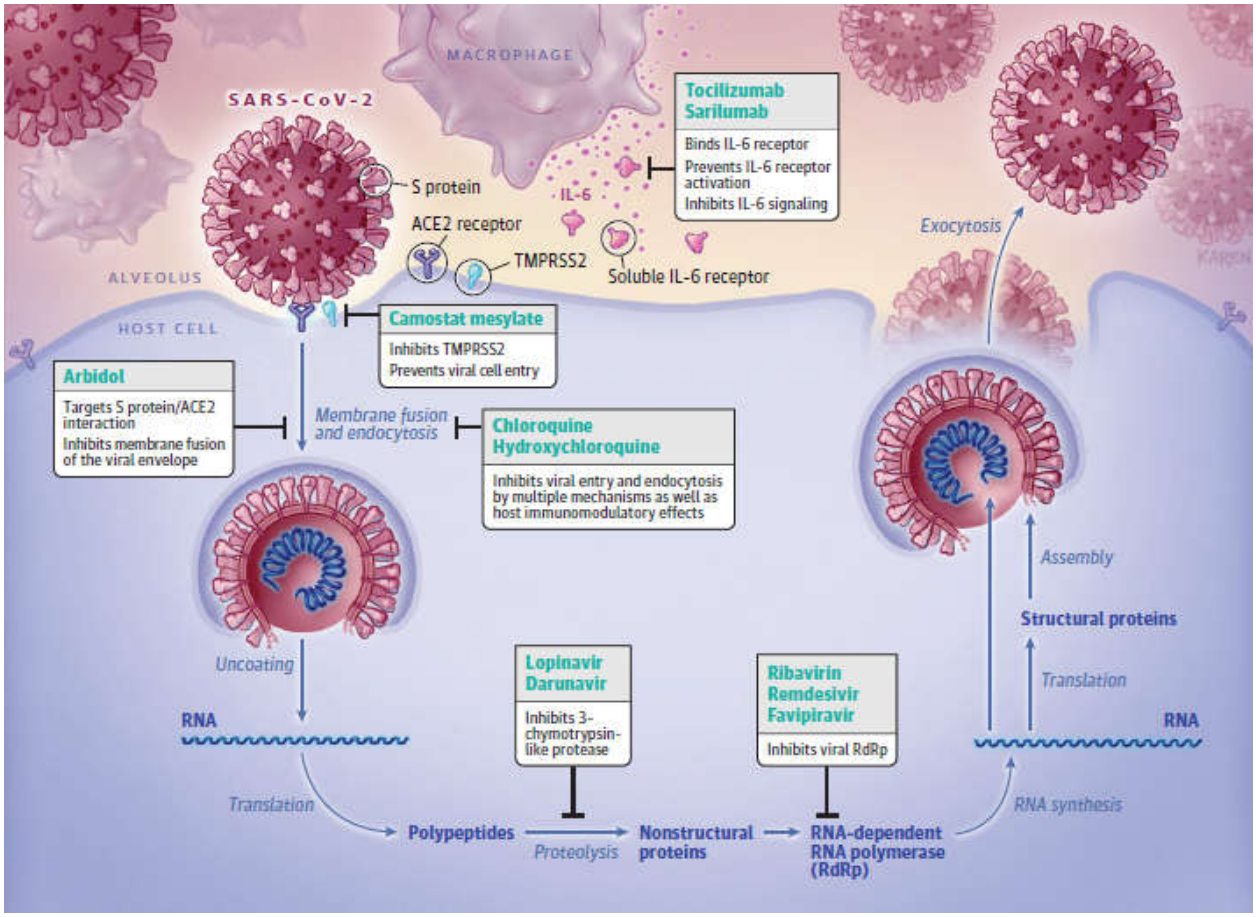

Figure 2: Simplified Representation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Viral Lifecycle and Potential Drug Targets. Schematic represents virus-induced host immune system response and viral processing within target cells. Proposed targets of select repurposed and investigational products are noted. ACE2, angiotensin-converting enzyme 2; S protein, spike protein; and TMPRSS2, type 2 transmembrane serine protease (13).

Review of Selected Repurposed Drugs:

Potential candidates to treatCOVID-19 are agents commonly used to treat SARS and MERS. During the SARS and MERS outbreaks, different agents with apparent in vitro activity against SARS-CoV and MERS-CoV were used, with inconsistent effectiveness. Meta-analysis of SARS and MERS treatment studies found no clear benefit from any particular treatment regimen (14, 15). Below, the in vitro activity and published clinical experiences of some of the most promising repurposed drugs for COVID-19 are reviewed.

1) Remdesivir:

Remdesivir is a nucleotide analog prodrug that is metabolized intracellularly to an analog of adenosine triphosphate inhibiting viral RNA polymerases. Remdesivir has extensive activity against members of multiple viruses (16, 17, 18, 19).

Remdesivir is a hospital-borne antiviral supplied by intravenous (IV) infusion. It is a brand new drug that has not yet been approved for commercial use by the FDA, and is being tested in closely regulated conditions. In cell and animal models it had previously been shown to have some effect against SARS, MERS, and Ebola. Remdesivir has stopped

human cells from being infected with SARS-CoV-2 (the virus that causes COVID-19) in a recent in vitro study (studies carried out in a petridish or test tube, rather than in animals or humans).

Doctors throughout the U.S. enroll patients with severe COVID-19 in clinical trials to see whether remdesivir is an effective treatment. Gilead recently announced early results from a Phase 3 trial. Half of the patients who received remdesivir, according to the manufacturer, saw improvements in about 10 days (regardless of whether they were being treated for 5 or 10 days) and more than half were released from hospital by week 2.

Early results from a large U.S. study of 1,063 patients showed that people who received remdesivir recovered more quickly than those who received placebo (11 days vs. 15 days, respectively). The death rate was also lower in the remdesivir group (8 percent) than the placebo group (11 percent). More details from this study, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), are expected to be shared soon.

On 1 May 2020, the FDA released an Emergency Use Authorization (EUA) for remdesivir based on the positive results from these two studies. The EUA does not mean remdesivir has been approved by the FDA for COVID-19 treatment. Rather, the intent of the EUA is to make it easier for doctors to get remdesivir for hospitalized patients with severe COVID-19 symptoms. These are patients requiring mechanical ventilation or additional oxygen. In addition to the above report, a small review was released earlier in April 2020 of 61 patients who had been seriously ill with COVID-19 and received remdesivir via a compassionate use programme. (Compassionate use is a way for people to receive experimental drugs without being in a clinical trial.) Data for 8 patients was unavailable, but for the remaining 53 patients, 36 (68%) needed less oxygen support after treatment, and 7 (13%) died.

Because this was gathering limited data through a compassionate use program. For example, there was no information on viral load (the amount of virus in the body) so we do not know if remdesivir was effective in clearing the virus. Additionally, there was no reference community, so it's hard to say whether patients would have changed themselves without taking remdesivir.

Not all the research on remdesivir have been successful. Take a sample for example of 236 COVID-19 patients in China. (This was a randomized , double-blind study which is the gold standard for clinical trials.) In one specific study, a group of patients receiving remdesivir within 10 days of symptoms recovered slightly faster than those receiving placebo. The difference, however, was not statistically significant, which means it may have been due to chance. There was no gap in time for progress relative to placebo when looking at all patients in the sample (regardless of when they obtained remdesivir). The researchers state that they need larger studies to confirm the results (20).

2) Hydroxychloroquine and chloroquine:

Hydroxychloroquine is an antimalarial 4-amino-quinoline medication widely used for the treatment of systemic lupus erythematosus (SLE), rheumatoid arthritis, and related inflammatory and dermatological conditions. It is a hydroxylated chloroquine version, with similar action mechanism. However, tissue levels of chloroquine are 2.5 times those of hydroxychloroquine following an equal dose of hydroxychloroquine and chloroquine. Because of its healthier profile hydroxychloroquine is favoured (21).

Hydroxychloroquine and chloroquine are two medicines which have been used to treat malaria and autoimmune conditions such as rheumatoid arthritis and lupus for many decades. A couple of small studies suggest they may also be helpful in treating hospitalized patients with mild COVID-19 cases, while other studies have shown that hydroxychloroquine has not made a difference. Stronger studies are needed to confirm whether these medicines are actually working (20).

3) Azithromycin:

Azithromycin is a broad-spectrum macrolide antibiotic with a long half-life and a high degree of tissue penetration (22). It was first approved in 1991 by FDA (23). Azithromycin (informally called a Z-pak) is an antibiotic commonly used to treat infections of bacteria such as bronchitis and pneumonia. It has been shown to have some activity against viruses such as influenza A and Zika in vitro, but has not worked against the coronavirus that causes MERS. One study group was studying azithromycin for COVID-19 in conjunction with

hydroxychloroquine. They reported that after 8 days, 93 per cent of patients cleared the virus, but there was no control group so we don't know if people would have cleared the virus alone without the medicines. Concern over potentially harmful side effects when azithromycin and hydroxychloroquine are used together (20).

4) Actemra (Tocilizumab)

Tocilizumab, also known as atlizumab, is an immunosuppressive drug, primarily used to treat rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis, a severe form of childhood arthritis. It is a monoclonal, humanized antibody against the interleukin-6 receptor (IL-6R). Interleukin 6 (IL-6) is a cytokine that plays an significant role in immune response and is implicated in the pathogenesis of several diseases, including autoimmune disorders, multiple myeloma, and cancer of the prostate. It was brought together by Hoffmann – La Roche and Chugai (24).

Humans can be at risk of cytokine storms with COVID-19 as their bodies continue to ramp up their immune system to fight off the infection. Actemra helps to calm the immune system by blocking IL-6, and is believed to help manage cytokine storms as well. A French study stated that people who got Actemra were less likely to need ventilation or die. Other medications that affect the body's immune response are also being tested for COVID-19. These include:

- Calquence (acalabrutinib)
- Xeljanz (tofacitinib)
- Jakafi (ruxolitinib)
- Olumiant (baricitinib)
- Kineret (anakinra)
- Ilaris (canakinumab)
- Otezla (apremilast)
- Mavrilimumab

Kevzara (sarilumab), which works similarly to Actemra, is also undergoing COVID-19 testing. Early findings had not been encouraging. They showed patients with moderate symptoms getting Kevzara did worse than placebo, but patients with even more serious (critical) symptoms improved compared with placebo. The manufacturers are now scaling back their studies to only include COVID-19 patients in critical condition (20).

5) Kaletra (lopinavir/ritonavir)

Kaletra is an HIV drug that includes a mixture of lopinavir and ritonavir, two antivirals. In vitro and clinical studies of patients who had received these antiviral agents earlier suggest that they may have some activity against SARS and MERS (infections caused by other coronaviruses). Data is limited for using Kaletra in COVID-19.

There was no difference in one randomized study of 199 people hospitalized with COVID-19 between using Kaletra and not using it in terms of how long it took for patients to improve. Another small study of 127 people with mild COVID-19 symptoms examined Kaleta alone in combination with interferon beta-1b and ribavirin as compared to Kaletra. They found that the group who got all three medications improved sooner and cleared the virus faster (7 days) than those who only got Kaletra (12 days) (20).

6) Tamiflu (oseltamivir)

Amid the influenza A (H1N1) pandemic, Tamiflu (Oseltamivir), a potent neuraminidase enzyme inhibitor, has gained worldwide attention. It is one of the most significant effective drugs against the novel influenza virus (25). Tamiflu is an antiviral drug used to treat influenza (flu). Chinese hospital outcomes in Wuhan were not promising. Of the 138 patients admitted, 124 received Tamiflu along with other medicines. 85 patients (62 per cent) were already hospitalized by the end of the study and 6 had died. Nonetheless, several clinical trials are currently investigating Tamiflu in combination with other coronavirus medicines (20).

7) Avigan (favipiravir) and other antiviral medications

Favipiravir (also known as Avigan) is an antiviral drug approved for influenza in Japan and China. In vitro experiments have shown that large doses of favipiravir have been able to avoid infection with SARS-CoV-2 in human cells. In China, two studies looked at how favipiravir worked as compared to other antivirals. In a study of 240 patients with mild COVID-19 symptoms in China, 71 percent of patients administered favipiravir recovered after 7 days , compared to 56 percent administered umifenovir (Arbidol). Another small study in China looked at 80 patients with moderate COVID-19

symptoms and found that favipiravir helped clear the virus faster than Kaletra (respectively 4 days vs. 11 days). The patients who took favipiravir also showed greater improvements in their lungs based on chest images. The first U.S. clinical trials for favipiravir were recently approved to start in Boston.

Other antivirals being tested for COVID-19 include umifenovir and galidesivir:

- Umifenovir (Arbidol) is a flu medication that is used outside the U.S. As mentioned above, it was not as good as favipiravir in helping patients recover in a study from China. Another study of 81 patients examined how long it took from when patients first experienced symptoms to when they tested negative for coronavirus, and it found that there was no difference between people who received umifenovir and those who did not. However, helping COVID-19 patients clear the virus appears better than Kaletra. The virus was not observed in any patients who received umifenovir after 14 days, in a small sample of 50 individuals. The virus was still present in nearly half of patients who received Kaletra.
- Galidesivir is a new drug that is currently being developed for a variety of viral infections; it has not yet been approved for human use. Clinical trials for galidesivir are starting in Brazil (20).

8) Ivermectin

Ivermectin is an oral drug used to treat parasite-infections. It is also used for treating the lice and rosacea as a lotion or cream. A recent in vitro study showed that ivermectin may be able to stop replication of SARS-CoV-2. Much further work is needed to see if the doses tested against the virus are safe and effective in humans (20).

TABLE 1: LIST OF DRUG AGAINST COVID- 19

S. No.	Drug	Category	Use
1	Remdesivir	Antiviral	Ebola) SARS-CoV, [MERS-CoV], SARS-Cov-2
2	Hydroxychloroquine & chloroquine	Antimalarial	Malaria, SARS-Cov-2
3	Azithromycin	Antibiotic	Common Cold, Flu, SARS-Cov-2
4	Actemra (Tocilizumab)	Immunomodulators	rheumatoid arthritis (RA), SARS-CoV-2
5	Kaletra (lopinavir/ritonavir)	Antiviral	HIV/AIDS, SARS-CoV-2
6	Tamiflu (oseltamivir)	Antiviral	Influenza A (H1N1), SARS-CoV-2
7	Avigan (favipiravir)	Antiviral	Against Influenza Virus and SARS-CoV-2
8	Ivermectin	Antiparasites	Antiparasites, SARS-CoV-2

CONCLUSION:

As the epidemic spreads, scientists around the world are actively exploring drugs which might be effective in fighting COVID-19. Generally speaking, there are currently no finally verified COVID-19-specific antivirals but Remdesivir is highly effective against corona virus. Further preclinical and clinical trials need to confirm the efficacy and safety of these candidate drugs in the treatment of COVID-19.

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CONFLICT OF INTEREST REPORTED: NIL ; SOURCE OF FUNDING: NONE REPORTED