



A Review on Drug Repurposing: A Strategy to Treat Human Coronavirus Disease (COVID-19)

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Authors' contributions

This work was carried out in collaboration among all authors. Authors SS and AB designed the study. Authors NB and SKM managed the analyses of the study. All Authors managed the literature searches. All authors wrote, read and approved the final manuscript.

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ABSTRACT

Novel coronavirus pandemic has created a massive public health emergency causing around 1.85 million deaths world-wide till 5th January, 2021. New SARS (Severe Acute Respiratory Syndrome) coronavirus strain known as SARS-CoV-2 is the causative agent which infected more than 84 million people across the globe. Current epicentre of the pandemic has shifted to Europe and United States and Indian subcontinent from its place of origin-Wuhan City, Hubei province in China. Due to limited availability of vaccines against SARS-CoV-2 or its related β -coronavirus (SARS-CoV or MERS-CoV), mass immunization is currently not possible. Thus, use of curative therapies could be the only choice of intervention. Therefore, rapid treatment of millions of COVID-19 patients in limited time can only be achieved by repurposing pre-approved and existing drugs. Network-based high-throughput computational approach has also predicted several repurposable drugs. Cheaper,

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less toxic and well tolerated drugs such as antimalarial drugs: Chloroquine (CQ) & Hydroxychloroquine (HCQ); antiviral drugs: Remdesivir, Lopinavir and Ritonavir are among many others that have been proposed for the COVID-19 treatment. Presently limited controlled clinical trials are underway to assess the therapeutic outcome of these repurposed drugs along with novel candidate vaccines and medicines. Beside these, convalescent plasma therapy has also emerged as potential therapeutic approach being tested in several countries. This review focuses on few of the promising repurposed drugs and their outcomes that are presently under evaluation for their safety and efficacy against the coronavirus disease 2019 (COVID-19).

Keywords: COVID-19; drug repurposing; remdesivir; lopinavir; ritonavir; hydroxychloroquine.

1. INTRODUCTION

A group of cases of pneumonia of unknown cause noticed in Wuhan City, Hubei Province of China was informed to World Health Organization (WHO) on 31 December 2019. Later on 30 January 2020, the WHO Director-General following the recommendations of the Emergency Committee declared that this outbreak represents a Public Health Emergency of International Concern (PHEIC). WHO officially declared this viral infection (Coronavirus disease-19, also known as COVID-19) as pandemic on 11th March, 2020 (Rolling updates on COVID-19: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen>). The causative agent is a novel coronavirus, which was provisionally named as 2019-nCoV and later re-named as SARS-CoV-2. This is a positive-sense single stranded RNA (+ssRNA) virus, and bats are natural primary reservoir [1]. Till date, WHO reported 84,233,579 confirmed cases with 1,843,293 confirmed deaths in nearly across 200 countries, areas or territories (as updated on 05 January 2021, 09:54am CET, WHO coronavirus disease (COVID-19) Dashboard) [2]. As of now, more than 1493 clinical trials are in progress and 233 clinical trials were completed with an aim to identify or test various pharmaceutical interventions against COVID-19. More than 90% of these trials include already FDA approved drugs for repositioning against COVID-19 infection (<https://clinicaltrials.gov/ct2/results?recrs=aef&cond=COVID-19>) [3]. However, drug repurposing approach of withdrawn or already permitted drugs for the treatment of new diseases has proved promising and valuable for the pharmaceutical industry since several decades [4]. Noble laureate James Black once quoted 'The most fruitful basis for the discovery of a new drug is to start with an old drug' [5]. Drug repurposing, also known as drug repositioning, reprofiling or therapeutic switching is a way of finding or developing new clues for existing drugs

or biologics. The process of clinical development and regulatory review of new therapeutics is a laborious and expensive venture that costs nearly one billion US dollars. However, the cost of bringing repositioned drug to the market is around 60% cheaper than developing a novel drug [4]. Further the new drug *de novo* development requires a basic time estimated to be 10 to 17 years [6]. Repurposed drugs or biologics have the benefit of lower development costs and time, improved dosing or scheduling, better compliance and decreased launch time due to earlier collected pharmacokinetic, toxicology profile and safety approval process. This existing pharmacopoeia for repositioning candidates uses a cross-disciplinary focus on the discovery of the mechanisms of disease and molecular pathways involved, followed by matching of disease pathways with suitably targeted therapeutic agents. More and more biopharmaceutical companies are scanning through this novel discovery technology and increasing number of repositioning success stories are making their way [7].

As the COVID-19 pandemic spreads at an exponential rate, affecting persons of all ages, ethnicities and medical histories, pharmaceutical companies and research institutes have accelerated their efforts to create novel drugs and vaccines, and have begun several clinical trials for potential treatments. The WHO draft landscape of COVID-19 candidate vaccines sheet shows 3 candidate vaccines in clinical evaluation (Adenovirus Type 5 vector and LNP-encapsulated mRNA candidate vaccines) and 60 candidate vaccines in preclinical evaluation (Published on 11 April 2020; https://www.who.int/blueprint/priority-diseases/key-action/Novel_Coronavirus_Landscape_nCoV_11_April2020.PDF?ua=1) [8]. Several biotech laboratories have initiated trials of promising candidate drugs and intervention treatments. Some of the probable repurposed candidates

that are under clinical trials for COVID-19 treatment are hydroxychloroquine, chloroquine, human immunoglobulin, interferons, arbidol, oseltamivir, remdesivir, carrimycin, favipiravir, bevacizumab, methylprednisolone, thalidomide, vitamin C, bromhexine, pirfenidone, fingolimod, danoprevir, darunavir, cobicistat, xiyanning, ritonavir, lopinavir, and traditional Chinese medicines (TCM) [9]. Further using *in silico* molecular modelling screening and structure based drug design, new potential therapeutic targets and interventions have been elucidated. These candidate drugs, with significant safety data in humans are available, could rapidly advance into the clinic on a much quicker timescale than novel therapies for treatment of present coronavirus patients.

With this background, in this review we discussed three potential drugs and combinations that could be used to tackle COVID-19. These drugs were previously approved by FDA and are being widely used in treatment of different infective diseases.

2. NETWORK BASED REPURPOSED DRUGS

High-throughput genomics and computational biology approach facilitate novel testable hypothesis for systematic drug repositioning. Primarily, this method uses the curated library of already approved drugs and/or active therapeutic compounds to predict their possible use in the treatment of disease of concern. Potential drugs are computationally tested against druggable targets that include critical viral and human proteins. Surface Spike protein (S-protein) coded by S gene and replicase complexes, a non-structural proteins (Nsp) coded by ORF1a/b of SARS-CoV-2 implicated in cellular entry of viral particle and viral replication respectively, have been considered for such investigations [10]. However, random and rapid evolution of viral genome very often makes it difficult to target a protein of viral origin. Consensus amino acid sequence of SARS-CoV-2 proteins is presently available and for most of its protein, there are considerable homology with related coronavirus, such as SARS-CoV and MERS-CoV. Recent initiative also crystalized few SARS-CoV-2 proteins, which include Nsp3, Nsp9, Nsp10-16, N-terminal RNA binding domain of nucleocapsid protein [11-14]. Therefore, identification or prediction of interaction of key viral proteins with human proteome and protein-protein interaction

(PPI) network is being explored for network based drug repositioning.

A recent network based drug repositioning study utilized drugs which are already in use to treat related viral infections and identified 16 candidate drugs and 3 potential drug combinations that can be used for treating SARS-CoV-2 infection. This finding was based on previously published reports of drug targets and involvement of these drug targets in human protein interactome. This finding was not testified by any molecular study and thus molecular validation before clinical trial was recommended [15]. Another molecular study based on affirmed 332 PPIs between SARS-CoV-2 and human proteome, identified 67 human protein targets. Network based computational investigation further identified 69 drugs or compounds against these 67 human proteins, which were previously approved by FDA or under clinical trials [16].

Cellular receptor ACE2 is known for its role in entry of SARS coronaviruses (including SARS-CoV-2). A recent study investigated 222 ACE2 associated PPIs encompassing 193 genes, and identified 36 potential drugs that include Nimesulide, Fluticasone Propionate, Thiabendazole, Photofrin, Dianosine and Flutamide among others for treatment of SARS-CoV-2 infection [17]. Subsequent study by Li et al., 2020, identified 34 human proteins that interact with SARS-CoV-2 proteins and fall in 24 disease-related human pathways. This approach identified 30 potential repurposable drugs including Pseudoephedrin, Andrographolide, chloroquine, Abacavir and Thalidomide [18].

3. REPURPOSING OF KEY ANTI-MALARIAL AND ANTI-VIRAL DRUGS FOR COVID-19 TREATMENT

3.1 Antimalarial Chloroquine and Hydroxychloroquine

Quinoline-containing drugs such as chloroquine and quinine have been drug of choice for anti-malarial chemotherapy with a long and successful history [19]. Malaria is one of the most deadly parasitic diseases of mankind, which is caused by a mosquito-transmitted parasite, *Plasmodium falciparum*. Chloroquine (CQ) and its hydroxyl analogue, hydroxychloroquine (HCQ) are weak bases with almost 50 years long use as standard antimalarial agents. Hydroxychloroquine (HCQ) sulphate was first

synthesized in 1946. The animal toxicity and pharmacokinetic studies suggested much less (~40%) toxicity than CQ [20]. At present, HCQ is also widely used to treat autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. However recent studies have brought global attention to the promising benefit of CQ in the cure of patients infected by the novel emerged coronavirus (SARS-CoV-2). CQ is used widely for treatment against sensitive *Plasmodium* parasites although Artemisinin Combination Therapies (ACTs) are being used increasingly, especially for *Plasmodium falciparum* treatment in chloroquine-resistant regions [21]. The intraerythrocytic malaria parasite degrades the host hemoglobin in the digestive vacuole to acquire essential amino acids for its growth and division. This parasite subsequently polymerizes and detoxifies the heme (hemoglobin metabolite) to form hemozoin, a non-toxic molecule. CQ drugs (N4-(7-Chloro-4-quinolinyl)-N1,N1-diethyl-1,4-pentanediamine) are known to accumulate in the acidic food vacuoles of intraerythrocytic parasite by a weak base mechanism. CQ is further reported to interference with the hemo-polymerisation process leading to parasite death [22]. However, the precise molecular mechanism of action still remains unclear. Except for its bitter taste, CQ is considered safe and well tolerated by people of all ages, pregnant women and young children. It has a low incidence of serious adverse cases or contraindications reported. HCQ is prescribed for either prevention or treatment of malaria and also used as an arthritis medicine. Chloroquine resistance has spread throughout the malaria endemic world, Thailand (in 1957), Colombia (in 1959), Southeast Asia, India and Africa (in 1978). Since 2006, WHO has strictly recommended ACTs for treatment of uncomplicated *P. falciparum* malaria [23-24].

Apart from this well-known anti-malarial effect, CQ and HCQ have got extended attention in treatment of other infectious diseases due to their interesting biochemical properties, which have been evaluated against few viral infections in preclinical studies. CQ has shown the antiviral activity by inhibiting pH-dependent steps of the replication of several viruses including members of the retroviruses, flaviviruses, and coronaviruses [25]. The general proposed mechanism of viral inhibition by CQ or HCQ is by inhibiting the replication of different viruses either at the early stages by interacting with the endosome-mediated viral entry or late stages of viral replication [25]. Preliminary *in vivo* studies

suggest anti-HIV-1 putative activity of CQ alone or in combination with antiretroviral drugs [26]. Recent study reported that two drugs, remdesivir (GS-5734) and chloroquine (CQ) phosphate, competently inhibited SARS-CoV-2 infection tested against a clinical isolate of 2019-nCoV *in vitro* [27]. The inhibitory studies of CQ suggest that the effective concentration EC_{90} against the SARS-CoV-2 infection in Vero E6 cells was 6.90 μ M [26] while the half-maximal inhibitory concentration (IC_{50}) against SARS-CoV replication in Vero E6 cells was 8.8 μ mol/L [28]. These *in vitro* CQ inhibitory concentrations are substantially lower than the plasma concentrations that are reached in individuals undergoing prescribed treatment with CQ at a dose of 25 mg/kg over 3 days [29]. However limited *in vitro* data and lack of actionable data from large-scale clinical trials from the use of CQ and HCQ against SARS-CoV-2 have raised major concerns worldwide on drug's safety and efficacy in treatment of patients infected with COVID-19 and its potential side-effects of affecting patients' cardiovascular condition. Hence, the scientist needs to do extensive randomised clinical trials for pre-exposure and post-exposure prophylaxis and treatment regimes of CQ and HCQ. Chloroquine phosphate has presented apparent efficacy against COVID-19 associated pneumonia in multicenter clinical trials conducted in China. This treatment regime showed reduction in duration of symptom, severity of pneumonia (showing radiological improvement) and virus-negative seroconversion without any severe side effects [30]. On the contrary, a Chinese pilot study randomized controlled trial on 30 patients showed no significant effect of HCQ in treating COVID-19 [31]. The results of an open label non-randomized clinical trial (small sample size study) in France showed that hydroxychloroquine treatment caused a significant reduction/disappearance of the viral load in the COVID-19 patients and its effect is reinforced by Azithromycin addition [32]. In a recent case study, 67 years old COVID-19 positive patient with severe cardiovascular complications were treated successfully with combinations of pericardiocentesis, colchicine and corticosteroid along with HCQ [33]. In USA, a 61 year old kidney transplant patient with severe comorbidities was successfully treated for COVID-19 infection with HCQ and single dose of tocilizumab [34]. A recent study in Switzerland reported that HCQ induced severe haemolysis crisis in a Glucose-6-phosphatase dehydrogenase (G6PD) deficient patient while

being treated for COVID-19 [35]. However, recent development in clinical trial studies (Clinical trial number: NCT04322123, NCT04308668) have shown no significant effect of hydroxychloroquine alone or in combination with azithromycin in patients with mild to moderate COVID-19 symptoms [36-37].

3.2 Antiviral Remdesivir

Remdesivir (GS-5734) is a nucleoside analog, which target viral RNA-dependent RNA polymerase (RdRp) and inhibits viral transcription and replication whereas having no significant effect on human RNA Pol II and human mitochondrial RNA polymerase [38-39]. Remdesivir, which was synthesized for the lethal Ebola virus (EBOV) infection treatment, had been effective against multiple strains of Ebola in cell based assay and rhesus monkey model of Ebola virus disease. However, it did not show efficacy in randomised human clinical trial for Ebola treatment [40]. Other than EBOV, Remdesivir also possesses broad-spectrum activity against paramyxovirus, filoviruses, Nipah virus and coronaviruses infection confirmed by numerous *in vitro*, mouse and nonhuman primate model studies [27, 41]. The possible mode of action of Remdesivir is a delay chain termination mechanism [42]. Remdesivir is a monophosphoramidate equipped with the CN group prodrug of an adenine derivate (C-adenosine nucleoside analogue of GS-441524, a parent nucleoside capable of inhibiting replication of coronavirus strains SARS-CoV, MERS-CoV and Bat-CoV in primary human airway epithelial cells) and bears a similar chemical structure as HIV reverse transcriptase inhibitor, tenofovir alafenamide [27, 38-39, 42-43].

In context specifically to coronavirus, Remdesivir (GS-5734) reported potent activity against SARS-CoV and MERS-CoV infection [44]. It has been observed that treatment of remdesivir decreases lung virus titers and improved pulmonary function when administered 1 day after onset of disease whereas when administered 2 days after the onset of disease, the survival rate of mice were relatively low in Ces1c(-/-) mouse model [45-46]. The Remdesivir treatment also improves lung function and pathological damage to lung by reducing viral load in the MERS-CoV infected lung tissue in mice [43]. Resistant MERS-CoV strains showed sensitivity to the higher concentration of Remdesivir indicating its possible effectiveness in the wide-range treatment of CoV infections

with divergent RNA-dependent RNA polymerase activity [39, 42, 44]. *In silico* analysis of RdRp enzyme of SARS-CoV-2 targeted by anti-polymerase drugs suggests Remdesivir as one of the potent drug against the COVID19 [47]. Remdesivir has been identified to target and form a stable complex with SARS-CoV-2 viral polymerase nsp12. Since, T680 in nsp12 of SARS-CoV-2 is likely to form hydrogen bonds with incoming natural NTP, remdesivir also keeps an intact ribose group and hence 2' hydroxyl group of remdesivir can form stable hydrogen bond with T680 in SARS-CoV-2 nsp12 like a native substrate. Moreover, motif F also contain a hydrophobic side chain of V557, which stack with and stabilize the RNA uridine base of +1 template to base pair with the incoming ppp-remdesivir (triphosphate remdesivir) [48]. Recent *in vitro* study suggests low micromolar inhibitory concentration with high selectivity index (EC₅₀=0.77µm, CC₅₀>100µm. SI>129.87) in Vero E6 cells infected with SARS-CoV-2 and efficacy of the investigational antiviral remdesivir in first hospitalized patient diagnosed with COVID-19 in the United States [27, 43, 49]. Earlier phase I trial have shown no significant adverse effect like cytotoxicity, hepatorenal toxicity after intravenous injection of remdesivir till dose of 150 mg per day for 7-14 days in subjects indicating good safety and pharmacokinetics properties even in Phase II trial on Ebola infected patients [40, 46]. The treatment protocol of remdesivir followed for treatment of COVID19 infection in patient's involved intravenous injection for total duration of 10 days with 200 mg dose administered on 1st day followed by 100 mg per day for rest of 9 days [50-52]. One of the case study reports 40 years old male COVID19 patient, who on being treated with HCQ and azithromycin since 5th day of the illness till 9th day showed no symptomatic improvement. He was then put on remdesivir from 13th day and showed clinical improvement within 48 hours, indicating that remdesivir may be effective at later stages of severe COVID19. However, this study could not directly indicate the efficacy of remdesivir as the patient was initially on HCQ and azithromycin treatment for 5 days [50]. A cohort study revealed clinical improvement in 68% of hospitalized severe COVID19 patients treated with compassionate use of remdesivir treatment with an effectiveness period of 5 days. Hence, providing hope during this pandemic. The effect of remdesivir on viral load and viral suppression still needs to be addressed [51-52]. A clinical trial study (Clinical trial no: NCT04280705) on 1062 patients

hospitalised with COVID19 symptoms have shown that remdesivir treatment leads to lower respiratory tract infection and also reduces recovery period time in adults as compared to placebo [53].

3.3 Combination of HIV Drugs: Lopinavir and Ritonavir

The antiretroviral protease inhibitor, Lopinavir and Ritonavir which inhibits HIV protease activity essential for viral maturation are common drug combination used for treatment of human immunodeficiency virus (HIV) infection [54-56]. The combination of lopinavir and ritonavir inhibits the formation of infectious virions in host cells which prevent the following waves of cellular infection [57-58]. Lopinavir have insufficient bioavailability as it gets metabolized by cytochrome P459, whereas ritonavir is a potent inhibitor of cytochrome P450. Therefore, lopinavir is always co-administered with ritonavir in a particular ratio of 4:1 [55]. These drugs get absorbed in the gastrointestinal tract and are highly bound to the plasma protein [55, 59]. Clinical studies revealed that lopinavir/ritonavir treatment leads to reduced nasopharyngeal viral load, less lymphopenia, recurrence of fever, lower risk of acute respiratory distress syndrome, milder adverse outcome or death in SARS patients with limited side effects [60]. Increased bilirubin levels, nausea and diarrhea are documented complications of lopinavir/ritonavir treatment [60-61]. Further, MERS-CoV infected common marmosets showed decrease in viral loads in lung and most extrapulmonary tissues at necropsy with improved clinical, radiological, pathological features on lopinavir-ritonavir treatment and hence was recommended for patients with MERS-CoV [54, 56].

Recently Korean researchers showed reduced viral loads and improved clinical symptoms upon lopinavir/ritonavir treatment in COVID-19 patients [62]. Further, controlled clinical trials of lopinavir/ritonavir dose of 400mg/100mg twice daily for 14 days on COVID-19 patients conducted by Cao B et al., 2020 [63] suggested no effect of lopinavir-ritonavir on COVID-19. One study suggested that antiviral drug arbidol in combination with lopinavir-ritonavir caused decrease of viral load treatment in patients with COVID-19 and proposed to delay the progression of lung lesion and milder possibility of respiratory and gastrointestinal transmission [61]. The effect of lopinavir/ritonavir on reducing

mortality in COVID-19 patients has not been found in recent clinical trial studies [64]. However, further clinical trials (NCT04255017, NCT04252885, NCT04286503, NCT04291729, NCT04291729, NCT04275388, NCT04295551) are underway for these studies to identify the mode of action and potential of lopinavir/ritonavir alone or in combination with arbidol or other antiviral drugs for COVID-19 treatment [9].

3.4 HIV Drugs Combination Plus Interferon

Review of literature suggests use of interferon therapy in combination with antiviral drugs of HIV like lopinavir-ritonavir and hepatitis C virus (HCV) such as ribavirin for coronavirus infection. It has been observed that MERS-CoV selectively target and weakens interferon response in order to invade host immune system possibly by impairing antiviral adaptive type 1 T helper cell (Th-1) immune response [54, 56]. The existing studies have shown that both interferon- α and interferon β have more inhibitory outcome on MERS-CoV infection than SARS-CoV infection. The interferon β 1b, a subtype of interferon have shown strong inhibition on MERS-CoV *in vitro* and decreased severity of the disease with reduced viral loads in lung and extrapulmonary tissues of infected common marmosets [54, 56, 65]. Ribavirin treatment with pegylated interferon- α -2a lead to significant improvement in survival of MERS-CoV infected patients in 14 days, however, the therapy did not work well on 28 days showing adverse side effect [65]. The clinical assessment of Ribavirin with interferon subtypes is suggested to identify potential combination for effective therapy on patients with mild and severe MERS-CoV infection [65]. Further, the combination of lopinavir-ritonavir and interferon- β 1b (MIRACLE trial) has shown virus clearance and survival in MERS-CoV infected patients indicating potential of these drugs combination [56]. The lopinavir/ritonavir and interferon also lack drug interaction between them [55]. A recent literature proposes use of interferon alpha [60] specifically pegylated interferon- α -2a and 2b to stimulate innate antiviral response in COVID19 patients [66]. The trail testing of pegylated interferon and ribavirin is under process for COVID19 treatment. However, close monitoring on pharmacodynamics, possible combination of other antiviral drugs, like liponavir/ritonavir, ribavirin with interferon subtypes, and adverse side effects of treatment should be evaluated in clinical trials to develop

Table 1. List of proposed repurposed drugs that have shown promise in COVID-19 treatment

Drug Name	Mode of action	Drug use	Effect on Covid19	Clinical trail	References
Chloroquine	Inhibits viral replication either at the early stages by interacting with the endosome-mediated viral entry or late stages of viral replication	Anti-malarial	Inhibits SARS-CoV-2 infection tested against a clinical isolate of 2019-nCoV in vitro	NCT04303507	[9, 27, 30, 77, 78]
Hydroxychloroquine	Same mechanism of action as chloroquine	Anti-malarial	Shown to reduce viral load in COVID19 patients	Phase 3 NCT04261517	[9, 32, 77, 78]
Remdesivir	Delayed chain cessation of nascent viral RNA	Anti-viral	Shown to reduce viral load in vitro and improved clinical symptoms in some COVID19 infected hospitalized patients	Phase 3 NCT04257656 and NCT04252664	[9, 27, 43, 49, 50, 51, 67, 78]
Lopinavir and Ritonavir and or in combination with other anti-viral drugs like arbidol, interferon	Inhibits viral protease activity, prevent formation of infectious virions in host cells	Anti-viral	One study showed reduce viral loads and improved clinical symptoms COVID-19 patients. Another controlled clinical trial showed no effect of lopinavir-ritonavir on COVID19	Phase 4 NCT04255017, NCT04252885, NCT04286503, NCT04291729, NCT04275388,	[9, 61, 62, 63]

an alternative and effective treatment strategy for COVID-19 infection.

Apart from anti-malarial and antiviral drugs, fungus derived statins like lovastatin, pravastatin and simvastatin have been proposed for COVID-19 as a repurpose drug (Singh et al., 2020). Literature suggests statin being having immunomodulatory effect hypothesized as a candidate drug against MERS-CoV [67]. However, mode of action, controlled drug dose monitoring for effective dose and its side effects need to be scored and validated.

4. FUTURE DIRECTIONS

Convalescent plasma therapy is also referred as passive antibody therapy, in which collected convalescent plasma is transfused to active patients for treatment. Upon administration to the active patients, antibody present in the convalescent plasma (CP) acts to neutralize the pathogen, activate the complementation system, and antibody-dependent cytotoxicity [68]. Such affordable strategy has been used quite successfully in past flu epidemics [69]. This therapy has proven to be effective for reducing hospital stay and mortality during SARS-CoV outbreak in recent past [70-71]. However, till date the findings on their effectiveness in treating COVID-19 are inconsistent. Based on substantial evidences, recent reports suggested the use of this therapy to treat SARS-CoV-2 infection following controlled clinical trials [72]. It was also observed that SARS-CoV-2-inactivation of convalescent plasma from patients who recovered COVID-19 infection does not alter the therapeutic potency and could be used for plasma therapy to manage COVID-19 [73]. A small clinical study on 10 Chinese patients showed that CP therapy is well tolerated and could potentially improve the clinical outcome of COVID-19 patients. This study reported that following CP therapy serum neutralizing antibody titer increased to 1:640 from as low as 1:160 and helps in curing infection [74]. A recent study on Indian population did not find any association between convalescent plasma therapy and reduction in progression to severe COVID-19 or all causes mortality [75]. On 8th of April, 2020, United States Food and Drug Administration (US-FDA) released recommendations for the study of COVID-19 convalescent plasma therapy. Ten clinical trials are currently on-going to access the efficacy and treatment outcome of convalescent plasma therapy, as per the Clinical Trial registry of U.S National Library of Medicine

(ClinicalTrials.gov). Under the profound risk COVID-19 pandemic, besides considering the repurposed therapeutic drugs, use of convalescent plasma therapy could prove to be a game changer. It is noteworthy that on 23rd August 2020, FDA issued a guideline for Emergency Use Authorization (EUA) for convalescent plasma therapy in USA.

5. CONCLUSION

While the whole world is reeling under the novel coronavirus pandemic (COVID-19), it is of utmost interest to develop vaccines or therapeutics. Repurposing of pre-approved drugs has shown a silver lining while considering relatively long term effort to develop and implement effective vaccine treatment against SARS-CoV-2. It is also noteworthy that till date no vaccine have been developed for SARS-CoV (outbreak in 2002) and MERS-CoV (outbreak in 2012) even decades after their outbreak. Major expectations are thus focussed around already approved drugs that target to block or inhibit or modulate the function or expression of key protein components. As per the Global Initiative on Sharing Avian Flu Data (GSAID), more than 280 complete or partial SARS-CoV-2 genome sequences from nearly 70 countries across the world have been analysed and found to be highly similar (>99.9%) [76]. Due to considerable homology in the genomic and proteomic level with other β -coronaviruses, multiple studies have proposed repurposing of already approved drugs used for SARS-CoV and/or MERS-CoV treatment. Widely used and cost effective drugs such as Chloroquine (CQ) and hydroxychloroquine (HCQ), Remdesivir, combination of Lopinavir & Ritonavir have been tried in several countries (Table 1). Their efficacy and response across different populations and age groups in treating COVID-19 is still elusive. Further, till date case studies and pilot randomized controlled trials failed to show consistent results on the suitability of these drugs for COVID-19 treatment. However, remdesivir has been considered for potential use based on clinical trial studies. Network based approach extended the scope to identify probable drug target and thus extended the possibility to find additional drugs. In silico approach based on protein modelling and docking has also been successful to identify several therapeutic components. Predicted drugs identified based on silico approaches need to be prioritized and screened through controlled clinical trials in coming days.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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