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Heena Rani
Department of Biochemistry,
Punjab Agricultural University
(PAU), Ludhiana, Punjab, India

Simardeep Kaur
Division of Biochemistry, ICAR-
Indian Agricultural Research
Institute (IARI), New Delhi,
India

Rahul Sen
Department of Biochemistry and
Agricultural Chemistry, Assam
Agricultural University (AAU),
Jorhat, Assam, India

Mahesh Kumar Samota
Horticulture Crop Processing
Division, ICAR-Central Institute
of Post-Harvest Engineering and
Technology, Abohar, Punjab,
India

Repurposed drugs and their progression against COVID-19

Heena Rani, Simardeep Kaur, Rahul Sen and Mahesh Kumar Samota

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Abstract
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the causative agent of COVID-19 (Coronavirus disease), which was initially noticed in the seafood market at Wuhan, Hubei Province, China. Since then this deadly virus has outspread like wildfire across the globe and has put all the healthcare services at red alert. The outburst of COVID-19 has already taken the shape of the pandemic, affecting more than 200 countries in just a few months. A global response to prepare our health systems is very much imperative and the whole world is desperate to find ways to tackle this pandemic by developing effective treatments. Unfortunately, no reliable therapeutic interventions are available currently for critically affected ill COVID-19 patients. Treatment of COVID-19 patients is mainly based on symptomatic management. Emerging clinical trials and research data representing the structural and functional aspects of SARS-CoV-2 suggests testing of the repurposed drugs ranging from flu treatments to failed ebola drugs, to anti-malarial drugs that were first developed decades ago. The review focuses on the various already adopted and ongoing trials to date for developing effective therapeutic strategies to combat this viral outbreak. We hope that the accumulated information about various repositioning trials will help the international research community to lead potential clinical practices and to find solutions for COVID-19 treatment in this need of the hour.

Keywords: Coronavirus, COVID-19, pandemic, repurposed drugs, SARS-CoV-2, symptomatic, therapeutic, treatments

Introduction
The coronavirus pandemic is tightening its grip worldwide and it is very much clear that the pandemic isn't dying anytime soon. As the search for a potential vaccine or treatment plan continues, nationwide testing and social distancing is the only way we have against this disease [1]. The outburst of novel coronavirus is highly pathogenic and this transmittable disease was foremost reported in Wuhan, in the Hubei province of China, in December 2019. On 11 February 2020, this virus was named as SARS-CoV-2 by the International Committee on Taxonomy of Viruses [2]. On the same day, the World Health Organization (WHO) mentioned the virus as the "COVID-19 virus". Since then the virus has rapidly spread in various countries affecting Asia, Europe, Africa, North America Latin and Middle East America and has cost many human lives due to massive alveolar damage and respiratory failure. Globally, WHO has confirmed 95,612831 cases and 2,066,176 deaths till 21st January 2021 (WHO 2021, https://covid19.who.int). The virus belongs to the coronaviridae family, in which infections are associated mostly with mild respiratory conditions [3]. Based on the morphology of viruses with a core-shell and surface projections just like solar corona, the virus was named corona viruses (Latin word corona means crown). Although the major organ involved in COVID-19 is lungs however, the genitals, kidneys, heart and liver are also damaged. The incubation period of coronavirus is between 1-14 days, with an average of 3-7 days; COVID-19 patients (both symptomatic and asymptomatic patients) are considered as the major source of infection [4, 5]. The symptoms of this disease include sore throat, fever, runny nose, cough and shortness of breath.
(Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering 2020). SARS-CoV-2 has a stronger transmission and infectivity capacity in Comparison to SARS-CoV [6], which caused an outbreak of SARS and MERS in 2002 and 2012. The ongoing search for treatments to ease the COVID-19 pandemic concentrates on the development of a vaccine or medication to prevent and treat this disease. Researchers thus far have revealed various treatments and medicines that may have potential efficacy against COVID-19 [7].

Corresponding Author:
Heena Rani
Department of Biochemistry,
Punjab Agricultural University
(PAU), Ludhiana, Punjab, India

SARS-COV-2 Life Cycle

Coronavirus is one of the major pathogens that mainly target the human respiratory system. COVID-19 infected patients are reported to have a rapid rise in leukocyte numbers and abnormal respiratory syndromes along with the drastic increase in pro-inflammatory cytokines in plasma [8]. SARS-CoV-2 is enveloped positive-sense with the diameter ranging from 60 nm to 140 nm and genome comprised of 30000 nucleotides. Current studies illustrated that the hosts for SARS-CoV-2 maybe bats, pangolins and snakes [9, 10, 11]. However, COVID-19 showed approximately 50% genetic sequence similarity to the MERS-CoV and more than 80% similarity to SARS-CoV, but this virus spreads much quicker than its two ancestors i.e. SARS-CoV and MERS-CoV [12, 13]. Also, analysis of whole-genome sequencing showed that the homology between SARS-CoV-2 and bat coronaviruses is 96% which suggests bats as the host for this virus [9]. SARS-CoV-2 encodes four structural proteins; membrane (M) protein, nucleocapsid (N) protein, envelop (E) protein, spike (S) protein and other non-structural proteins (nsp) [14]. SARS-CoV-2 life cycle initiates when specific receptorbinding domain (RBD) of trimeric S protein binds to the human angiotensin-converting enzyme 2 (ACE2) [15] with specificity 20 times greater than SARS-COV. After attaching the receptor, S proteins of coronavirus are subjected to proteolytic cleavages by host proteases type-2 transmembrane serine protease (TMPRSS2). TMPRSS2 emerged as a key cellular factor necessary for the priming of S protein and the consequent membrane fusion and viral internalization by endocytosis in the pulmonary epithelium [16]. Both ACE2 and TMPRSS2 are the foremost determinants of the viral entry inside the host cell. Sungnak et al. [17] reported that nasal epithelial cells, specifically ciliated cells and goblet/secretory cells, exhibit the maximum expression of ACE2 all over the respiratory tract. Upon viral internalization, SARS-CoV-2 is uncoated and mRNA is released into the host cytoplasm, where it is replicated and translated. This generates two polyproteins; PP1AB and PP1A. Within the sequence of these proteins, coronavirus main protease (Mpro/3CLpro) and papain-like protease (PLpro) are present which cleaves the poly-proteins into various other functional proteins. Other structural components of the virus are also encoded by viral RNA i.e. membrane, nucleo-capsid, spike and envelope proteins. After all the components are reproduced, they are subsequently assembled into virions in Golgi and ER. Finally, the assembled virions are released out of the cell via vesicles [18]. About 80% of COVID-19 cases exhibit mild to moderate symptoms or they are asymptomatic due to activation of the body's innate immune system including natural killer (NK) cells, antiviral T cells, and induction of interferon (IFN), but approximately 20% of patients suffer critically from this disease, due to weak immune system or having other poor health conditions such as diabetics, pulmonary and cardiovascular problems, interstitial lung disease, chronic obstructive pulmonary disease, pulmonary fibrosis, hypertension, obesity and asthma [19, 20], resulting in enhanced viral load leading to oxidative stress/severe inflammatory response, cytokine storm and severe lung injury secondary to ARDS. Regardless of severe ARDS, evidences suggest that organs such as heart, kidneys and brain are also being affected by COVID-19 [19]. Furthermore, neurologic symptoms have also been observed in the brainstem of experimental animals as well as humans [20, 21]. Hence, it is a major challenge to discover/identify drugs with high target specificity and/or uncovering existing drugs that could be repurposed to treat COVID-19.

Possible therapeutic interventions against COVID-19

Until now, there are no specific therapeutic drugs or vaccines for confronting SARS-CoV-2 infection. The best way to protect yourself and others from the spread of COVID-19 is taking precaution which includes regularly and thoroughly cleaning hands, maintaining social distancing, wearing mask and gloves, avoiding unnecessary visits to crowded places, self-isolating even with minor symptoms and keeping yourself up to date on the latest information from trusted sources [1]. Nowdays, WHO has approved scientists and doctors to conduct the clinical trial with the combination of various FDA approved drugs to treat COVID-19 patients thus, to minimize the risks, time and cost of the drug development process, scientists/researchers are testing COVID19 patients by reusing already approved effective drug candidates [15]. Some of these repurposed drugs acting at different levels and stages of SARS-COV2 replication (Fig. 1) (such as membrane fusion and endocytosis, viral protease inhibitor, RNA-dependent RNA polymerase, TMPRSS2), anti-cytokine or immunomodulatory agents, convalescent plasma therapy and phytochemicals are discussed below;

Drugs Targeting RNA-Dependent RNA polymerase Inhibitor (RDRP)
Remdesivir

Remdesivir, a mono phosphoramidate prodrug of adenine nucleotide acts as an inhibitor of viral RNA polymerases. The drug was initially developed to combat the Ebola virus outbreak due to its low half-maximal effective concentration (EC50) and host polymerase selectivity [22]. Remdesivir exhibit potential antiviral effect against various other single-stranded RNA viruses such as pneumovirus, filoviruses, paramyxoviruses and the coronaviruses MERS-CoV and SARS-CoV [23, 24, 25]. From an animal experiment conducted in mice infected with MERS-CoV, it was reported that remdesivir can efficiently diminish the lung viral load, inhibited replication of the virus in the respiratory tissue, and reduced occurrence and severity of lung lesions [24]. Recently, Wang et al. [26] reported remdesivir as a potential therapy for COVID-19 with EC90and EC50 values of 1.76 μM and0.77 μM, respectively. Remdesivir is metabolized into its active form, GS-441524, that obscures viral RdRp and causes premature termination of viral RNA chain resulting in decreased viral RNA production [27]. Grein et al. [28] conducted a study by providing remdesivir on a compassionate-use basis to 61 Covid-19 hospitalized patients, who were provided remdesivir for 10-day, with an initial dose of 200 mg on day first and 100 mg on daily basis for the rest of the days of treatment. After 10 days, 68% oxygen improvement and 13% overall mortality were reported. Out of 61 patients, 32 (60%) reported adverse effects including increased diarrhea, hypotension, renal impairment, rashes and hepatic enzymes whereas 12 patients (23%) reported serious adverse conditions like acute kidney injury, multiple organ dysfunction syndrome, hypotension and septic shock. Remdesivir treatment was discontinued prematurely by four patients (8%) due to abnormalities like elevated aminotransferases, multiple organ failure, worsening of preexisting renal failure and maculopapular rash [28]. On 1st May 2020, FDA made remdesivir drug available for emergency against severe COVID-19 infection in hospitalized

adults and children. Dolin and Hirsch [29] reported that the utilization of remdesivir in people having severe COVID-19 infection reduced the recovery time from 15 days to 11 days among placebo recipients. Clinical trials are ongoing with remdesivir alone (NCT04292899, NCT04365725, NCT04323761, NCT04292730, NCT04280705, NCT04302766) or in combination with other drugs (NCT04410354, NCT04409262, NCT04401579, NCT04280705, NCT04321616, NCT04315948) to assess its safety and efficacy an anti-viral drug in COVID-19 treatment.

Favipiravir (Avigan TM)
Favipiravir (Avigan TM) (T-705; 6-fluoro-3-hydroxy-2-pyrazine carboxamide) is another anti-viral agent that acts as an inhibitor of viral RdRp activity. This drug was discovered by Fujifilm Toyama Chemical Co. Ltd (Japan) in 2014 to treat the patients infected with the influenza virus [30]. After entering the internal biota of the host cell, this drug undergoes phosphor-ribosylation to form active favipiravir ribofuranosyl-5'-triphosphate (favipiravir-RTP), which inhibits RNA polymerase activity of RdRp during viral RNA replication by interrupting the nucleotide incorporation process. Favipiravir is found effective against influenza viruses and other RNA viruses *viz.,* filoviruses, bunyaviruses and arenaviruses that cause fatal hemorrhagic fever [31]. Currently, clinical trials on this drug are being carried out in the UK, Italy and China for COVID-19 treatment, although a precise mechanism of this drug against COVID-19 is missing. Shannon *et al.* [32] performed deep sequencing of viral RNA after infecting vero cells with SARS-CoV-2 in the presence or absence of 500 μM favipiravir. They observed G to A and C to U transitions in the already low cytosine content of SARS-CoV-2 genome. Associated with this increase in mutation frequency, favipiravir has an antiviral effect on SARS-CoV-2, as illustrated by a decrease in viral RNA copy number, virus induced cytopathic effect and reduced yield of infectious particle. Altogether, these observations demonstrate that the mutagenic effect induced by favipiravir are responsible for its inhibitory effect on viral replication. An open-label non-randomized trial was conducted in China on 80 COVID-19 patients and a significant decline in SARS-CoV-2 viral clearance time was reported in patients treated with favipiravir in comparison to controls treated with lopinavir/ritonavir and adverse events rate were also less in patients receiving favipiravir [33]. *In vitro* study by Wang *et al.* [26] showed that the half-maximal effective concentration (EC50) of T-705 against SARS-CoV-2 was 61.88 μM/L in vero E6 cells and half-cytotoxic concentration (CC50) at over 400 μM suggesting that large concentration is required for the treatment to be effective. Results obtained from clinical and *in vitro* studies of favipiravir against COVID-19 demonstrated that there is a need of conducting further studies to assess the effectiveness of favipiravir against COVID-19. Several ongoing clinical trials of favipiravir alone (NCT04358549, NCT04336904, NCT04402203, NCT04333589) and in combination with other drugs (NCT04376814, NCT04310228, NCT04411433) will provide information on the effectiveness of this drug.

Ribavirin
Ribavirin (Guanosine analog) is one of the antiviral compounds that inhibit RdRp of various viruses including respiratory syncytial virus, hepatitis C virus and some viral hemorrhagic fevers. Its extensive use during the MERS and SARS outbreak may account for the efficacy in curing COVID19 infected patients. However, *in vitro* activity of Ribavirin against SARS-CoV was found to be limited and required a large amount to inhibit replication of virus, signifying increased dosage and combination therapy [22]. The high dosage of this drug in the SARS trials affected more than 60% of patients with hemolytic anemia [34]. Apart from this, its use in the largest MERS observational trial raised some safety concerns as about 40% of patients taking ribavirin along with interferon reported the need for blood transfusions [35]. Also, ribavirin is contraindicated in pregnancy as it is a known teratogen. Studies suggested that severe doses of ribavirin cause hematologic toxicity, but if used in combination with other drugs it may provide clinical benefits against COVID-19 [36].

Inhibitors of membrane fusion and endocytosis
Chloroquine and Hydroxychloroquine
Chloroquine and hydroxyl-chloroquine are quinine-related compounds that have been utilized for malaria treatment and chronic inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis (RA) [37]. The anti-inflammatory and anti-viral properties, wide availability and low cost make these drugs a potential candidate against treating COVID-19. The efficiency of Chloroquine and hydroxychloroquine has been attributed to various mechanisms. For example, they decrease the acidification in the intracellular compartments, resulting in inhibition of the nucleic acid replication, virus assembly, viral protein glycosylation and exocytosis process. These drugs also hinder the glycosylation of host cell ACE-2 receptors [38, 39]. Along with this, the immune modulatory effects of these drugs have also been reported [40, 41]. Hydroxychloroquine (EC50 = 0.72 μM) has been reported to be more effective than chloroquine (EC50 = 5.47 μM) [42], as the presence of hydroxyl group in hydroxyl-chloroquine reduce its permeability to blood-retinal barrier and allows quick clearance from retinal pigment cell, thereby resulting in a reduced danger of retinal toxicity in comparison to chloroquine [43].

On March 22, 2020, the National Task Force for COVID-19 by the Indian Council of Medical Research (ICMR) provided recommendations for use of hydroxychloroquine for prophylaxis of SARS-CoV-2 infection in the high-risk population. The US FDA has also issued emergency authorization for hydroxyl-chloroquine use to treat COVID-19 patients [44]. A study reported that hydroxychloroquine did not enhance negative conversion rates, but had decreased clinical symptoms through the recovery of lymphopenia and anti-inflammatory properties [45]. A recent study on COVID-19 patients who were receiving 600 mg of hydroxyl-chloroquine daily and then the viral load in the nasopharyngeal swabs was tested, showed that hydroxyl-chloroquine treatment was significantly associated with viral load disappearance/reduction in patients, and its effect was reinforced by its association with azithromycin but study suffered from limitation as the sample size was small and most of the data was from same research group and [46]. Various potential side effects of chloroquine and hydroxychloroquine have been reported including cardiac arrhythmias, muscle weakness and retinopathy [41]. Recently, the literature also demonstrated the reports of ototoxic effects after chloroquine and hydroxychloroquine treatment [47]. From all the above reports it can be concluded although chloroquine and hydroxychloroquine are affordable and ideal therapies

against COVID-19 but suffers from health concerns and more clinical trials should be conducted to uncover their efficacy. Large numbers of clinical studies are ongoing which will offer new evidence of the role of chloroquine and hydroxychloroquine in clinical practice for COVID-19 (NCT04340544, NCT04351620, NT04329832, NCT04345692, NCT04382625). The synergistic effects (antiviral, anti-inflammatory and immunomodulatory action) of these two drugs make them a good choice that can be considered in the treatment of the COVID-19. Apart from this, both the drugs are cheap, easily available and could have a vital role in the treatment of respiratory distress due to the COVID 19.

Umifenovir (Arbidol)
An indole derivative, Umifenovir (Arbidol™) [48], prevents the virus entry inside the host cell by inhibiting membrane fusion between the viral envelope and cytoplasmic membrane of host cell by selectively inhibiting the process of clathrin-mediated endocytosis, resulting in the prevention of virus infection [49, 50, 51]. Umifenovir is licensed in Russia and China for treating infection caused by influenza viruses, oral prophylaxis and other respiratory viruses. This drug has been shown to inhibit SARS-CoV-1 and SARS-CoV-2 *in vitro* as well [48, 7], therefore it is gaining a lot of interest in treating COVID-19. A study conducted on sixty-nine COVID-19 patients found that arbidol could improve discharge rate and lower down the mortality rate [52]. Another study, which compared the lopinavir-ritonavir (LPV-RTV) group along with the umifenovir shown that a combination of LPV-RTV and umifenovir enhanced negative conversion rate of SARS-CoV-2 and also improved chest CT scan results in 7-day [53]. A study conducted by Chen *et al.* [54] reported that this drug has inferior results as compared to favipiravir in terms of recovery of patients from clinical symptoms. Lian *et al.* [55] said that for non-ICU COVID-19 patients, arbidol might not be able to increase SARSCoV-2 clearance nor it can improve prognosis in comparison to the reference group. However, all the studies described above are retrospective studies having controversial results. The randomized and open-label trial (NCT04260594), trying to find out the effect of umifenovir in china may help to investigate the safety and efficacy of this drug to combat COVID-19.

Inhibitors of proteases
Lopinavir-Ritonavir
Lopinavir is an inhibitor of chymotrypsin-like protease which plays a vital role in viral RNA processing and is FDA approved drug against HIV [56, 57]. Due to its poor oral bioavailability, it is formulated exclusively in combination with ritonavir. Ritonavir acts as boosting agents by inhibiting the enzymes cytochrome P450 3A that are required for the metabolism of lopinavir and thus resulting in its increased half-life [58]. *In vitro*, studies have shown antiprotease activity of lopinavirritonavir against other novel coronaviruses such as SARS. A study compared 111 SARS patients treated with ribavirin alone and 41 patients treated with lopinavir/ritonavir and ribavirin, combined therapy had less risk of ARDS and death [56]. Lopinavir-ritonavir was investigated in Wuhan, China, where 400 mg/ 100 mg dose of lopinavir-ritonavir were given daily to COVID19 patients for two times. Lopinavir-ritonavir treatment failed to show earlier clinical improvement as it caused severe serious issues like GI distress like nausea and diarrhea along with the hepato-

toxicity but it showed a potential advantage in many secondary outcome parameters [59]. The conclusion and limitations of the study can benefit and guide further research in gaining success in COVID-19 treatment. Such research suggests the earlier use of drugs, different dose and duration, clinical endpoint, blind RCT, combination therapy and larger sample size. A report from Korea [60], reported that lopinavirritonavir dosage significantly reduces viral replication and significantly improved symptoms during the treatment but this study included one patient in the starting phase of the outbreak, however far more proofs are required to prove the clinical efficacy of this drug based on highly controlled research trials. Hung *et al.* [61] analyzed the safety and efficacy of combined interferon beta-1b, ribavirin and lopinavir-ritonavir (NCT04276688) for COVID-19 treatment and observed that this therapy was very much safer and better as compared to lopinavir-ritonavir monotherapy in decreasing the symptoms and reducing the viral shedding in COVID-19 patients with little mild to more moderate infection, but the study suffered from various drawbacks, the trial was an open-label, without a placebo group and confounded by a subgroup omitting interferon beta-1b within the combination group and there was the absence of critically ill patients in trail and trail. Clinical trials are ongoing with Lopinavir/Ritonavir alone (NCT04321174, NCT04372628, NCT04455958) or along with other drugs (NCT04499677, NCT04330690, NCT04376814). Darunavir is another HIV protease inhibitor that was announced by researchers in China to inhibit SARS-CoV-2 infection *in vitro* [7]. Clinical research and further trials of darunavir/cobicistat in China (NCT04252274) and darunavir/cobicistat vs. lopinavir/ritonavir (NCT04425382) in Qatar is underway.

Inhibitors of tmprss-2
Camostat mesylate (CM)
Camostat mesylate (CM) is an approved drug and is used in Japan to treat reflux esophagitis and chronic pancreatitis [62]. As reported by Hoffmann *et al.* [63], SARS-CoV-2 uses TMPRRS2 for priming of its spike proteins and CM, an inhibitor of TMPRSS2, blocks the entry of SARS CoV-2 in lung cells *in vitro*. The efficacy of the drug in cell cultures has already been demonstrated in various studies [63, 64, 65]. Therapeutic efficacy in COVID-19 patients still has to be tested in clinical trials, however, the major benefit of this drug is that it can save the lives of many people even those who belong to very poor families because of its low cost or affordable price [62]. Some relevant trials registered at Clinical trials.gov include CM alone (NCT04321096, NCT04353284, NCT04455815, NCT04435015, NCT04321096, NCT04470544), or in combination with hydroxyl-chloroquine (NCT04338906) or combination of treatment with hydroxyl-chloroquine, ivermectin, azithromycin (NCT04374019).

Nafamostat mesylate (NM)
Nafamostat mesylate (NM) is one of the most potent serine protease inhibitors possessing anti-cancerous and antiviral properties and is used to treat acute pancreatitis [66]. According to the new research, Nafamostat can prevent spike protein-mediated entry of SARS CoV2 into host cells with near about 15 fold more efficiency as compared to CM, with a 50% effective concentration [EC50] in the low nano-molar range [67]. The registered trials at clinicaltrials.gov include (NCT04418128, NCT04352400, NCT04390594).

Anti-cytokine or immuno-modulatory agents
Tocilizumab

Tocilizumab is a monoclonal antibody against interleukin-6 (IL-6), which play role in "cytokine storm", which is out of control, runaway immune response associated, multiple organ dysfunction, cardiovascular collapse and rapid death in some COVID-19 patients. This drug is FDA approved to treat rheumatoid arthritis (RA) and cytokine release syndrome [37]. Retrospective studies reported improved clinical symptoms after treatment with tocilizumab in COVID-19 patients [68, 69, 70]. A study conducted in Italy, on one hundred patients reported that patients with coronavirus disease (having high fever, shortness of breath thus had respiratory failure) along with the hyperinflammatory response responded to

tocilizumab immediately and had clinical improvements in their health [71]. By seeing the success of previous studies a large number of trials of tocilizumab alone or with other drugs, are underway (NCT04445272, NCT04479358, NCT04317092, NCT04310228, NCT04345445, NCT04412772, NCT04332094, NCT04377659, NCT04359667).

The matter of concern is that tocilizumab has many side effects like intestinal perforation, candida infection, and disorders of lipid metabolism [72, 73, 74]. Several other registered clinical trials are being conducted globally to assess the efficacy of the various potential drug against COVID-19 (Table 1).

Table 1: Clinical trials identified at clinicaltrials.Gov (For various potential drugs against COVID-19

Drug	Drug originally used for	Clinical Trial in COVID-19	Status
Corticosteroids	Reduce the host inflammatory responses in the lungs, which may lead to ARDS	NCT04374474,NCT04360876,NCT04416399, NCT04359511	Not yet Recruiting
		NCT04348305,NCT04344288,NCT03852537, NCT04361474,NCT04344730,NCT04325061, NCT04327401,NCT04355637,NCT04395105, NCT04355247	Recruiting
		NCT04374071, NCT04273321	Completed
Azithromycin	Antibiotic fighting against various infections caused by susceptible bacteria	NCT04381962, NCT04329832, NCT04332107	Recruiting
Nitric Oxide and Epoprostenol	Pulmonary vasodilator agents	NCT04388683,NCT04338828,NCT04305457, NCT04337918, NCT04306393	Recruiting
		NCT04383002, NCT04421508, NCT04397692, NCT04312243, NCT04420741	Not yet Recruiting
Sarilumab	Modified human IL-1 receptor antagonist (IL-1RA) against rheumatoid arthritis (RA)	NCT04315298,NCT04357808,NCT04359901, NCT04327388 NCT04386239, NCT04357860	Recruiting Not yet Recruiting
Anakinra	Modified human IL-1 receptor antagonist (IL-1RA)	NCT04366232, NCT04357366 NCT04362111, NCT04341584	Recruiting Not yet Recruiting
Nitazoxanide	Antiprotozoal agent with an antiviral capacity	NCT04423861 NCT04406246, NCT04348409, NCT04343248	Not yet Recruiting Recruiting
Traditional Chinese Medicine	A total of eight medicinal herbs and proven to be clinically effective for the treatment of upper respiratory tract infections, vastly used for influenza diagnosis	NCT04323332, NCT04285190 NCT04251871, NCT04388644	Not yet Recruiting Recruiting
		NCT04306497	Completed
Ibuprofen	Propionic acid-derived non-steroidal anti-inflammatory drug (NSAID)	NCT04382768, NCT04334629 NCT04383899	Recruiting Not yet Recruiting
TMC310911 (ASC- 09)	Protease inhibitor (PI) used against HIV-1 infections	NCT04261270	Recruiting
		NCT04261907	Not yet Recruiting
Interferon alfa-2a and alfa-2b	Approved for the treatment of Hepatitis B virus (HBV) and Human Coronavirus (HCV)	NCT04379518	Not yet Recruiting
Galidesivir	Antivirus agent against many RNA viruses, like SARS and MERS2	NCT03891420	Recruiting
Colchicine	Anti-inflammatory drug	NCT04392141,NCT04375202,NCT04355143, NCT04360980,NCT04350320,NCT04328480, NCT04326790,NCT04322565,NCT04403243, NCT04363437, NCT04322682,NCT04367168	Recruiting
Indomethacin	Non-steroidal anti-inflammatory drug (NSAID)	NCT04344457	Recruiting
Vitamin C	Positively affects the development and maturation of Natural killer cells and T lymphocytes and involved in the immune response to viral agents	NCT04363216, NCT04401150 NCT04264533, NCT04323514, NCT03680274, NCT04357782, NCT04344184	Not yet Recruiting Recruiting

Convalescent plasma therapy

Convalescent plasma (CP) therapy is a kind of immunotherapy used for the treatment against pandemic infectious diseases like H1N1, SARS and MERS with high safety and efficacy [75, 76, 77, 78].

This therapy is based on the usage plasma which has neutralizing antibodies of the recovered patients from COVID-19 to reduce the symptoms and mortality rate. Hence, convalescent plasma transfusion is gaining a lot of attention in

the wake of the COVID-19 pandemic. FDA also suggested that the intervention of CPT might provide a better clinical treatment of COVID-19. As per FDA recommendations, the plasma must be collected from a donor who showed no symptoms for the last 14 days and had negative recent COVID-19 results. The first study conducted by Duan *et al.* [79], reported the clinical improvement by CP therapy in terms of high fever, shortness of breath and cough along with the chest pain but there were no serious side effects, researchers

also suggested the clinical significance of CP therapy, needs more research in larger highly controlled trials. After COVID-19 was declared a global pandemic, many scientists suggested that CP could be used as a promising therapeutic strategy to alleviate the infection's symptoms [80, 81, 82]. Based on these positive results of CP therapy various ongoing trials are registered on clinicaltrails.gov, some of that include (NCT04323800, NCT04345679, NCT04345523, NCT04372979, NCT04380935, NCT04425915, NCT04334876, NCT04377568, NCT04476888, NCT04342182, NCT04403477).

Phytochemicals/natural agents targeting COVID-19
Although the conventional drugs discussed above are giving promising therapeutic potential but they are not very encouraging and toxicity remains an inevitable issue causing serious adverse effects. Inspired from the earlier trends, plants derived drugs are bringing a new revolution to the vaccine development and it has been reported that approximately 85% of the dwellers of china recovered from the COVID-19 infection by mixed treatment with traditional Chinese medicine (TCM) [83]. On April 14, 2020, in a press conference, a Chinese official announced the three potential herbal drugs Lianhuaqingwen and Jinhuaqinggan for treating mild and Xuebijing drugs to fight for a severe condition associated with the viral infection [84]. On January 29, 2020, Indian nationals have also released an advisory to utilize 4 herbal plants and 11 Unani medicines in combination with conventional allopathic drugs to combat the emerging danger of the novel coronavirus [85]. So far, there is no high quality, scientifically or clinically proved herbal drug against COVID-19 and action mechanism *in vivo* have also not been reported yet in any high-value peerreviewed journal, but several phytochemicals and natural agents are being studied for their chemical action against COVID-19 through molecular docking studies. For an illustration, by using molecular docking analysis [86], have predicted the protease inhibitor activity of several natural compounds (βsitosterol, glycyrrhizin, tryptanthrine, bicyclogermecrene, indirubin, indigo, indican, hesperetin, berberine, chrysophanic acid and β-caryophyllene) that can emerge as potential drug candidates inhibiting viral protease. Apart from this, various flavonoids [87], alkaloids [88], caffeic acid phenolic ester [89], and other potent phytochemical derivatives from ayurvedic herbal plants *viz.* turmeric, neem, ashwagandha and ginger extract are found to have potent 3-Chymotrypsin Like (3CL) cysteine protease inhibiting activity and low toxicity as compared to conventional anti-malarial drugs that are currently being utilized for COVID-19 treatment across the globe [90]. Patanjali India in one of their molecular docking study Led by CEO Acharya Balakrishna on ashwagandha (*Withania somnifera*) has reported that herb with combination with the hydroxyl-chloroquine can be effective against blocking the entry of the highly infectious novel coronavirus into the human body [91]. Although herbal remedies and drugs are found to be effective against lowering the viral impact and boosting the immunity but there is no proper mechanism and clinical trials to support the exact mechanism of the leading compounds against the virus. Promising docking outcomes of ongoing studies on natural products and their combination with other potential drugs might help soon to make an effective treatment to combat COVID-19. Various natural compounds and their combinations as mentioned in the Indian traditional health systems have been reported to exhibit potent immuno-modulatory and immune-boosting effects [92], screening these compounds may provide a treatment to combat COVID-19.
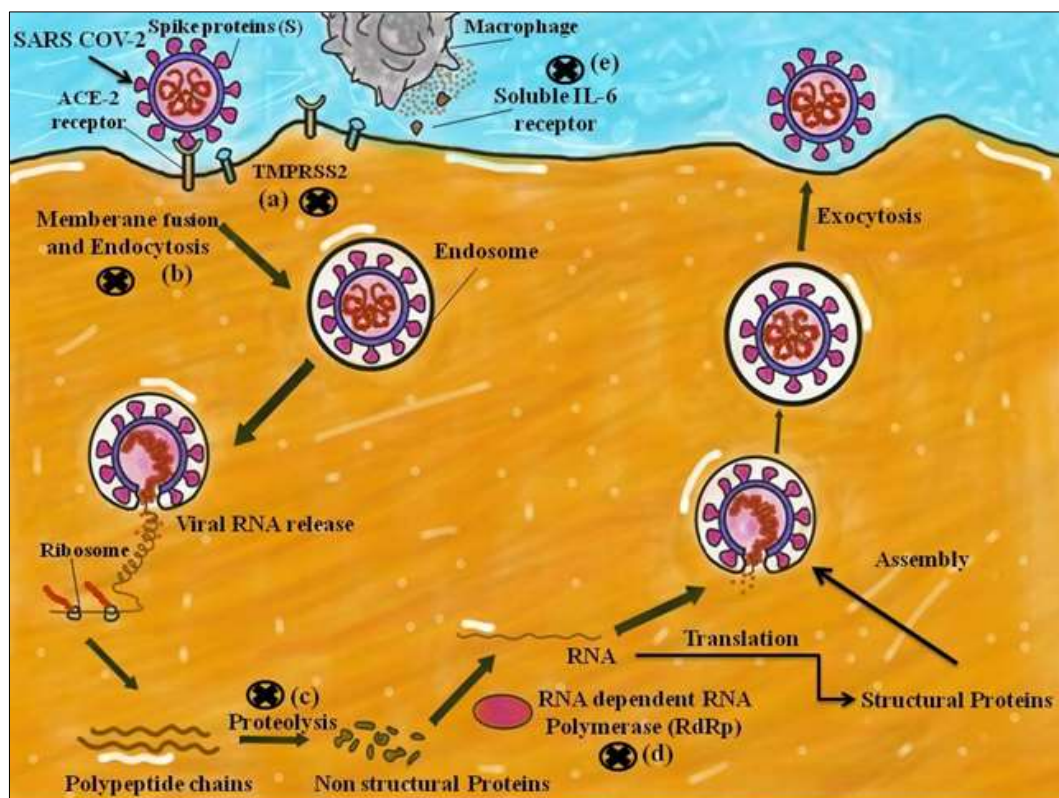

Fig 1: SARS-CoV-2 lifecycle and mechanisms of selected repurposed drugs that may combat the emerging COVID-19 (a) Camostat mesylate and Nafamostat mesylate (b) Chloroquine, Hydroxychloroquine and Umifenovir (c) Lopinavir/Ritonavir and Darunavir (d) Remedesivir, Favipiravir and Ribavirin (e) Tocilizumab and Sarilumab

Conclusion

COVID-19/SARS-CoV-2 is the third spillover of animal coronavirus to humans, that has emerged as the most petrifying and intense viral infection to be managed by the human race. Till now, millions of people around the world have become victims of COVID-19 and lakhs of people have lost their life. This "Pandemic Outbreak" prompted the physicians and researchers to use "Drug repositioning strategy", to stop the spread of this pandemic infection until the suitable vaccination is developed. Some repurposed drugs and ongoing clinical trials discussed in our review may help in improving the clinical outcomes of critical COVID-19 patients. Along with repositioning strategy, the drug designing process also races against time, to find a new drug against COVID-19 beginning from drug design in silico, ending with clinical trials. Spike glycoprotein and ACE2 enzyme used by SARS-CoV-2 at the atomic resolution has now been determined. These discoveries are expected to prompt quick efforts to develop antibodies and vaccines. However, this process requires time and can be obstructed by the potential for blunted antigenicity of epitopes due to the genetic drift of the virus. Further researches should be conducted toward the investigation of SARS-CoV-2 in reasonable creature models, for uncovering its replication mechanism, transmission and pathogenesis. Apparently, in addition to the drugs currently prescribed to treat COVID-19, more studies are required to confirm the use of certain drugs like corticosteroids, which have conflicting reports regarding their safety and efficacy.

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