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REVIEW ARTICLE

A Comprehensive Review on Covid and Drug Repurposed Candidates for SARS Covid 19 Virus

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ABSTRACT

As the source of the continuing COVID-19 pandemic, the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) has quickly become a threat to global health. This thorough analysis gives a general overview of the SARS-CoV virus, covering its history, makeup, modes of transmission, clinical symptoms, modes of diagnosis, available therapies, and repurposed candidates for coronavirus.Positive-sense, single-stranded RNA virus of the Coronaviridae family, SARS-Covid virus. Most often, the virus is transmitted through respiratory droplets and intimate contact with infected people. There are a variety of clinical signs and symptoms of COVID-19, from minor flu-like symptoms to severe pneumonia, acute respiratory distress syndrome and multi organ dysfunction. Age, co-morbid conditions such diabetes and cardiovascular disease, and immunosuppression are risk factors for severe illness. For the virus to be effectively managed and contained, early and precise diagnosis is essential. Antigen testing, reverse transcription-polymerase chain reactions (RT-PCR), and serological assays are examples of diagnostic techniques.SARS-CoV-2 does not have a particular antiviral therapy, although a number of therapeutic approaches have been used to treat the disease, including the use of monoclonal antibodies, immunomodulators, and repurposed antiviral medications.In this current COVID-19 pandemic, when discovering effective therapies is of the utmost importance, drug repurposing may give a crucial tool to aid in the fight against this widespread virus outbreak. By utilising their well-established clinical and safety characteristics, FDA-approved medications currently on the market are the ideal candidates for being repurposed to treat COVID-19.

Keywords: *SARS Covid 19, Drug Repurposing, Approaches of Drug Repurposing, Candidates for Drug Repurposing*

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INTRODUCTION

SARS Covid 19 emerged as one of major pandemic that spread across the world as on October 5, 2020, more than 35.1 million confirmed infections have been reported with approximately 1 million deaths (WHO: https://covid19.who.int/) [9]. The disease is caused by a novel coronavirus termed as SARS Covid 19 belonging to family Coronaviridae [9]. This virus was reported to be a member of the ß group of coronaviruses. The novel virus was named as 2019 novel coronavirus (2019-nCov) by the Chinese researchers but the official recognition was given by The International Committee on Taxonomy of Viruses (ICTV) named the virus as SARS-CoV-2 and the disease as COVID-19 [8]. Transmission rate of SARS-CoV-2 is higher than SRAS-CoV because of genetic recombination event at S protein in the Receptor Binding Region (RBD) region of SARS-CoV-2 may have enhanced its transmission ability [8].

STRUCTURE OF SARS COVID 19

Structure: Coronavirus
Family: Coronaviridae
Order: Nidovirales
Information: Four main structural proteins contain spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Most abundant structural protein is the membrane (M) glycoprotein; it spans the membrane bilayer three times, leaving a short NH2-terminal domain outside the virus and a long COOH terminus (cytoplasmic domain) inside the virion.The spike protein (S) as a type I membrane

glycoprotein constitutes the peplomers which is the main inducer of neutralizing antibodies is S protein [8].

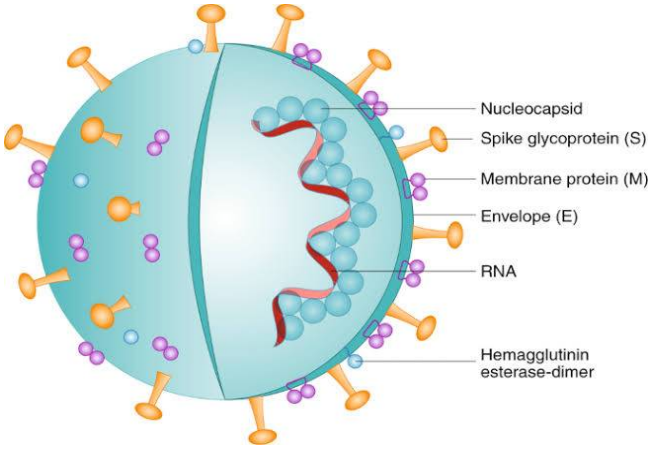

Fig 1: Structure of SARS covid 19

Symptoms of SARS Covid 19. [2]

- Dysguesia
- Hposmia
- Fever
- Headache

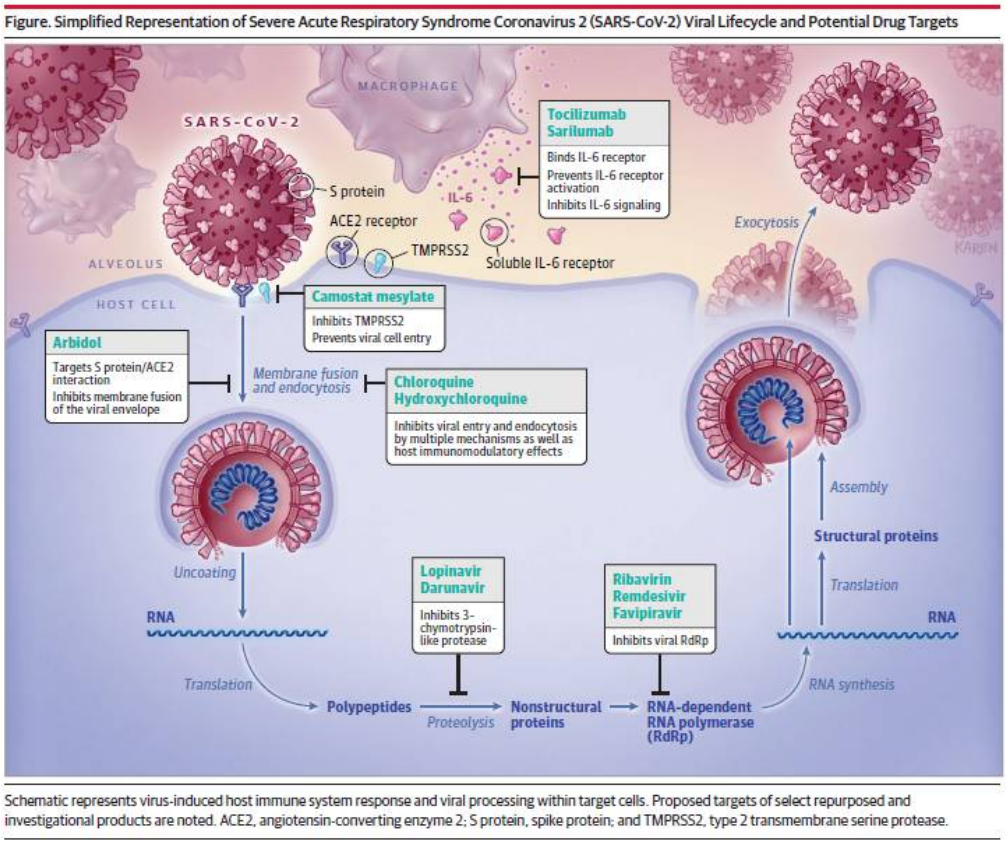

Fig 2 : SARS Covid 19 Lifecycle and targets of slected repurposed drugs [21]

DRUG	TARGET SITE	DOSE
Hydroxychloroquine sulfate [Brand Name : Plaquenil]	Blockade of viral entry by inhibiting glycosylation of host receptors. Proteolytic processing, and endosomal acidification. Inhibition of cytokine production. Autophagy and lysosomal activity in host cells	400 mg by mouth every 12 h × 1 d, then 200 mg by mouth every 12 h × 4 d; alternative dosing: 400 mg by mouth daily × 5 d or 200mg by mouth 3 times/d for 10 d. Available as: 200-mg tablets of hydroxychloroquine sulfate (salt) = 155 mg hydroxychloroquine base.
Lopinavir/Ritonavir [Brand Name : Kaletra]	3CL protease	400 mg/100 mg by mouth every 12 h for up to 14 d.
Remdesivir [Brand Name :Covifor]	RNA polymerase inhibitor	200 mg × 1, 100 mg every 24h IV infusion. Available as: 5-mg/mL vial (reconstituted).
Favipiravir [Brand Name : Fabiflu]	RNA polymerase inhibitor	200-mg tablet daily for 7 days.
Tocilizumab [Brand Name : Actemra]	IL-6 inhibition- reduction in cytokine storm	400 mg IV or 8 mg/kg × 1-2 doses. Second dose 8-12 h after first dose if inadequate response.
Corticosteroids [Brand Name :Dexonal]	Anti inflammatory effect	Dexamethasone dose of 6mg daily for 10 days
Camostat Mesylate [Brand Name : Foipan]	Inhibits TMPRSS2 Prevents viral cell entry	300 mg × 3 times a day for 10 days
Arbidol [Brand Name : Arbidol]	Targets S protein Inhibits Membrane Fusion of the viral envelope	200 mg × 3 times a day for 10 days

INTRODUCTION FOR DRUG REPURPOSING

A approach called medication repositioning, also referred to as drug repurposing, aims to find new uses for licenced or investigational pharmaceuticals that go beyond their initial medical uses. Repurposing candidates would have already been multiple stages of clinical development and have well-established safety and pharmacological characteristics, resulting in reduced costs and quicker development durations, which considerably reduces the development risk. If safety evaluation and formulation development have already been completed for a certain drug candidate, it might be viable to skip preclinical testing and start phase II clinical trials right away. Because biopharmaceutical corporations have created drug screening libraries, academic and small laboratories can have a significant impact on the drug discovery process. This will shorten the time needed for a biopharma to look through the pharmacopoeia for potential candidates for repurposing. The formulation and manufacturing chains of the pharmaceutical companies will be prepared for large-scale manufacture for emergency usage once a good repurposing candidate is identified, reducing the launch costs necessary for a de novo medicine. To prevent or lessen monotherapy resistance, combination techniques can be used with repurposed medications.

DRUG REPURPOSING APPROACHES

COMPUTATIONAL APPROACH :

1. Machine learning (ML)-based:

In general, computational techniques heavily rely on machine learning to extract data dependencies from exponentially growing biological data sets. The development of new drug repurposing hypotheses against SARS-CoV-2 will therefore be aided by the methodical examination of omics (e.g., genomics, transcriptomics, proteomics, and metabolomics) data, chemical structure, molecular docking studies, and prior SARS-CoV and MERS-CoV clinical data. To find candidates for repurposing, researchers use a number of machine learning (ML)-based techniques, including deep learning and neural networks. To uncover novel drug-protein interactions in this epidemic, numerous deep-learning algorithms have been developed, such as the molecular transformer-drug target interaction (MT-DTI), a deep learning model created to predict the affinity of a medication for a protein. According to this model, the inhibitor Atazanavir is effective against the SARS-CoV-2 3C-like proteinase[16].

2. Structure-based:

Structure-based screening studies for inhibitors against SARS-CoV-2 have received a lot of attention from numerous research groups around the world due to high computational power and the availability of 3D structures of drug and receptor targets. This method of drug repurposing may be one of the most well-known during the COVID-19 pandemic. Antiviral target-based and host target-based techniques are the two broad categories into which structure-based approaches can be divided. In contrast to host target-based approaches, which use the 3D structures of the host proteins, antiviral target-based approaches use the 3D structures of viral proteins to screen for possible inhibitors. Both the host target-based strategy and the antiviral target-based approach can be further broken down into a drug-centric approach and a target-centric approach in order to further define the techniques used. Molecular docking is used in the drug-centric method to identify possible docking sites (or molecular targets) for the drug candidate. Target-centric approaches involve knowing the target protein and using molecular docking to search for potential inhibitory ligands of the identified targe[16]t. The SARS-CoV-2 RNA-dependent RNA polymerase (RdRP) was used as an example of an antiviral target-based, target-centric approach. Various currently approved anti-polymerase medications were screened, and it was discovered that Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir were all effective RdRP inhibitors [16].

3. Signature-based:

The signature-based method contrasts the distinctive properties, or "signatures," of one medicine with those of another, with those of a disease, or with clinical phenotypes. omics data, chemical structures, and adverse event profiles can all be used to find drug signatures. Here, it is possible to leverage drug-disease comparison, drug-drug comparison, and chemical structure-biological activity comparison to extract meaningful data on repurposing candidates from signature matching. By contrasting the gene expression profile of a cell or tissue before and after drug therapy, it is possible to determine a proposed drug's distinct transcriptome signature for drug disease comparison. Then, using comparisons between healthy and ill situations, this transcriptome signature is compared against an expression profile linked to a particular disease. Differentially expressed genes (DEGs) would be used in this procedure to ascertain whether the potential medicine.

4. Artificial intelligence-based:

Artificial intelligence (AI)-based drug repurposing has gained international attention in this big data era because to the pandemic. This was made possible by the impressive computing capacity of AI models and algorithms in assessing and processing enormous amounts of surveillance data on infectious diseases and public health. Since that time, this technology has gained more and more traction among researchers who use it to analyse millions of patient trial records to uncover data insights using AI techniques like deep learning architecture and graph representation learning. The construction of web servers and other tools, such to those found in the CLAIRE Innovation Network (https://covid19. claire-ai.org), are part of the global research efforts currently underway to apply AI-based drug repurposing for COVID-19. Despite the fact that AI-based drug repurposing is still in its infancy, numerous papers have demonstrated hopeful outcomes. For instance, utilising AI's knowledge scientists have found Baricitinib as a viable therapy for SARS-CoV-2 from a list of licenced pharmaceuticals[16]. To speed up the screening of drug libraries, AI may also be combined with other computational methods. To find possible therapeutics against COVID19, for instance, molecular docking and AI were used in two distinct investigations.

EXPERIMENTAL APPROACHES

1. Target-based:

In a target-based screening, the ability of the medications to block a single target important for the course of the disease—typically a protein or a gene—is used to assess how effective they are. In this instance, the action's mechanism is well recognised. There are usually a few phases involved in target-based pharmacological screening. Target identification is the initial step, during which critical pathways or cellular processes for the development of the disease are first discovered. Target validation then confirms the significance of the target to the disease. The development of the assay is the next phase, which allows for drug screening by modelling the target-disease interaction using a cell-free binding assay. Then, hit identification is performed, in which several medicines are examined and judged according to how well they block the specified target. In the final step, the hits are chemically modified to increase their potency, stability, and safety.

2. Binding assays:

When researching prior pandemics and epidemics like SARS-CoV and MERS-CoV, mass spectrometry-based proteomic approaches have been used successfully to find the binding partners for therapeutically licenced medications. Affinity purification mass spectrometry was utilised to identify 332 high-confidence

protein-protein interactions between SARS-CoV-2 and 29 FDA-approved medicines that could be used to treat COVID-19. Although binding assays have demonstrated their potential as an important COVID-19 research tool, the development of quick and sensitive mass spectrometry techniques has not reached a point where they can be used to their full capacity in the COVID-19 pandemic.

3. Drug-centric:

In this approach, a medicine that has been shown to be effective against a certain disease is selected, then the mechanism of action is examined for possible activity against additional disorders. Remdesivir has been shown to be effective against human coronaviruses, including the original SARS-CoV and MERS-CoV, in a 2017 study by [16]. Investigations on remdesivir efficacy against SARS-CoV-2 and discovered that remdesivir was also successful in reducing SARS-CoV-2 infection. This was based on the mechanism of action by targeting viral RdRP and the demonstrated efficiency against human coronaviruses.

CONCLUSION

In the current COVID-19 pandemic, when discovering effective therapies is of the utmost importance, drug repurposing may give a crucial tool to aid in the fight against this widespread virus outbreak. By utilising their well-established clinical and safety characteristics, FDA-approved medications currently on the market are the ideal candidates for being repurposed to treat COVID-19. Hydroxychloroquine sulphate, Vortioxetine hydrobromide, Amlodipine besylate, Arbidol hydrochloride, Celecoxib, Tilorane hydrochloride, Dronedarone hydrochloride, Mefloquine, and Remdisvir showed higher efficacy and inhibited the activity of SARS Covid 19 virus, among the repurposed medications for this virus listed above[14]. In contrast to Hydroxychloroquine, which in comparable tests had a safety index of 22, five of the newly discovered medicines had a safety index (cytotoxic/effective concentration) of >600, indicating a broad therapeutic window. Five of the successful drugs (Fendiline HCl, Sertraline HCl, Vortioxetine, Monensin sodium salt, and Salifungin) were discovered to disrupt the SARS-CoV-2 S protein-mediated cell fusion mechanism[14].

DRUG REPURPOSING CANDIDATES FOR SARS COVID 19

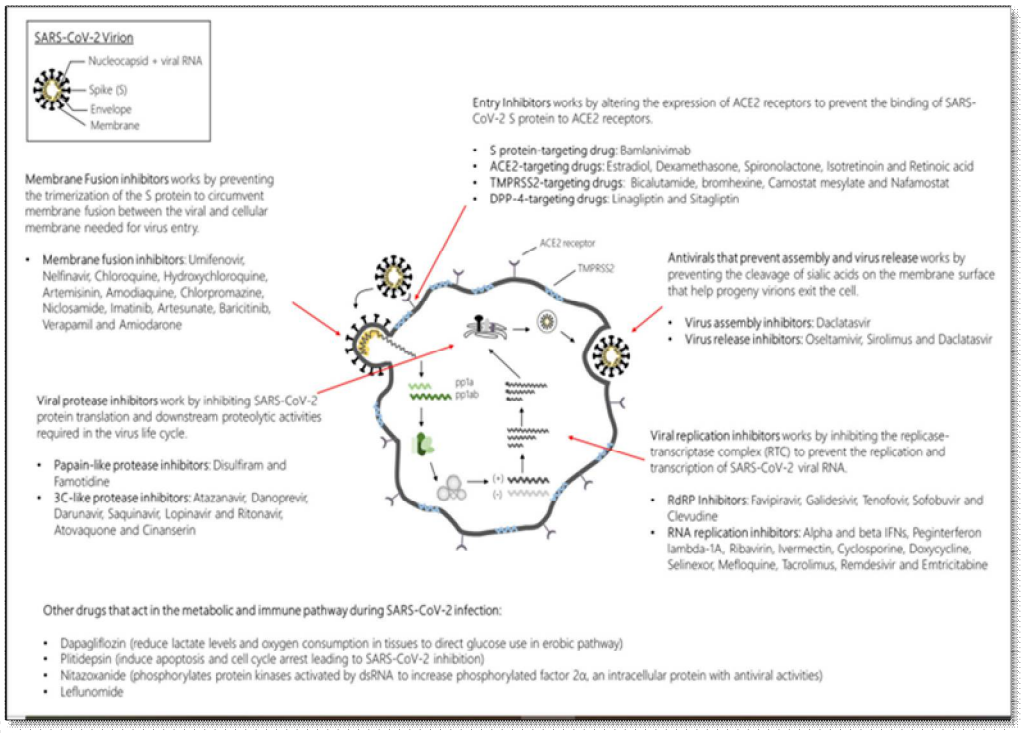

Fig 3: Drug repurposing candidates for SARS covid 19 virus [16]

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