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An Update on Therapeutic Repurposing Strategies for COVID-19

Prakash Katakam [1*], Shanta K. Adiki [2], Fathi H. Assaleh [3], Mohammed M. Ahmed [4]

[1] *Indira College of Pharmacy, Nanded, Maharashtra, India*

[2] *Nirmala College of Pharmacy, Mangalagiri, Andhra Pradesh, India*

[3] *Faculty of Pharmacy, University of Zawia, Al-Zawia, Libya*

[4] *College of Pharmacy, Prince Sattam bin Abdulaziz University, Al-Kharj, Saudi Arabia*

Address for Correspondence: Prakash Katakam, **pkatakam9@gmail.com**

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ABSTRACT: The severe acute respiratory syndrome coronavirus 2, well known as COVID-19 has become the current health distress to the entire world. In the pandemic scenario the research on the rapid development of new drug molecules is highly risky and tedious process. The current COVID-19 emergency demands an urgent development of possible strategies to protect people at high risk of infection and hence the drug repurposing became an emerging approach to fight COVID-19. This review summarizes an update on various therapeutic strategies with special attention on repurposing of drugs to fight against SARS-CoV-2 worldwide. The investigation of existing drugs for new therapeutic purposes is one line of scientific research followed to develop safe and effective COVID-19 treatments. Broad-spectrum antiviral agents (BSAAs) that have been believed to be safe through testing on early phase clinical trials have been hyped as good drug repurposing candidates. Broad-spectrum antiviral drugs such as Ribavirin, Umifenovir were advised for COVID-19 treatment. Some antibiotics may be repurposed as COVID-19 treatments such as teicoplanin, oritavancin, dalbavancin, monensin and azithromycin. Ivermectin an antiparasitic is recently repurposed. Hydroxychloroquine and chloroquine, having immunomodulating effect on humans, have been shown to have antiviral activity at starting and post-entry stages of the SARS-CoV-2 infection. There is a need for global health emergency to call for a courageous, global response at the political and governmental levels. Therefore, the regulatory agencies must act swiftly to lessen any financial obstacles involving private companies and update guidelines for drug licenses by repurposing if necessary.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2, well known as COVID-19 has become the current health distress to the entire world. Initially appeared in Wuhan, Hubei, China around December 2019, it had spread to almost 210 countries due to its high contagious nature.[1] Preventive measures remain the only way to stop the person to person transmissions until any successful method of treatment or vaccine is developed. In the pandemic scenario the research on the rapid development of new drug molecules is highly risky and tedious process.

The genetically varied *Orthocoronavirinae* (coronavirus, CoV) family occurs in many avian and mammalian species. Phylogenetically, CoVs are divided into four genera: α (group 1), β (group 2), γ (group 3) and δ (group 4). Three new human CoV have emerged in the past two decades; in the year 2002 severe acute respiratory syndrome CoV (SARS-CoV), in 2012 Middle East respiratory syndrome CoV (MERS-CoV), and now in December 2019 SARS-CoV-2.[2-4] All human CoV are expected to have emerged firstly as zoonoses[5]. The current SARS-CoV-2 pandemic referred to as COVID-19 (Coronavirus disease 2019), has resulted in over 2,630,000 infections and over 184,000 deaths in 213

countries as on 23 April, 2020. COVID-19 has now been reported on every continent except Antarctica. This review summarizes an update on various therapeutic strategies with special attention on repurposing of drugs to fight against SARS-CoV-2 worldwide.

THERAPEUTIC AGENTS FOR COVID-19

The current COVID-19 emergency demands an urgent development of possible strategies to protect people at high risk of infection, specifically close contacts of patients and health-care workers, among others. Reliable and strong data on antiviral therapies is nevertheless to come. The main problem regarding authentic data generation is high approximation for the secondary SARS-CoV-2 attack rates among the family members (~15%) and close friends (~10%) of confirmed patients.[6] Preexposure and postexposure prophylaxes (PEP) with antimicrobial drugs are effective in preventing infection before possible exposure or after confirmed exposure to a variety of pathogens and in reducing the risk of spreading secondary infection. Based on previous knowledge with PEP for earlier infections such as Ebola, SARS and MERS, Mitjà and Clotet recommended that PEP should be initiated earliest possible soon after possible exposure to SARS-CoV-2.[7] World Health Organization has suggested PEP with rifampicin for invasive meningococcal infection, and oseltamivir for pandemic influenza.[8] The implementation of prophylaxis and antiviral treatment has various requirements. For an existing drug candidate to be qualified there should be adequate drug stocks with high safety and of ideally low cost. Hydroxychloroquine is licensed to use for prophylaxis and treatment of malaria and rheumatism and has a history of high tolerance and safe at usual doses. Indicatively, this drug showed antiviral activity *in vitro* against coronaviruses distinctively on SARS-CoV-2 (ClinicalTrials.gov Identifier: NCT04261517).[9],[10] Yao *et al*., found that hydroxychloroquine was more effective than chloroquine at inhibiting growth of SARS-CoV-2 *in vitro*. Hydroxychloroquine sulfate 400 mg twice daily for first day and followed by 200 mg twice daily for following four days is suggested to treat SARS-CoV-2 infection.[9]

As the COVID-19 spreads, several efforts are being made by the governments to reduce transmission through standard public health interventions based on isolation of cases and rigorous tracing of contacts of infected people. In a study, Hellewell *et al*.[11] predicted that such a strategy could contribute in reducing the overall magnitude of an outbreak, however it is still insufficient to achieve control of COVID-19 outbreak when the basic reproduction number (R0) is higher than 1.5 or the percentage of contacts identified is lower than 80%. That means the reproduction number (R0) should be < 1.0 to flatten the curve at earliest possible time.

Internationally as of April 2020, about 200 pharmaceutical firms, biotechnology companies, universities and health organizations are involved in various stages of therapeutics and vaccine development [12],[13]. As on 9 April, there have been 115 vaccine candidates and 116 potential therapies for COVID-19 disease in various stages of development [6].

The World Health Organization (WHO), European Medicines Agency (EMA), US Food and Drug Administration (FDA), and the Chinese government and pharmaceutical companies were coordinating with academic and industry researchers for rapid development of antiviral drugs, vaccines and post-infection medications.[14] The International Clinical Trials Registry Platform of the WHO confirmed 536 clinical studies of drug therapies for COVID-19 infections,[15] along with various existing antiviral drugs for repurposing against COVID-19 are under clinical research.[16],[17] The review in April 2020 tracked the ongoing research on registered clinical trials for COVID-19 vaccine and therapeutic drug candidates [8]. Four possible post-infection therapies such as favipiravir, remdesivir, lopinavir and hydroxychloroquine/chloroquine are in the final stage of human testing by April 2020[18],[19] Phase III-IV clinical trials – and five vaccine candidates had entered Phase I.[20] As the present review focuses on therapies only, the details of drug candidates under pipeline for treatment of COVID-19 are shown in **Table 1**.

So far only one new drug named, EIDD-2801, is being flaunted as a 'relief drug' for Covid-19. The results of the anti-viral drug being developed by researchers at UNC-Chapel Hill Gillings School of Global Public Health was recently published, which showed that it could "…prevent severe lung injury in mice infected with the associated SARS-CoV-2". USFDA has given nod for human clinical trials of this drug. Similar results were visible with cultured human lung cells infected with SARS-CoV-2 as well. EIDD-2801 assures most effective and dedicated drug against the entire family coronavirus [22].

Remdesivir (development code GS-5734) is another investigational drug and nucleotide analog with broad-spectrum antiviral activity. It is being studied during 2020 as a possible drug candidate for treating post-infection of COVID-19 [23, 33].

Table 1: COVID-19 Drug candidates for treatments in Phase III-IV trials [21]

Drug candidate	Description	Existing disease approval	Trial sponsor(s)	Location(s)	Expected results	Notes, references
EIDD-2801	interferes SARS-CoV-2 reproduction mechanism	investigational	Ridgeback Biotherapeutics, USA	USA	Human trials pending	[5, 22]
Remdesivir	protease inhibitor against coronaviruses	investigational	Gilead, WHO, INSERM	GSDT	April (Chinese, Japanese trials) to mid-2020	emergency access.[23]
Hydroxychloroquine or chloroquine	antiparasitic and antirheumatic	malaria, rheumatoid arthritis	CEPI, WHO, INSERM	GSDT, Europe, international	April 2020	@[24],[25]
Favipiravir	antiviral against influenza	influenza (China)	Fujifilm	China	April 2020	[26]
Favilavir, the first approved coronavirus drug in China	inhibits the RNA-dependent RNA polymerase or the RdRp.	Anti-viral	The National Medical Products Administration of China	70 patients. Shenzhen, China	2020	[27]
Lopinavir/ritonavir without or with Rebif	antiviral, immune suppression	investigational combination; lopinavir/ritonavir approved[28]	CEPI, WHO, UK Oxford, INSERM	GSDT	mid-2020	[12]
Sarilumab	human monoclonal antibody against interleukin-6 receptor	rheumatoid arthritis (USA, Europe)[29]	Regeneron-Sanofi	Multiple countries	Spring 2020	[30]
ASC-09 + ritonavir	antiviral	combination not approved; ritonavir approved for HIV [19]	Ascletis Pharma	Multiple sites in China	Spring 2020	[19]
Tocilizumab	Same as Sarilumab	immunosuppressant, rheumatoid arthritis (USA, Europe)[31]	Genentech-Hoffmann-La Roche	Multiple countries	mid-2020	[32]

GSDT: Global Solidarity and Discovery Trials; @: multiple side effects, drug interactions

REPURPOSING OF APPROVED DRUGS

COVID-19 has now been declared as pandemic and new treatments are immediately required as we entered beyond containment phase. New drug discovery is a tedious and lengthy process, costs over $1 billion for *de novo* drug development against SARS-CoV-2 and not practical at this stage of COVID-19 outbreak.[34] Drug repositioning is well known as drug repurposing, is the concept of identifying therapeutically effective drugs from the list of existing drug molecules. Drug repurposing became an emerging approach to fight COVID-19. The investigation of existing drugs for new therapeutic purposes is one line of scientific research followed to develop safe and effective COVID-19 treatments. [11, 35] Broad-spectrum antiviral agents (BSAAs) that have been believed to be safe through testing on early phase clinical trials have been hyped as good drug repurposing candidates. Andersen *et al.* have recently identified 31 potential candidates for COVID-19 from the database of 120 experimental, investigational and approved agents.[36]

Various presently available antiviral drugs previously used in the treatment of SARS, MERS, HIV/AIDS, and malaria, are now investigated for COVID-19 treatments, and some are under clinical trials. During the COVID-19 epidemic, drug repurposing is the process of clinical research of swift selection and establishing the safety and efficacy of existing drugs which are approved for other ailments to be used for people with COVID-19 infection.[37] In the routine drug development process, corroboration of repurposing for new disease management can catch many years of clinical research as well as essential Phase III clinical trials on the proposed drug to guarantee its safety and efficacy especially for treating COVID-19 contagion [33]. In the crisis of a increasing COVID-19 pandemic, the drug repurposing procedure is being hastened in March 2020 to treat patients with COVID-19. [11,32, 38]

Clinical trials employing repurposed, usually safe, existing medicines for hospitalized COVID-19 patients might take less time and have lower overall medication-cost to obtain end-points proving safety (absence of severe adverse effects) and post-infection effectiveness and may speedily access existing drug supply-chains for producing and world-wide distribution [8]. In a global effort to capture these benefits, the World Health Organization began in March 2020 accelerated international Phase II and III trials on 4 promising treatment choices: the SOLIDARITY trial [45] with various alternative drugs having potential for repurposing in several disease treatment approaches, like anti-inflammatory, corticosteroid, antibody, immune, and growth factor therapies, among others, being advanced into Phase II or III trials during 2020 [32, 33, 39].

Broad-spectrum antiviral membrane fusion inhibitors like Ribavirin and Umifenovir (ClinicalTrials.gov ID: NCT04255017) were advised for COVID-19 treatment according to Chinese 7th edition guidelines.[40],[41] Some antibiotics such as as teicoplanin, oritavancin, dalbavancin, monensin and azithromycin may be repurposed for COVID-19 treatment. [42],[43] Ivermectin an antiparasitic is recently repurposed for COVID-19 therapy.[44] Chloroquine, having immunomodulating effect on humans, has been shown to have antiviral activity at starting and post-entry stages of the SARS-CoV-2 infection. It potentially can enhance the antiviral effect of remdesivir and can synergize this effect along with other BSAAs.[45]

In March, the United States Centers for Disease Control and Prevention (US-CDC) issued a suggestion to physicians regarding remdesivir, a viral RNA-dependent RNA polymerase inhibitor,[46] (ClinicalTrials.gov Identifier: NCT04252664) for hospitalized patients having pneumonia effected by COVID-19 as follows: "While clinical trials are vital to establish the safety and efficacy of this drug, clinicians without access to a clinical trial may request remdesivir for compassionate use through the drug manufacturer for patients with clinical pneumonia."[47] The viral RNA polymerase inhibitor favipiravir in combination is also on a Phase II clinical trial for pneumonia effected by COVID-19 (Chinese Clinical Trial Registry Identifier: ChiCTR2000029544).[48] Preclinical investigations of ribonucleic analog, ribavirin showed *in vitro* antiviral activity on SARS-CoV-2 [45].

Shaha *et al*., selected 61 presently available antiviral drugs and studied molecular-docking interactions with COVID-19 enzymes [2]. It was found that out of the 61 drug candidates, 37 molecules were found interacted with s2 protein structures of COVID-19. HIV protease inhibitors and RNA-dependent RNA polymerase inhibitors showed promising features of binding to COVID-19 enzyme. They also found that methisazone (protein synthesis inhibitor), CGP42112A (AT2 receptor agonist) and ABT450 (non-structural protein 3-4A inhibitor) may become useful treatment against COVID-19. The drug repurposing approach provides an insight about the therapeutics that might be helpful in treating COVID-19.

Wu *et al*., used target-based virtual ligand screening, 21 targets were evaluated against drug molecules including zinc and natural products databases. Structure and screening of various targets such as proteases of 3-chymotrypsin (3Clpro) and papain (PLpro), Spike, RdRp were discussed. Database of 78 anti-viral drugs that are marketed and on ongoing clinical trials for SARS-CoV-2 was created and possible targets were predicted.[49]

NETWORK - BASED DRUG REPURPOSING

Recently Zhou *et al*., studied on novel network-based integrative methodology for rapid antiviral drug repurposing against 2019-nCoV/SARS-CoV-2. [50] This method combines a systems pharmacology-based network drug platform which quantifies the interaction between the virus-host interactome and drug targets in the human PPI network. Phylogenetic analyses of 15 HCoV whole genomes disclosed that 2019-nCoV/SARS-CoV-2 contributes the highest nucleotide sequence characteristics with SARS-CoV (79.7%).

The drug repurposing procedure is as follows as shown in **Fig. 1**. (a) HCoV-associated host proteins were gathered to generate a pan-HCoV protein sub-network. (b) Network proximity between drug targets and HCoV-proteins was assessed to screen for repurposable drugs in the human protein interactome model. (c, d) Gene set enrichment analysis was used to validate the network-based prediction. (e) Top candidates were further prioritized for drug combinations employing network-based technique captured by the "*Complementary Exposure*" pattern where the targets of the drugs both hit the HCoV–host sub-network, but target separate vicinities in the human interactome network. (f) Overall hypothesis of the network-based method: (i) the proteins associated functionally with HCoVs are localized in the corresponding sub-network inside the comprehensive human interactome network; and (ii) proteins that serve as drug targets for a specific disease may also be suitable for possible antiviral infection due to common protein–protein interactions elucidated by the human interactome.

Using network proximity studies of drug targets and HCoV–host interactions in the human's interactome, they prioritized 16 potential anti-HCoV repurposable drugs for e.g., melatonin, mercaptopurine, and sirolimus. These drugs are validated by enrichment analyses of drug-gene signatures and HCoV-induced transcriptomics information in human cell-lines. They also identified three prospective drug combinations such as sirolimus+dactinomycin, mercaptopurine+melatonin, and toremifene+emodin captured by the "*Complementary Exposure*" pattern by targeting separate neighbors in the human interactome network.[50]

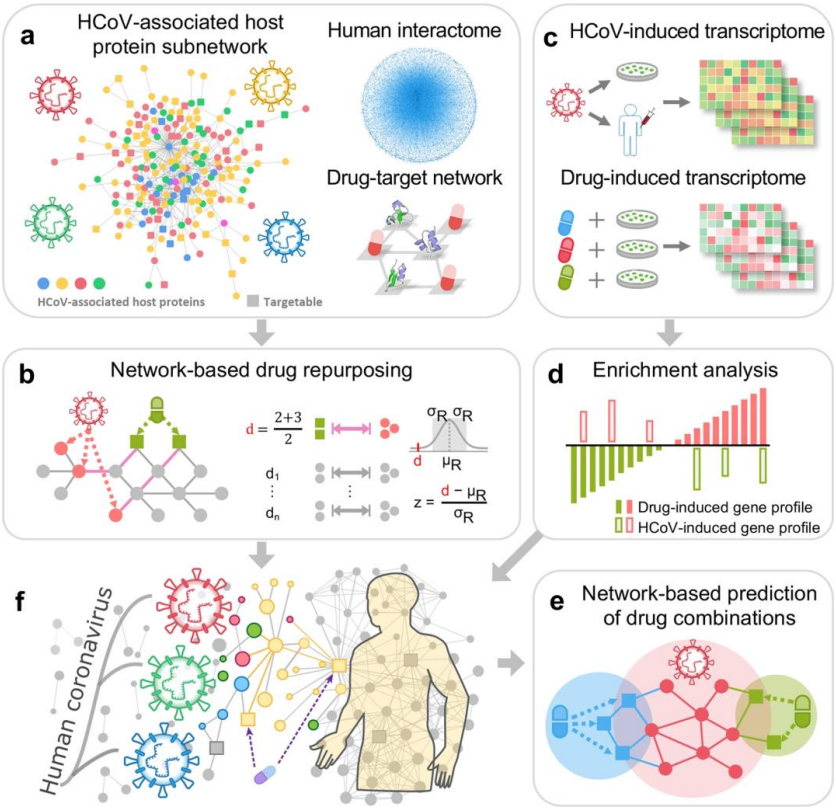

Figure 1: Network-based drug repurposing procedure (Zhou *et al*., 2020) [50] https://creativecommons.org/licenses/by/4.0/

FUTURE CHALLENGES

The lack of precise BSAAs may be resulted in the emergence of more virulent and drug resistant strains. An important aspect in this pursuit for repurposed drugs entails patent protection concerns under national and international drug-regulations.[51] There is a need for global health emergency to call for a courageous, global response at the political and governmental levels. Therefore, the regulatory agencies must act swiftly to lessen any financial obstacles involving private companies and update guidelines for drug licenses by repurposing if necessary.

The urgent launch of global clinical trials on investigational medicinal products for the current COVID-19 outbreak should read out within weeks to months. We can anticipate the notion of drug repurposing for emerging viral diseases to be scrutinized based on these results. At a deeper level, this is a battle not only against COVID-19 but for the very soul concept of new antimicrobials and their clinical indications: 'one drug, one virus vs one drug, multiple viruses or multiple drugs, one virus are the contenders'. [40, 52, 53]

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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