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Biology and Landscape of Drugs against SARS-COVID-19 Viral Infection: A Detailed Review

Dipro Mukherjee[1], Sayantani Garai[1], Sanchari Das[1], Rina Rani Ray[2], Moupriya Nag[1*] and Dibyajit Lahiri[1]

[1]Department of Biotechnology, University of Engineering and Management, Kolkata, India

[2]Maulana Abul Kalam Azad University of Technology, Kalyani, Haringhata, West Bengal, India

[*]**Corresponding author:** Moupriya Nag, Department of Biotechnology, University of Engineering and Management, Kolkata, India, Tel: 9448981427981; E-mail: moupriya.nag@uem.edu.in

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Abstract

The online SARS-CoV-2 or the COVID-19 pandemic taking place globally, occurs as a result of the SARS-CoV-2 viral infection that has caused death of innumerable numbers of people and is responsible for a massive drop in the Global Economy. Millions of people are infected with a steep increase in death rate. So, there is an urgent requirement of the invention of some effective and efficient drugs that can prevent the deadly viral infection. Throughout the world, there have been many efforts carried out in different labs to invent such a drug and also identifying any pre-existing drugs which can fight against the virus. In this review, an attempt has been made to understand the drug biology used against the SARS-CoV-2 viral infection and the potential drug targets against SARS-CoV-2. Again, the strategies on the current and the future drug discovery mechanisms against the SARS-CoV-2 are also mentioned. It also lists the varied drugs made, drugs re-used and also the drugs under development in different research laboratories across the world.

Keywords: ***Corona virus; COVID-19; Drug discovery; Drug repurposing; Drug target; SARS-CoV-2; Pneumonia***

Introduction

The virus SARS-CoV-2 had emerged in December 2019 and rapidly spread across the world especially in Japan, China, and South Korea with fast advancement towards the European countries [1-2]. As of February 21, 2020, a total of 76288 cases have been confirmed out of which 2345 affected people passed away with non-availability of cure to the present infection. Scientists from all over the world are now venturing to find drugs against this deadly virus. Among them approximately 30 agents have been listed to possess the ability to stop this disease. Some of these agents that have proved to be effective against SARS- CoV-2 includes chloroquine phosphate, interferon alpha, ribavirin, etc. and recently these drugs have been incorporated in the latest version of the guidelines for the prevention, diagnosis and treatment of novel Corona virus- induced pneumonia issued by the national health commission of the PRC for tentative treatment of Corona virus 2019.The fifth edition of the guidelines included antiviral including IFN-α, lopinavir/ritonavir, and ribavirin for the treatment of COVID-19 [3-5]. Chloroquine phosphate and

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arbidol are included in the sixth edition of the guidelines completely based on the outcomes of the clinical studies. The method through which IFN- α antiviral drug can be applied is vapour inhalation at a dose of 5 million U (and 2 mL of sterile water for injection) for adults, 2 times /day. The dosage of lopinavir/ritonavir is 400 mg/100 mg for adults, 2 times/ day. Ribavirin has to be given through intravenous infusion at a dose of 500 mg for adults, 2 to 3 times/ day in combination with IFN-α or lopinavir/ritonavir. Chloroquine phosphate has to be given orally at a dose of 500 mg (300 mg for chloroquine) for adults, 2 times/day. Again, Arbidol has to be given orally at a dose of 200 mg for adults, 3 times/day. The treatment duration is not more than 10 days [6].

As we all know that IFN-α is a broad-spectrum antiviral drug that is being usually used against hepatitis, though it is being reported to inhibit SARS-CoV reproduction *in vitro*. Lopinavir/ritonavir on the other hand is a medication for the Human Immunodeficiency Virus (HIV) used in combination with other drugs to treat adults and children over 14 days of age who are infected with HIV-1. Chu has found that lopinavir/ritonavir has an anti-SARS-CoV activity *in vitro* and also in the clinical studies. Ribavirin is a nucleoside analogue having a broad-spectrum activity against viral diseases or infections [7-9]. A study was made by comparing 111 patients with Severe Acute Respiratory Syndrome (SARS) being treated with ribavirin mono-therapy and 41 patients with SARS being treated with lopinavir/ ritonavir and ribavirin. Therefore, it has been seen that patients treated with the combined therapy had a comparatively lower risk of Acute Respiratory Distress Syndrome (ARDS) and death. Chloroquine is a widely used and a very popular anti-malarial which was found to have an antiviral effect in 2006 [10]. It was found to inhibit or resist a SARS-CoV-2 infection data in a very low micro molar concentration, with a half-maximal Effective Concentration (EC-50) of 1.13 μM and a half-Cytotoxic Concentration (CC-50) greater than 100 μM. Arbidol is also an antiviral drug that can be used to inhibit the influenza virus. A study has revealed that arbidol can effectively resist SARS-CoV-2 infection at a concentration of 10-30 μM *in vitro*. Above all the drugs that have been incorporated in the Guidelines, favipiravir is a drug that was being approved for the treatment of novel influenza on February 15, 2020 in China [11-13]. This drug is currently undergoing clinic trials to see whether it can treat COVID-19. Favipiravir is a new type of RNA-dependent RNA polymerase (RdRp) inhibitor. Along with its anti-influenza virus activity, favipiravir is capable of blocking the replication of Flavi-, Alpha-, Filo-, Bunya-, Arena-, Noro-, and other RNA viruses [14]. Favipiravir is converted into an active Phosphoribosylated form (favipiravir-RTP) in cells and is being recognized as a substrate by the viral RNA polymerase, thereby helps in inhibiting RNA polymerase activity. Therefore, favipiravir may have a very high potential against the SARS-CoV-2, which is an RNA virus. On February 14, a clinical trial on favipiravir for the treatment of COVID-19 has been initiated by the clinical medical research centre of the national infectious diseases and the third people's hospital of Shenzhen and has achieved very heartfelt results [15]. The primary results obtained from a total of 80 patients (including the experimental group and the control group) have indicated that the favipiravir has more antiviral action than that of lopinavir/ritonavir. No adverse reactions were noted due to the application of favipiravir in the favipiravir treatment group, and surprisingly it has fewer adverse effects than the lopinavir/ritonavir group. Remdesivir on the other hand is another potential drug for treatment of COVID-19. Remdesivir is a nucleoside analogue and a broad-spectrum antiviral [16-18]. Animal experiments have shown that remdesivir can effectively cut down the virus in the lung tissue of mice infected with MERS-CoV, improving the lung function, and alleviating the pathological damage to the tissues of the lungs. Wang et al. found that remdesivir blocks the SARS-CoV-2 infection at a low micro molar concentration and has a high selectivity index (half-maximal Effective Concentration (EC-50), 0.77 μM; half-Cytotoxic Concentration (CC-50) >100 μM; SI>129.87). Holshue reported that remdesivir has yielded surprising

results in the treatment of a patient with COVID-19 in the United States [19-21]. In order to test the efficacy and safety of the drug on the COVID-19 patients, a randomize placebo-controlled, double-blind, multicentre, phase III clinical trial has been launched on February 5, 2020 in China where patients in the experimental group have received an initial dose of 200 mg of remdesivir and a subsequent dose of 100 mg for 9 consecutive days *via* intravenous infusion in addition to normal treatment [22]. Patients in the control group have also received the same treatment and the same dose of a placebo. The trial is expected to be concluded by the end of April 2020. Studies have also revealed that some other drugs can be effective in treating the COVID-19 of which one is darunavir that is a second-generation of HIV-1 protease inhibitor [23-25]. On February 4, 2020, researchers in China announced that darunavir has successfully inhibited SARS-CoV-2 infection *in vitro*. Cell experiments indicated that darunavir significantly inhibited the viral replication at a concentration of 300 μM *in vitro* and it has an inhibition efficacy of around 280-fold in the untreated group. Other drugs included type II Transmembrane Serine Protease (TMSPSS-2) inhibitors and BCR-ABL kinase inhibitor imatinib. Hoffmann indicated that the SARS-CoV-2 uses the SARS-CoV receptor, ACE-2, and the cellular protease TMPRSS-2 to enter the target cells. A TMPRSS-2 inhibitor would block the entry of the virus and therefore can constitute a treatment option. Imatinib has a primary anti-coronal activity because it inhibits the fusion of virions with the endosomal membrane. A joint research team of the Shanghai Institute of Materia Medical and Shanghai Tech University have performed a drug screening in silicon and an enzyme activity test, and they have reported that 30 agents with potential antiviral activity against SARS-CoV-2 on January 25, 2020 are indinavir, saquinavir, lopinavir, carfilzomib, ritonavir, remdesivir, atazanavir, darunavir, tipranavir, fosamprenavir, enzaplatovir, presatovir, abacavir, bortezomib, elvitegravir, maribavir, raltegravir, montelukast, deoxyrhapontin, polydatin, chalcone, disulfiram, carmofur, shikonin, ebselen, tideglusib, PX-12, TDZD-8, cyclosporine A, and cinanserin. The same study also found that the Chinese herbal medicines such as Rhizoma Polygoni Cuspidati and Radix Sophorae Tonkinensis can have ingredients that can inhibit against SARS-COV-2 infection [26]. As the epidemic spreads worldwide, scientists from around the world are actively busy in exploring drugs that will be potentially effective in diminishing the COVID-19. Generally, there are 60 finally verified antiviral specific to COVID-19 at present. The efficacy and safety of these candidate drugs are yet to be confirmed in further preclinical and clinical trials.

Literature Review

Approaches for drug discovery targeting SARS CoV-2: All the drugs characterized and synthesized as anti-viral till date, usually target the SARS-CoV-2 virus. These drugs can be divided into two kinds. In the first kind, the virus is targeted, its host interactions are targeted or the viral assembly is inhibited. In the second kind, the drugs are used for modulation of broad-spectrum host with innate response of the immune system or the process of undergoing changes with the several cells signaling pathways, which is associated with the replication of the SARS-CoV-2 virus. These drugs possess the ability for engagement of host receptors or proteases which is used for the mechanism of entry of the virus or which may affect the endocytosis pathway. Usually, there are three different ways of screening of antiviral compounds which possess the ability of inhibition of the SARS-CoV-2 viral infection [27-29].

Repurposing of antiviral compounds: The first way of screening of antiviral compounds is to first observe the already present antiviral compounds and molecules and to observe their several impacts on the mechanism of replication and packaging of the virus. There are several such molecules, for example the interferon alpha, beta and gamma, ribavirin and cyclophilin 8 and its

different chemical inhibitors. These can be detected and observed for their anti-viral properties. These known molecules first of all have an anti-viral property and secondly, they possess a strategic advantage as they are used actively for clinical purposes. Moreover, their pharmacokinetic and pharmacodynamics properties are well known and documented. Again, on the contrary we can say that they may not have enough needed specificity against the COVID-19 virus and thus they cannot resist the extreme ill effects caused by the SARS-CoV-2 viral infection [30].

High-throughput screening of compounds: The second way expresses the involvement of the screening method of chemical libraries which includes the binding of the molecules to the transcriptional pathway of the different cell lines. The highly efficient screening technology has the efficiency of screening huge libraries of drug like capacity of chemical compounds for some chemical groups having many anti-viral properties. Many biological libraries, possessing bioinformatical data sets of all drugs that exist can be checked for the purpose of all the evidences needed for supporting drug repurposing processes which in turn leads to discovery of many new roles of some selected drug molecules [31-32].

There are already some drugs in the market like Lopinavir/ritonavir that are actually available for its usage in the treatment of anti-HIV drug treatment but as these viruses have more or less similar properties to the SARA-CoV-2 virus, these are used against the viral infection based on a prediction that they will work on these too. But instead, these drugs have been observed to possess serious disadvantages. For example, the screenings of these drugs have immunosuppressive and cytotoxic effects in high level of concentrations. Another popular opinion states that the half value of the maximum value of effectiveness of the concentration of drugs is needed in response of the COVID viral infection [33]. These however, can cross the largest serum concentrations of dosage of pharmacological treatments.

Inhibition of SARS-CoV-2 replication mediated by siRNA: The last of the three ways for screening of antiviral compounds can be said as the process of improvement of some selected new and novel agents, which results from some vivid research activity located around the genomic and biophysical framework of the SARS-CoV-2 viral life cycle. siRNA inhibitors or molecules which has the capacity for inhibition of specific viral enzymes, are usually associated with the process of viral replication cycle and the process of monoclonal antibodies which targets the host receptor ACE-2. But the biggest drawbacks in this case are the molecules of drug delivery sites that do not have the concept of siRNA-based therapy [34-35].

Approaches for drug repurposing: Because of the recent money constraints, the resource gathering and the time required in the process of development of a new drug are two big factors which are holding back drug delivery process. Because of this, pharmaceutical companies and various research labs are rather suggesting to the subject of drug re-purposing thing than that of the discovery of drug. Drug re-purposing is a way of a predicting and concluding based on the drugs are safe for human use and can be affective against the corona virus infection. In this process, efficacy of a previously known drug molecule is observed continually for a few days against the virus [36]. The term drug re-purposing is also sometimes termed as ‘drug repurposing’ as drug repositioning, drug re-profiling or drug re-tasking. These naming conventions depend on the results of the studies. This way of drug application can reduce the risk of health hazards and can reduce the toxicity profile checking as these drugs have already gone through the three phases of trials and their safety guidelines and health hazard parameters are measured already thus saving time. Even their formulation has completed the parameters to call themselves as repurposed drugs. So, these drugs

can easily escape the trial phases I and II and based on the results of their performance on the trial phase III, they can be launched into the market [37-39].

Computational approach: There are several bio-computational or bio-informatics based approaches for drug repurposing. Mainly computational approaches for drug repurposing have huge databases which include a structured way of seeing the gene expression, chemical structure, proteomic data or electronic healthcare history of data. Usually, the most known computational procedure possess signature matching computational molecular docking, genomic association analysis. Several cellular mechanisms or mapped networks and also some retrospective detection which uses historical data of approved drugs [40].

Signature matching or unique character: When a drug is being made or developed, it should have a unique character or signature like its transcriptomic effect profile, structural or adverse effect profile and thereby by matching or linking these characters, repurposing can be done. Now using this approach for drug repurposing the researchers actually believes in drug-drug or drug disease comparison. Now on the very first time, the gene expression of a drug's usage before and after is being compared with the differential gene expression obtained by comparing profiles of healthy individuals with the diseased one. One example of drug repurposing is the topiramate which is an antiepileptic drug and has an antagonistic effect for GABA [41-43]. Research has also showed that this topiramate can be used for IBD (Inflammatory Bowel Disease) because of its signature characteristics. The drug-drug similarity approach identifies a common mechanism of action for drugs that belong to different classes and are usually structurally dissimilar.

Computational molecular docking: This is a very important and indispensable tool for drug repurposing activity. Here we use structure based computational strategy, through which the binding efficiency is predicted between the drug and the target molecule. However, each and every technique in biological sciences has something or the other disadvantages or limitations. This technique's limitations are lack of available screen able macromolecular database that can provide structural information for a drug or for a number of targets 3D structure will not be elucidated [44-45].

Network mapping: This is one of the most predominantly used methods for drug repurposing. Many drug targets that are identified may not be directly targeted because their direct inhibition can actually lead to some serious effects and this network or molecular pathway is done which will give us an idea about the upstream and downstream druggable targets. Drug and disease connection can be done or created using this network mapping and therefore can open huge possibilities for drug repurposing [46].

Artificial intelligence and drug repurposing: Artificial intelligence is changing or revolutionizing drug repurposing efforts and studies through its own way. With help in Machine learning tools, computational algorithms can be developed which will thereby help in predicting newer drug target sites and thus with greater accuracy than the earlier methods. Huge data that has been generated by high-throughput Next Gen Sequencing (NGS) from a number of patients, when combined with the characteristics of the diseases and treatments can thereby lead to the identification of the new biomarkers that can be utilized. AI supervised machine learning algorithms can be used to implement multiomics and multitask learning to facilitate the drug response by

engaging multiple drugs [47-49]. For example, recently a study has been done in which a methodology was developed that can use heterogeneous data derived from previously described drug target interaction to predict new interactions with even greater efficiency. This method is known as 'deepDTnet' that can integrate multiple drugs with drug targets and diseases with the help of deep learning.

Drug repurposing in antiviral drug discovery: There are 3 different approaches that can be discussed to facilitate the antiviral drug development. They are as follows.

Known target/new virus: In this approach, an established antiviral drug is found to have an antiviral activity against viruses like favipiravir and sofosbuvir, were initially developed for influenza and hepatitis C viral infection and were then repurposed or reused for Ebola and Zika viral infection [50].

Known target/new indication: In this approach, the target is allowed to infect new pathogenic infection and thus in some cases, it has been seen that the drugs that will be targeting these proteins can be implicated to affect new infection and thereby in these cases, the drugs which are targeting the proteins can be termed as effective. One of the main examples is an anticancer agent Imatinib. Cellular Abelson (ABL) kinase is the target of Imatinib and it was shown to be active against corona viruses [51].

New target/new indication: In this approach, a modified or an approved drug is found to be targeting additional proteins and the examples are some of the antimicrobial agents (Table 1) like teicoplanin, invermectin, itraconazole or nitazoxanide which were found to be surprisingly effective against viral infections [52].

TABLE 1. **List of probable drug targets against SARS-CoV-2 and compounds/agents effective against these targets.**

Sl. no	Targeted viral component	Mechanism	Examples	Advantages	Disadvantages	Status	Reference
1	Inhibition of SARS -CoV-2 fusion/entry RBD of the S_1 subunit of S	Antibodies target the RBD domain of the S_1 subunit	REGN3051 and REGN3048 mAbs	Efficacy demonstrated *in vitro*	Narrow spectrum	Preclinical	[53]
2	S_2 subunit of S	Antiviral peptides that inhibit fusion of S with host cell receptor	HR2P and P1 peptides	anti-HIV peptidel has been marketed	Narrow spectrum	Preclinical	[54]
3	TMPRSS2	TMPRSS2 inhibitor that blocks the TMPRSS2-entry pathway	Camostat Mesylate	Promising results *in vitro*. Effect on patients need to be tested	Broad spectrum. Developed for therapy against SARS	Marketed	[55]
4	Inhibition of endocytosis endosomal acidification	An antimalarial that sequesters protons in lysosomes to increase the intracellular pH	chloroquine	Broad spectrum; many SARS-CoV-2 affected patients show good recovery	No concrete clinical data to suggest efficacy	Marketed	[56]

5	Clathrin mediated endocytosis	ATP1A1-binding steroids; inhibits clathrin-mediated endocytosis	Oubain	Active against MERS-CoV	May have risk of cardiac toxicity	Marketed	[57]
6	Inhibition of Viral Enzymes 3CLpro	Inhibits 3CLpro activity	Lopinavir	Broad spectrum	Toxicity Adverse impact on immune system	Marketed	[58]
7	PLpro	Inhibits PLpro activity	GRL0617	Narrow spectrum	No animal or clinical data available	Preclinical	[59]
8	RdRp	Nucleotide analogue; Broad spectrum: many viral infections, inhibits viral RNA synthesis	Remdesivir	Active against SARS-CoV and MERS-CoV at high doses *in vitro*	Side effects are common and may be severe with high dose regimens	Marketed	[60]
9	Inhibition of Viral envelope (E), membrane (M), Nucleocapsid (N) and accessory proteins E and M Protein	Short chains of dsRNA that interfere with the expression of SARS-CoV proteins	siRNA	Promising *in vitro* studies.	Optimal delivery method in humans uncertain	Preclinical	[61]
10	Pj34	Impairs viral replication	Pj34	Narrow spectrum Effective *in vitro* and in animal studies	Optimal delivery method in humans is uncertain	Preclinical	[62]
11	Lj001 and JL103	Induces membrane damage	Lj001 and JL103	Broad spectrum	Anti-CoV activity yet to be demonstrated Unstable physiologically and photo dependent	Preclinical	[63]

Pharmacological interventions: Lessons that have been obtained from SARS and MERS epidemic have helped us in developing some therapies against SARS-CoV-2. Drugs that are used previously for the treatment of viral infection like oseltamivir, peramivir, zanamivir, ganciclovir, acyclovir and ribavirin are not recommended for COVID-19 treatment. Also, systemic corticosteroid treatment such as methylprednisolone cannot be used as a treatment for SARS-CoV-2 infected patients. Now in these cases, the similarity between the MARS, SARS and SARS-CoV-2 will provide more inspiration for Drug discovery and repurposing. But however, for both the MARS and SARS no treatment method was recommended because as per guidelines of WHO, the disease must be controlled by realizing the symptoms of the affected patients [64,65].

Key CoV targets for drug development and available therapies: As of now, there is no specific antiviral drug which can one used solely for CoV associated pathologies. But some of the drug target sites have been identified which if targeted can

control the disease. Since the previous global corona virus pandemics like MERS and SARS have come into existence hence considerable amount of research has been done for suitable drug targets and subsequent drug candidates. Based on this and life cycle stages of SARS-CoV virus, the therapies that have the potential to act on Corona viruses can be divided into five broad categories/approaches [66]. They are as follows:

Inhibition of virus binding to drugs: Inhibiting the ability of the virus binding to the host receptor by chemical compounds or monoclonal antibodies. These agents can block the host's cell surface receptors and thereby can resist the virus binding and subsequent internalization [67].

Targeting the viral endocytosis: It enables the virus to enter the host cell and release its genetic material for further replication and therefore blocking virus-mediated endocytosis is a logical target for antiviral therapy [68].

Neutralizing the virus particle: This can be done by some of the compounds or antibodies that are acting on enzymes or functional proteins that are critical to virus replication and multiplication. Targeting the viral structural proteins like the membrane, envelope and Nucleocapsid protein helps in blocking the virus repackaging. Restoration of host's innate immunity by the agents capable of producing virulent factors [69].

Inhibition of SARS -CoV-2 fusion/entry: SARS-CoV-2 uses the viral spike protein to make its entry into the host cells and therefore causes several protein interactions which will thereby take place between the spike protein of SARS and in the region of ACE-2 receptor and thereby can be targeted for drug action. Like other viral infection, the coronavirus also causes mutation specifically in the spike protein. As a result of mutation, the spike protein recognizes the ACE-2 receptor much more efficiently and thus the previously studied RBD or the receptor bonding domain is the target for the drugs [70].

Another strategy that can be developed is to engage the ACE-2 receptor which is normally present on the cell surface and thus excess ACE-2 will thereby cause the neutralization of the virus by competitively binding to SARS-CoV-2 (rhACE-2; GSK2586881). An open-labelled, randomized, controlled pilot clinical trial is in progress to evaluate this approach (NCT04287686) [71]. Apart from the ACE-2 receptor, the cellular serine protease TMPRSS-2 also plays an important role in facilitating the entry of the virus in host cells. A clinically proven chemical inhibitor of TMPRSS-2, is Camostat Mesylate which is able to significantly reduce infection in cell lines of human lung origin. In addition to this, the Heptad Repeats 1 (HR-1) and Heptad Repeat 2 (HR-2) presents on the SARS-CoV-2 have also been implicated in the facilitation of cell membrane fusion. HR2– derived peptides exhibit effective fusion inhibitory activity [72].

Inhibition of endocytosis: After the fusion between the spike and ACE-2 protein the virus is ingested in the cells in a pH and receptor dependent endocytosis. Targeting the endocytosis can be one of the mechanisms of inhibiting the disease and thereby can be a target site for developing drugs. Clathrin mediated endocytosis is regulated by AP-2- Associated protein Kinase-1 (AAK1). Based on a library screening process, JK inhibitor Baricitinib was identified as a possible drug candidate for SARS-CoV-2 and also can be used as an inhibitor of clathirin mediated endocytosis is also being tested for its effectiveness in drug trials for SARS-CoV-2 positive patients. Recently, Chloroquine and its derivative hydroxychloroquine have gained popularity as a therapeutic drug against SARS-CoV-2 infection. Several clinical trials are underway to assess the contribution of

chloroquine therapy in inhibiting SARS-CoV-2 viral progression. Also, it was shown *in vitro*, that a derivative of Chloroquine, hydroxychloroquine (EC-50=0.72l M) is far more potent in inhibiting SARS-CoV-2 infection than Chloroquine (EC-50=5.47l M). Although the exact molecular mechanism of hydroxychloroquine in the treatment of COVID-19 remains elusive, it is believed that hydroxychloroquine may impair endosome-mediated viral entry or the late stages of viral replication [73].

Inhibition of viral enzymes: As an outcome of aggressive antiviral drug development and discovery programs that has been undertaken, multiple drugs have been developed against viral proteases, polymerase and hence the drugs that were been developed earlier against antiviral infections are now being examined against this COVID-19 such as Remdesivir, Flavipiravir, Lopinavir/Ritonavir in clinical trials for their efficacy against the COVID-19 pandemic. Remdesivir, an antiviral drug developed against Ebola which is an adenosine analog which inserts into viral RNA chains by RNA-dependent RNA polymerases (RdRps) and results in premature transcription termination. Similarly, Favipiravir and Ribaviorin are guanine analogues and are approved for some viral diseases. EIDD-2801 is another oral antiviral drug that acts as a nucleotide analog, like Remdisivir, albeit with lower EC-50, and is administered orally. Other antiviral compounds like Lopinavir and Ritonavir are protease inhibitors that target 3-C Like protease (3-CLpro) of SARS-CoV-2. The main protease, 3-CLpro is responsible for processing the polypeptide to NSPs. By utilising high-throughput screening for compounds against 3-CLpro, four molecules, *viz.* Prulifloxacin, Tegobuvir, Bictegravirand and Nelfinavir, were identified [74].

Inhibition of viral envelope, membrane, Nucleocapsid and accessory proteins: SARS-CoV-2 Envelope (E), Membrane (M) and Nucleocapsid (N) protein is extremely necessary for virus survival and propagation, and therefore such structural proteins are the best drug targets. Since these proteins are structurally different from the host proteins hence the drugs targeting these proteins will have minimal effect. These proteins help in protecting the viral genome and therefore these structural proteins are involved in suppressing the immune system and therefore the virus has an additional advantage over the host cell. The N protein helps in suppressing the RNA interference and hence many siRNA-based treatments can target viral E, M, N and hence can inhibit protein translation *in vivo*. However, these technologies are still not available for human use due to unavailability of reliable delivery methods. The E protein serves as an ion channel and this action is inhibited by hexamethylene amiloride. Another chemical inhibitor PJ-34 targets the ribonucleotide binding pocket at the N terminal domain of the N protein and hence it is very important to note the fact that these inhibitors were designed against the SARS virus but due to the mutations taking place in COVID-19 these inhibitors may not be effective. LJ001 and LJ003 are broad-spectrum antiviral compounds that not only inhibit viral entry in the host cells but also damage the viral membrane by producing singlet oxygen molecules. Unfortunately, LJ001 is physiologically unstable and is photo-dependent but LJ001 defines a new class of antiviral compounds, and further research into this class of compounds will yield encouraging results [75].

Suppression of excessive inflammatory response: A well cytokine response is absolutely critical for the host immune response. It has been reported that patients suffering from COVID-19 disease show a hyper inflammatory reaction due to deregulation of cytokine receptor. It has been reported that COVID-19 patients who are in the Intensive care unit have more cytokines on plasma than the normal or non-ICU ones thereby helps in suggesting that cytokine dysregulation is involved in the severe form of COVID-19 disease. Moreover, SARS-CoV-2 infected patients admitted in ICU are reported to display increased levels of GM-CSF and IL-6 CD_4T cells when compared to non-ICU patients. Thereby it can be said that inhibition in the inflammatory response can reduce the severity of COVID-19 disease. Corticosteroids are known to have excellent

pharmacological potential in suppressing systemic inflammation. But their use in COVID-19 patients is still unsure and requires a detail study but it has been demonstrated that after the COVID-19 infection the CD4T cells are activated to produce GM-CSF and other inflammatory cytokines, thereby resulting in further induction of CD-14 CD-16 monocytes with high expression of Interleukin 6 (IL-6). This observation leads to the possibility that by blocking the IL-6 receptor we could potentially reduce immune stress caused by SARS-CoV-2. In line with this observation, a multicentre, randomized, controlled clinical trial is currently underway using an IL-6 receptor-specific antibody Tocilizumab (NCT04315480). Another advancement in this COVID-19 field is the Convalescent plasma treatment where the plasma obtained from a donor who has recovered this particular disease is been used to develop a humours immunity against COVID-19 patients. The plasma from the donor patient acts as a source of human antibodies against the infection. However, large scale human trials need to be conducted to better understand and evaluate CP as a method of treatment for COVID-19 (Table 2) [76].

TABLE 2. **List of companies actively involved in finding a drug to treat SARS-CoV-2 patients.**

Sl. no	**Candidate drug**	**Company/ organization**	**Timelines**	**Current status and plans**	**Development phase**	**References**
1	Remdesivir	Gilead	CT is anticipated to be completed by end of April 2020	Remdesivir is now being tested in five COVID-19 clinical trials that have been set up at lightning speed	III	[33]
2	Hydroxychloroquine	Sanof	N.A.	Conduct additional CTs and supply millions of doses of an existing anti-malaria product	Preclinical	[35,36]
3	Lopinavir/ritonavir combination	Abbvie	N.A.	Collaboration ongoing with select health authorities and institutions globally to determine antiviral activity against SARS-CoV-2	III	[37]
4	Monoclonal antibody therapy	Regeneron	Potential to enter human CT by early summer 2020	Aiming to select the top 2 antibodies for a cocktail therapy, which can either be administered to at-risk -vaccine naive population or as treatment for those already infected	Preclinical	[38]
5	Combination of two antivirals	Ascletis	N.A.	The Chinese company is testing a combination of antivirals, developed against HIV and the other approved for hepatitis C	I	[39,40]
6	Polyclonal antibody therapy	Takeda	Program initiated in March 2020	Collaboration with several health and regulatory agencies and health care partners across the globe on polyclonal antibody TAK-888	Preclinical	[41]
7	Antibody drug	Lilly	CTs in humans to be started in the next four months of 2020	Eli Lilly developing antibody treatments for coronavirus infection. Using a blood sample from a coronavirus survivor Partner company AbCellera identified more than 500 antibodies that might protect against the virus	Preclinical	[42]

Results

List of drugs which are developed and used against the SARS-COV-2 viral outbreak: COVID-19 is one of the greatest hardships that modern medical system has ever faced. Scientists have focused on findings of a certain drugs which can help in beating this pandemic or can actually help in saving the precious lives of the patients suffering from this disease. Now here are some of the most searched or experimented drugs about the treatment for the coronavirus. But despite of all these most of the drugs are on their early stage of research. Now there are certain labels that have been given by the researchers and are used widely by the doctors and nurses to treat the patients suffering from COVID-19 and also to the patients having cardiovascular diseases [81].

Promising evidence: This label includes treatments that have responded improvements in morbidity, mortality and recovery in at least one random controlled trial, in which some people will get a treatment and others get a placebo [82].

Tentative or mixed evidence: This is the label where treatments showed promising results in cells or animals, but that are yet to be confirmed in people. Some treatments have produced different results in different experiments when performed, thereby raising confusion or a need for more rigorous studies to remove the confusion that whether these treatments will be helpful in humans or not [83].

Not promising: These are the treatments which gives us an idea about the fact that these treatments do not work [84].

Pseudoscience or fraud: These are the treatments that researchers have not given permission for using them in the treatment of COVID-19. Scientists have warned against trying them, because they will not help to combat the disease and will thereby be dangerous [85].

Evidence in cells, animals or humans: These labels give us an idea that from where the evidence for a treatment will come from. Researchers first start their experiments on cells and then move onto higher order of animals. Many of these animal experiments often fail but if they don't or they get promising results researchers will then move to humans, such as random clinical trials. Sometimes, scientists try out other treatments that were meant for other diseases and thereby move directly for human trials for COVID-19. Drug which gave the most promising evidence is Remdesivir, made by Gilead sciences and was also the first drug to get emergency authorization from the F.D.A. for the use on COVID-19. Remdesivir have the capability of interfering or inserting them within the new viral genes and thereby helps in controlling the disease. Remdesivir was originally tested as an antiviral against Ebola and Hepatitis C. But a random trial published during May concluded that the drug had reduced the recovery time of people who were hospitalized with COVID-19 from 15 to 11 days. The trial did not show any effect on mortality, though retrospective data released in July hints that the drug might cut down death rates those who are very sick [85]. The FDA responded to this data and issued its use in critically ill patients who need supplemental oxygen and also in the month of August, they extended that approval after researchers found that patients with less severe forms of COVID-19 will get benefitted from a five-day treatment course of remdesivir. Revised approval allowed the usage of this drug on all patients

hospitalized with COVID-19, regardless of how severe their disease is. This move was criticized by some of the experts who said that FDA had expanded remdesivir's use without strong evidence to back the change. Another drug that gave a promising result is MK-4482 which was made to fight the flu, MK-4482 (previously known as EIDD-2801). This drug has promising results against the coronavirus when it has been studied in cells and on animals. Recombinant ACE-2 proteins: Corona virus has a very proper affinity towards ACE-2 protein and thereby forming a recombinant one by some scientists will thereby decrease the rate of the infection and thus will lire the virus away from vulnerable cells. But this experiment has shown promising results on cells but not in humans and animals [86].

Invermectin: For more than 20 years, this potent drug has shown its effect against parasitic worms. Doctors have used it against river blindness, while veterinarians have used it against heartworm in dogs. But when it's been studies in cells this drug has shown a possibility of killing virus also. But this is not yet checked or tested by a researcher or scientist that whether this drug will be a potent antiviral. Hence it cannot be used as an antiviral drug for treating COVID-19 patients. But it has been seen that this drug has the capacity to control Corona virus in cells but the amount of dosage given is so high that it will yield a dangerous effect on an Individual's health thereby can lead to some serious harm. Hence FDA has issued some guidelines or warnings against the usage of this drug. Lopinavir and ritonavir are the drugs that are used together to combat against HIV virus. Now recently it has been seen by the researchers that these drugs have the ability to stop the virus from replicating but surprisingly it showed not much promising results when tested in patients during its clinical trials. But this drug can be used with other drugs thereby can cause some effect when done in combination. Oleandrin is a drug derived from a plant called oleander shrub. This drug has proven to be effective against cancer but this drug showed result when the drug was given to the cells of monkey kidney which was infected with coronavirus [87].

Hydroxychloroquine and chloroquine: Chloroquine is the drug which was originally been used against malaria and the lesser toxic version the hydroxychloroquine was used against lupus and arthritis. But during the initial stages of COVID-19 pandemic these drugs have proved to be limiting or inhibiting the replication of virus in the cells and it was given to patients suffering from COVID-19. But it has been observed that experiments done on mice and monkey have no results and thus will not help in preventing the disease and thus the trials were stopped. Despite of getting some negative results trials were done but in a very small scale and thus it can be given to patients theoretically in early stages of this disease and thus only well and proper designed trials can determine this [88]. Hydroxychloroquine is generally a derivative of chloroquine that has both antimalarial and anti-inflammatory activities and is now most often used as anti-rheumatologic agent in systemic lupus erythematosus and rheumatoid arthritis. Hydroxychloroquine therapy is not associated with liver function abnormalities. It is also known as oxychlorochin which belongs to the class of organic compound known as 4-aminiquinolines. These organic compounds containing an amino group attached to the fourth position of a quinoline ring. The molecular quantum mechanical modelling of the interaction of hydroxychloroquine to the SARS-CoV-2 spike protein-ACE2 complex has also been performed. Angiotensin converting enzyme -II (ACE-2) is the critical receptor of SARS-CoV-2 virus, the principle is inhibiting this interaction with a suitable drug. According to the molecular modelling studies, hydroxychloroquine does not bind to ACE-2 but increases it acidity in the interaction between the ACE-2 and the spike protein thus results in the degradation in the spike and lowering the ability to spread the virus [89]. Hydroxychloroquine is the first metabolite of chloroquine. Besides it also helps in raising the p^H within the endosomes and lysosomes and interfering with viral infection and major role of hydroxychloroquine is the inhibition

of three key pro-inflammatory cytokines tumour necrosis factor alpha, interieukin-1, and interieukin-6 produced from the immune response from mononuclear phagocytes in response to the viral infection. Hydroxychloroquine prevents the possibility of a cytokine storm, which has been implicated in many fatal outcomes of COVID-19. Clinical records show that out of 1446 consecutive patients, 70 were intubated, died or discharged within 24 hours after analysis. The remaining 1376 patients after a follow of 22.5 days, 811 (58.9%) received hydroxychloroquine (600 mg twice on day 1, then 400 mg daily for 5 days),45.8% of the patients were treated within 24 hours in the emergency department and 85.9% within 48 hours. In the main analysis, there was no significant association between intubation or death. Results were similar in multiple sensitivity analyses [90]. In this deep observational study hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk of the composite end point of intubation or death. Randomized, controlled trials of hydroxychloroquine in patients with COVID-19 are needed.

Dexamethasone and other corticosteroids: Corticosteroids are often called as steroids in short that can be used to tamp down inflammation and also can be given to person suffering from conditions such as allergies and asthma. Thus, doctors began using these drugs as a treatment for pneumonia and other severe respiratory illnesses, but the clinical trial results were inconclusive. This pandemic brought a new interest in these drugs, and trials were launched. Now in June, a steroid called dexamethasone was the first shown to reduce deaths and thus when it has been evaluated it has been seen that from more than 6,000 people, dexamethasone has reduced deaths by one-third in patients who were on ventilators, and by one-fifth in patients who were on oxygen [91]. Thus, in its treatment guidelines, the national institutes of health recommends only using dexamethasone in patients with COVID-19 who are either on a ventilator or are receiving supplemental oxygen. After that researcher reviewed the results obtained from the trials of dexamethasone, along with two other steroids, hydrocortisone and methylprednisolone and suggested that steroids were linked with one-third reduction in deaths among COVID-19 patients and thus gave a very promising result [92].

Cytokine inhibitors: Human body produces some important molecules called cytokines to fight against diseases and one of the most important features of this cytokine molecule is that they can cause cytokine storm and thereby researches have made some drugs which can halt these storms and these have proved to be effective against arthritis and other inflammatory diseases. Now against the Corona virus some drugs have given modest help during trials but some of the drug companies like Roche and Regeneron have announced that two drugs called sarilumab and tocilizumab which will both target the cytokine IL-6 but did not gave promising result to patients in Phase 3 clinical trials. Table 2 lists some of the drugs that are being marketed by various companies to treat SARS-CoV-2 patients [93].

Blood filtration systems

The FDA has granted the use of several devices that can filter cytokines from the blood to cool down cytokine storms. One machine known as Cytosorb, can reportedly purify a patient's entire blood supply about 70 times within 24 hours and in a small study being conducted in March suggested that Cytosorb had helped many of the severely ill COVID-19 patients in Europe and China, but it was not a randomize clinical trial that will exclusively demonstrate that it was effective [94]. Now, a number of studies on blood filtration systems are undergoing, but experts expect some caution or risks that these devices carry some risks like, these blood filters can remove beneficial components from blood like vitamins etc. Prone positioning is the process or act

in which the COVID-19 patients are flipped onto their bellies which will thereby cause the opening of the lungs. This manoeuvre has become common in the hospitals around the world since the initiation of the pandemic. It will help others individuals not to need any ventilation but the treatment benefits continued to be tested in a range of clinical trials.

Anti-coagulants

The coronavirus invades cells which are present on the inner lining of the blood vessels and thereby leading to tiny clots that can cause strokes and other serious conditions. Anticoagulants are used when covid patients have developed clots or to slow down the formation of clots and also during the treatment of any heart disease. Some of the clinical trials are also looking at whether giving an anticoagulant before any sign of clotting is beneficial or not [95].

Ventilators and other devices

These devices are an essential tool that helps a person to breathe during any respiratory or any kind of illness. Some people perform or response well if they get any external oxygen supply. But in case of a patient suffering from COVID-19, it has been seen that sometimes these ventilators are lifesaving [96].

UV light can act as a sterilizer and thereby can sterilize surfaces, scan kill viruses or can even kill other group of microorganisms but exposure of UV light to the body will cause a tremendous harm in the body because ultraviolet ray can destroy the skin cells and moreover this UV light cannot control the infection when it's on the sick person's body. UV light can cause skin cancer and thereby will increase many problems rather than suppressing it [97].

Silver has been seen that many metals have antimicrobial effects but till now none of the metals have shown an anti-effect against coronavirus. As for silver, the NIH has warned the usage of silver as an antiviral agent. This metal if taken can cause people skin to turn blue and thereby making it difficult for them to absorb antibiotics and other drugs [98].

Favilavir

The NMPAC has approved the usage of Favilavir which is an antiviral drug which can be used for coronavirus treatment. The drug has shown its efficacy in treating the disease with fewer side effects on a clinical trial containing 70 patients and this has been done in Shenzhen Guangdong province in China. Entos pharmaceutical has been developing a DNA vaccine using the Fusogenix drug to treat the COVID-19 patients. It is currently working on developing multiple protein epitopes from SARS-COV-2 proteins, which will actually stimulate the immune response in the body to prevent the COVID-19 infection [99].

ChAdOx1 nCoV-19 by university of oxford: It is an adenovirus vaccine developed by Jenner institute and the institute has planned to test the vaccine in the Thames valley region and there will be around 510 volunteers aged between 18 to 55 years [100].

Gimsilumab by roivant Sciences: It is human monoclonal antibody which is in its clinical trial stage. The drug targets Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), which is an inflammatory cytokine found in high levels in the

serum of COVID-19 patients. Targeting the GM-CSF is expected to reduce lung damage and reduce mortality rate in COVID-19 patients [101].

AdCOVID by alti-immune: Alti immune has made collaboration with the University of Alabama to develop an intranasal vaccine for Corona patients named AdCOVID [102].

TJM2 by I-Mab Biopharma: I-Mab Biopharma is being developed by TJM-2 which is a neutralizing antibody which will treat the cytokine storm that occurs in patients suffering from severe Corona virus infection. This drug targets the Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF), which is responsible for acute and chronic inflammation [103].

Coronavirus vaccine by Medicago: Medicago has been developing potent drug candidates against the SARS-CoV-2 after the production of Virus-Like Particles (VLP) of the coronavirus. The company have formed a research collaboration with Laval university's infectious disease research centre to develop antibodies against SARS-CoV-2 [99].

AT-100 by airway therapeutics: Airway therapeutics is developing a human recombinant protein named AT-100 (rhSP-D) as a treatment for coronavirus. This protein AT-100 has shown efficacy in preclinical trials in reducing the inflammation and infection in the lungs, while also performed by generating an immune response against various respiratory diseases [98].

TZLS-501 by Tiziana Life Sciences: Tiziana life science is developing a monoclonal antibody named TZLS-501 for the treatment of COVID-19. TZLS-501 is a human anti-Interleukin-6 receptor (IL-6R), which helps in preventing lung damage and elevated levels of IL-6. The drug works by binding to IL-6R and depleting the amount of IL-6 circulating in the body thereby reducing chronic lung inflammation [101].

OYA1 by OyaGen: OyaGen's has developed a drug called OYA-1 which has shown strong antiviral efficacy against coronavirus *in vivo*. It was found to be more effective than chlorpromazine HCl in inhibiting the SARS-CoV-2 from replicating in cell culture. OYA-1 was also earlier approved for treating cancer but was withdrawn due to lack in efficacy. OyaGen plans to conduct furthermore research on this drug to determine the efficacy in treating the coronavirus [102].

BPI-002 by beyond spring: Beyond Spring's BPI-002 is a small molecule agent which has been developed for treating various infections including COVID-19. It has the ability to activate CD_4+ helper T cells and CD_8+ cytotoxic T cells and generating an immune response in the body. Now if combined with another COVID-19 vaccine the efficacy of the drug increases and thus was able to generate long-term protection against viral infections. Beyond spring has filed US patent protection for the drug for treating viral infections [103].

NP-120 (Ifenprodil) by Algernon pharmaceuticals: Algernon pharmaceuticals are now busy in exploring the drug Ifenprodil as a potential treatment for COVID-19. If enprodil is an N-methyl-d-aspartate (NDMA) receptor glutamate receptor antagonist who was sold under the brand name Cerocal. It has showed efficacy in increasing the survivability in mice infected with H_5N_1, influenza [97].

APN01 by university of British Columbia and APEIRON biologics: A drug was developed by APEIRON biologics named APN01 which is being tested in China in a phase one trial as a treatment against COVID-19. APN01 is based on research that was carried out at the university of British Columbia for treating SARS. The research revealed that the ACE-2 protein was the main receptor for the SARS virus. The clinical trial in China will thereby give an idea about the efficacy of the drug. mRNA-1273 vaccine by Moderna and Vaccine Research Centre, a unit of the National Institute of Allergy and Infectious Diseases (NIAID), have collaborated to develop a vaccine for coronavirus. This vaccine targets the Spike (S) protein of the coronavirus. The first vials of the vaccine have been manufactured at Moderna's Massachusetts manufacturing plant and shipped to NIAID for phase one human clinical trial. The trial had begun on 16 March at the Kaiser Permanente Washington Health Research Institute in Seattle, Washington with a total of 45 males and females aged between 18 and 45 have been enrolled for the trial. The participants will be divided into three cohorts who will be given 25 microgram (mcg), 100 mcg or 250 mcg dose 28 days apart [96].

Avian Coronavirus Infectious Bronchitis Virus (IBV) vaccine by MIGAL research institute: The MIGAL research institute in Israel has announced that an Infectious Bronchitis Virus (IBV) vaccine is developed to treat avian coronavirus has been modified to treat COVID-19. The vaccine has demonstrated efficacy in pre-clinical trials conducted by the volcanic institute. The IBV vaccine was developed after four years of extensive research and it has high genetic similarity with that of the human Corona virus and thus it will be available in oral form [83-86].

TNX-1800 by Tonix pharmaceuticals: Tonix pharmaceutical has collaborated with Southern research, a research organization, to develop a vaccine for coronavirus named TNX-1800. The vaccine is made of a modified horse pox virus developed using Tonix's horse pox vaccine platform and it is designed to express a protein which has been derived from the virus that causes the coronavirus infection. Southern Research will be responsible for evaluating the efficacy of the vaccine, under the partnership [81-82].

Brilacidin by innovation pharmaceuticals: Innovation pharmaceuticals are evaluating Brilacidin which is a defensin mimetic drug which has a potential in treating the coronavirus. Brilacidin has surprisingly shown many properties in several trials like antibacterial, anti-inflammatory and immunomodulatory properties and now the company is aiming for exploring research collaboration and also to seek grant for manufacturing the drug. It is already investigating the drug for inflammatory bowel disease and oral mucositis in cancer patients. This drug was scheduled for its testing in the third week of March [82-84].

Recombinant subunit vaccine by Clover biopharmaceuticals: Clover biopharmaceuticals is developing a recombinant subunit vaccine using its patented Trimer-Tag technology. The company is developing the vaccine based on the trimeric S protein (S-Trimer) of the COVID-19 coronavirus, which is responsible for binding with the host cell and thereby causes viral infection. Using Trimer-Tag technology, Clover successfully produced the subunit vaccine in a mammalian cell-culture based expression system. The company also identified antigen-specific antibody in the serum of fully recovered patients who were previously infected by the virus. The company is equipped with in-house cGMP bio manufacturing capabilities to scale-up production if the vaccine is proven to be successful. Clover is also collaborating with GSK to develop a vaccine using the latter's pandemic adjuvant system [60].

Vaxart's coronavirus vaccine: Vaxart is developing an oral recombinant vaccine in the form of tablet using its proprietary oral vaccine platform, VAAST. The company has planned to develop vaccines based on the published genome of 2019-nCoV that is to be tested in pre-clinical models for mucosal and systemic immune responses [61].

CytoDyn-leronlimab: CytoDyn is busy in testing the leronlimab (PRO-140) which is a CCR-5 antagonist and also a potential coronavirus drug. The drug has already been investigated in phase two clinical trials for treating HIV and has also been awarded fast-track approval status by the United States Food and Drug Administration (FDA) [62].

Linear DNA vaccine by applied DNA sciences and Takis biotech: Applied DNA sciences' subsidiary LineaRx and Takis biotech formed a joint venture to develop a linear DNA vaccine as a treatment for coronavirus. The JV will use Polymerase Chain Reaction (PCR) based DNA manufacturing technology to develop the vaccine [63]. The PCR technology offers several advantages including high purity, increased production speed, and absence of antibiotics and bacterial contaminants. Further, the vaccine gene developed through this technology can be effective without being inserted into the patient's genome. The design for four DNA vaccine candidates is expected to be produced using the PCR technology for carrying out animal testing. The design of one of the vaccine candidates is based on the entire spike gene of the coronavirus, while the remaining are designed based on the antigenic portions of the protein [64].

BXT-25 by BIOXYTRAN: To treat late-stage Acute Respiratory Distress Syndrome (ARDS), BIOXYTRAN has developed BX-25, as a treatment for Acute Respiratory Distress Syndrome (ARDS) in late-stage patients infected with the coronavirus. The size of this BX-25 is 5,000 times smaller than the blood cells and thereby can efficiently transport oxygen through the body for a period of nine hours before being processed by the liver. The drug can help in supplying oxygen to the vital organs and enable the patient to recover and survive [65].

Novavax's MERS coronavirus vaccine candidate: Novavax has developed a vaccine candidate against MERS in 2013 where the candidate can primarily bind to the S protein and it was developed by using recombinant nanoparticle vaccine technology. Tested along with the Novavax's proprietary adjuvant Matrix-M™, it inhibited infection by inducing immune responses in the laboratory studies. The SARS and MARS are related to each other and for that the company has developed a recombinant nanoparticle candidate [66].

Inovio pharma's INO-4700: The investigational DNA immunotherapy, INO-4700 (GLS-5300) is being developed by Inovio in partnership with Gene One Life Science. It is delivered as vaccine intramuscularly, using the cellectra delivery device. The vaccine was demonstrated early and it has showed high immune response in 94% of patients in the early-stage clinical trial in July 2019. It has also generated broad based T cell responses in 88% of the subjects [67].

Actemra by Roche: To treat coronavirus-related complications, drugs like Actemra have the ability to prevent cytokine storms or overreaction of the immune system which causes organ failure leading to death in some coronavirus patients. Actemra has been evaluated in a clinical trial in China [68].

Biocryst Pharma's Galidesivir, a potential antiviral for coronavirus treatment: The drug Galidesivir (BCX4430) has shown its broad-spectrum activity against a wide range of pathogens including coronavirus. It is a nucleoside RNA polymerase inhibitor that disrupts the process of viral replication. The drug has already shown survival benefits in patients infected with Ebola, Zika, Marburg, and yellow fever. Galidesivir is now under the last developmental stage under the Animal Rule to combat multiple potential viral threats including coronaviruses, flaviviruses filoviruses, paramyxoviruses, togaviruses, bunyaviruses and arenaviruses [69].

Regeneron's REGN3048-3051 and Kevzara: Regeneron has made the drug by using two neutralizing monoclonal antibodies REGN3048 and REGN3051 against coronavirus infection in a first-in-human clinical trial sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). The efficacy of the drug will be studied in 48 patients [70]. Both the antibodies bind to S-protein of MERS coronavirus and the intravenous application of this drug has caused neutralization of the coronavirus and thereby reduces viral load in lungs. Regeneron has partnered with Sanofi to evaluate Kevzara which is a fully-human monoclonal antibody against Covid-19. Kevzara is approved for the treatment of rheumatoid arthritis and is known to block the Interleukin-6 (IL-6) pathway, which causes an overactive inflammatory response in the lungs of COVID-19 patients [71].

SNG001 by Synairgen research: Synairgen research's SNG001, which is an inhaled drug, is planned to be tested to treat asthma, chronic obstructive pulmonary disease and lower respiratory tract illnesses caused by coronavirus. This drug is a formulation of naturally occurring Interferon-β, which is administered through a nebulizer and is delivered directly to the lungs to reduce the infection caused by coronavirus [72-73].

AmnioBoost by lattice biologics: This drug has shown efficacy in reducing the inflammatory conditions caused by several diseases including coronavirus (Table 3). It reduces the production of pro-inflammatory cytokines while boosting the production of anti-inflammatory cytokines [74].

TABLE 3**. Antivirals included in the Guidelines (version 6) for treatment of COVID-19.**

Sl. No	Drug	Duration of treatment	Method of administration	Dosage	References
1	IFN-α	No more than 10 days	Vapour inhalation	5 million U or equivalent dose each time, 2 times/day.	[75]
2	Lopinavir/ ritonavir	No more than 10 days	Oral	200 mg/50 mg/capsule, 2 capsules each time, 2 times/day.	[76]
3	Ribavirin	No more than 10 days	Intravenous infusion	500 mg each time, 2 to 3 times/day in combination with IFN-α or lopinavir/ritonavir.	[77]
4	Chloroquine phosphate	No more than 10 days	Oral	500 mg (300 mg for chloroquine) each time, 2 times/day.	[78]
5	Arbidol	No more than 10 days	Oral	200 mg each time, 3 times/day.	[79]

Cardiovascular drug therapy against COVID-19

COVID-19 affects people suffering from cardiovascular disease out of any proportion. Scientists have raised their concern about the ACE inhibitors and angiotensin receptor blockers in the clinical context. An observational database has been made by taking the patients who died in COVID-19 and tried to find out a relationship between the cardiovascular disease and drug therapy among the diet patients who were admitted within a time limit of December 20, 2019 to March 15, 2020 and were recorded in the surgical outcomes collaborative registry as either died or survived to discharge on march 2020. Among the 8910 patients affected with COVID-19, the discharge status at the time of the analysis were a total of 515 died in the hospital (5.8%) and 8395 survived to discharge [80-82]. The factors to be independently associated with an increased risk of death in the hospital were age greater than 65 years (mortality of 10.0%, *vs.* 4.9% among those ≤ 65 years of age; odds ratio, 1.93; 95% Confidence Interval (CI), (1.60 to 2.41), coronary artery disease (10.2%, *vs.* 5.2% among those without disease; odds ratio, 2.70; 95% CI, 2.08 to 3.51), heart failure (15.3%, *vs.* 5.6% among those without heart failure; odds ratio, 2.48; 95% CI, 1.62 to 3.79), cardiac arrhythmia (11.5%, *vs.* 5.6% among those without arrhythmia; odds ratio, 1.95; 95% CI, 1.33 to 2.86), chronic obstructive pulmonary disease (14.2%, *vs.* 5.6% among those without disease; odds ratio, 2.96; 95% CI, 2.00 to 4.40) and current smoking (9.4%, *vs.* 5.6% among former smokers or non-smokers; odds ratio, 1.79; 95% CI, 1.29 to 2.47). No death occurred with the use of ACE inhibitors (2.1% *vs.* 6.1%; odds ratio, 0.33; 95% CI, 0.20 to 0.54) or the use of ARBs (6.8% *vs.* 5.7%; odds ratio, 1.23; 95% CI, 0.87 to 1.74). It has been confirmed that previous observations suggested that cardiovascular disease is associated with an increased risk of death among the patients who were hospitalized with COVID-19 [83].

As this coronavirus disease 2019 (COVID-19) pandemic has spread worldwide, there has been growing possibility that persons with cardiovascular risk may be affected in higher numbers. Several studies have noted cardiac arrhythmias, cardiomyopathy, and cardiac arrest as terminal events in patients with COVID-19. Higher incidences of cardiac arrhythmias, acute coronary syndromes, and heart failure related events have also been reported during influenza outbreaks which made a possibility of the activation of coagulation pathways, proinflammatory effects, and endothelial cell dysfunction. In addition to, cardiovascular disease might specifically contribute more to the severity of illness in patients with COVID-19. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is the causative agent of COVID-19 and to establish itself in the host cell it has to use Angiotensin-Converting Enzyme-2 (ACE-2) as its cellular receptor. ACE-2 is a membrane-bound monocarboxypeptidase found ubiquitously in humans and expressed predominantly in heart, intestine, kidney and pulmonary alveolar (type II) cells [86]. The entry of SARS-CoV-2 into human cells is being facilitated by the interaction of a receptor-binding domain in its viral spike glycoprotein ectodomain with the ACE-2 receptor. ACE-2 has a counter activity to angiotensin II generated through ACE-1 and thereby helps in protection against the detrimental activation of the renin angiotensin aldosterone system. Angiotensin II is catalysed by ACE-2 to angiotensin which exerts vasodilatory, anti-inflammatory, antifibrotic, and antigrowth effects [84]. It has been suggested that the ACE inhibitors and Angiotensin Receptor Blockers (ARBs) may increase the expression of ACE-2, which has been shown in the heart in rats, and thereby can cause more severe infection and adverse outcomes during COVID-19. Others have suggested that ACE inhibitors may encounter the anti-inflammatory effects of ACE-2. However, *in vitro* studies have not shown any inhibitory effects of ACE-2 [85]. However, several scientific societies, including the American heart association, the American college of cardiology, the heart failure society of America, and the council on hypertension of

the European society of cardiology, have urged that these important medications should not be discontinued in the absence of clear clinical evidence of harm.

Discussion

The population which was studied included 8910 COVID-19 patients from 169 hospitals who were admitted within a time limit of December 20, 2019 to March 15, 2020 and also considered those patients who have already completed their treatment and were then being preparing for either discharged alive or died by march 28 2020 [87-88]. The studying sample consisted of 1536 patients (17.2%) from North America, 5755 (64.6%) from Europe, and 1619 (18.2%) from Asia. The mean (± SD) age group that were taken were 49 ± 16 years (16.5% of the patients were >65 years of age), 40.0% of the patients were women, 63.5% were white, 7.9% were black, 6.3% were Hispanic, and 19.3% were Asian. Now coming to some specific diseases, persons having cardiovascular risk, 30.5% of the patients had hyperlipidemia, 26.3% had hypertension, 14.3% had diabetes mellitus, 16.8% were former smokers, and 5.5% were current smokers. People having early cardiovascular disease in this sample were also included [89]. It comprises persons with coronary artery disease (present in 11.3% of the patients), a history of congestive heart failure (2.1%), and a history of cardiac arrhythmia (3.4%). Other conditions included COPD (in 2.5% of the patients) and an underlying immunosuppressed condition (2.8%). Medical therapy included ACE inhibitors (8.6% of the patients), ARBs (6.2%), statins (9.7%), beta-blockers (5.9%), and antiplatelet agents (3.3%). Insulin hormone was used in 3.4% of the patients, and similar or other hypoglycemic agents were also used in 9.6%. The number of days for which people stayed in the hospital was 10.7 ± 2.7 days, with an overall mortality rate of 5.8% (515 of 8910 patients) in this population of patients with completed outcomes. Out of the patients who were admitted to an ICU, 24.7% died in comparison with 4.0% who had not been admitted to an ICU [90].

It was observed that the non-survivors were older and were more likely to be men with diabetes mellitus, hyperlipidaemia, coronary artery disease, heart failure, and cardiac arrhythmias [91]. Patients who had died also had COPD and also had a smoking history. Now, as far as the medications are concerned ACE inhibitors and statins were more commonly used by survivors than non-survivors whereas no connections between survivals to that of ARBs were found. The length for which the survivors and non survivors stayed differed from (10.5 ± 2.5 days *vs.* 7.5 ± 2.8 days) [92-94]. The data has been analyzed according to age, continent, or income category of the country where the hospital was located (high income or low–middle income), the results were found to be surprisingly similar. A multivariable logistic-regression model was being developed in which the independent predictors of in-hospital death and their corresponding odds ratios and 95% confidence intervals were shown. Persons having age greater than 65 years, coronary artery disease, congestive heart failure, cardiac arrhythmia, COPD, and current smoking were more prone to in-hospital death. Whereas in females, the use of ACE inhibitors and statins were associated with a better chance of survival in the hospital and there has been no information about the usage of ARBs. Now in case of females, the odd ratios of dying in the hospital premises were 0.79 (95% Confidence Interval (CI), 0.65 to 0.95). When ACE inhibitor was used the odds ratio came down to 0.33 (95% CI, 0.20 to 0.54); and for statin, the odds ratio was 0.35 (95% CI, 0.24 to 0.52). For ARB use, the odds ratio was 1.23 (95% CI, 0.87 to 1.74) [93-95].

The presence or absence of an immunodeficient condition, the ethnic or race group, and also the presence or absence of hyperlipidaemia or diabetes mellitus was dependent on the predictors that have been made prominent on the death in the

hospital [96]. The analysis was based on continent and the income category of the country (high or low-middle) was consistent with the overall results. Studies performed so far confirms or gives us an idea about the previous reports which were absolutely independent on older age, cardiovascular diseases, smoking and COPD with death in COVID-19 with women having greater chances of survival than men. Neither harmful nor beneficial association was noted regarding the antiplatelet theory, betablockers or hypoglycaemic therapy. It has been observed that during viral infections such as influenza, age of the person is directly proportional to increased risk of cardiovascular diseases and death. During the pandemic in 2003 of SARS-CoV-1 it has been observed that women have more innate immunity than men and thereby they have greater resistance towards any viral infections.

SARS-CoV-2 infection may progress towards a very severe case characterized by a hyper inflammatory syndrome, multiple organ failure and thereby leading towards death. In lungs, the viral spike glycoprotein of SARS-CoV-2 interacts with cell-surface ACE-2, and the virus is incorporated by endocytosis [97]. The endocytic event thereby helps in up regulating the activity of ADAM metallopeptidase domain 17 (ADAM-17), which cleaves ACE-2 from the cell membrane, resulting in a loss of ACE-2 mediated protection against the effects of activation of the tissue renin–angiotensin–aldosterone system thereby helps in the release of proinflammatory cytokines into the circulation. Vascular endothelial cell dysfunction, inflammation-associated myocardial depression, stress cardiomyopathy, direct viral infection of the heart and its vessels, or the host response may enhance heart failure and will thereby cause ischemia, and arrhythmias [98]. These factors are the key factors behind our observation between cardiovascular disease and death in COVID-19. In recent research works it has also been found that the use of either ACE inhibitors or statins was associated with better survival among patients suffering from COVID-19. But these associations should be considered with extreme caution. Therefore, a cause and effect relationship between drug therapy and survival should not be inferred. These data also do not offer information about the potential effect of initiation of ACE inhibitor or statin therapy in patients with COVID-19 who do not have an appropriate indication for these medications [99].

Conclusion

Recent evidences have suggested that the most common complications due to COVID-19 are sepsis and cardiovascular or respiratory troubles. They usually occur more in elderly or old aged people and also the people having less or poor immunity. Now a question comes that “Does using Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) increase these risks?" It has been observed that long term use of NSAIDs such as ibuprofen, naproxen, and diclofenac is linked with higher rates of severe cardiovascular outcomes such as myocardial infarction, heart failure, and stroke-2 albeit with current debate about residual confounding. Acute respiratory tract infections are already link with increased risk of stroke and myocardial infarction, and short-term use of NSAIDs during the illness is also associated with further increases in risk. NSAIDs cause nephrotoxicity, which is predominantly seen among the patient groups who are seriously affected by COVID-19 and is accompanied by fever and dehydration. A recent review of case-control studies suggested that NSAIDs are linked with higher rates of complications after respiratory tract infections, including complicated pneumonia, pleural effusions, prolonged illness, peritonsillar abscess, dissemination of infection to more than one site, or suppuration [100]. NSAIDs were also prescribed lately to patient’s prescription requiring hospital admission. It has been said that the findings can be plausibly explained by the inhibiting effect of NSAIDs on cyclo-oxygenases, which lowers the polymorphonuclear recruitment and also inhibits the synthesis of lipoxins and resolvins, thereby delaying the resolution of inflammation. Moreover, one large case-control study found an association

between NSAIDs and respiratory complications. Whether the NSAIDs should be taken for long term or just to treat a short acute illness. This actually gives us a suggestion that this association is not an outcome of increased prescription in response to acute illness. Now a question comes "what about the trial evidence in primary care settings? "A large trial (n=889) has been done where patients having respiratory tract infections were advised to take paracetamol, ibuprofen, or both. New or unresolved symptoms or complications were listed in 12% of the paracetamol group and 20% of the ibuprofen group (adjusted risk ratio 1.67, 95% confidence interval 1.12 to 2.38). The 11 complications recorded in the ibuprofen group were quinsy, sinusitis (n=3), meningitis, pneumonia, otitis media (n=3), and progression or non-resolution of otitis media (n=2). A second random trial was done by taking 3044 primary care patients and thereby gave half access to a website which was seen to be advising on self-management of respiratory tract infections, including advice to use NSAIDs. Multivariate analyses suggested that among the participants who had developed respiratory tract infections, and also those having access to the website had more prolonged illness than controls without access which means that more days of illness rated moderately bad or worse (difference 0.52 days; 95% CI 0.06 to 0.97, P=0.026).

The effect could not be explained by reporting bias or confounding by indication and was attenuated after controlling the use of the ibuprofen web pages. This practical trial evidence supports observational data suggesting that NSAIDs can cause more prolonged illness when taken during any respiratory tract infections about COVID-19. The most and the biggest unknown fact is that whether any of these evidences will apply in the COVID-19 pandemic [101-103]. The evidences till date are not so strong to support against the usage of NSAIDs: the primary care trials tested more normal or regular dosing during respiratory tract infections, so we have very little evidence about intermittent use, and it seems to be likely that intermittent or occasional use could relief the patients suffering from COVID-19 pandemic.

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