FEATURE ARTICLE

Drug Repurposing for COVID-19 Therapy

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"It is within the power of man to eradicate the infection from the earth": Louis Pasteur

Discovery of drugs for the treatment of human ailments continues to remain an arduous, expensive and slow process. Loss of over a 6 lakh lives and destruction of the economy globally caused by COVID-19, however, warrants fast-tracking of the discovery process. Drug repurposing seems to be an attractive alternative and major drug companies, research institutions and universities are currently making impressive efforts to repurpose drugs developed for other ailments to alleviate human suffering caused by COVID-19. While some successes for containing COVID-19 in patients with mild, moderate and severe symptoms are emerging, only additional investigations will decide on the usefulness of their efficacy.

THE task of taking drugs from discovery to the market requires durations up to 10 years and costs around 2.5 billion US$. If a virus spreads to 213 countries in a six-month time period, infects over 15 million people, killing over six hundred thousand people, fast-tracking of the process is imminent. This explains the unprecedented exigency being shown in finding a cure for the new disease caused by the SARS-CoV-2 (named CoronaVirus Disease discovered in 2019, COVID-19).

The first case of human infection of COVID-19 was reported by Chinese officials in December 2019. Beginning from early January, scientists all over the world are striving hard to develop drugs and vaccine candidates for prevention and/or treatment of COVID-19. Due to the impending urgency, drugs that have already gone through all the time-consuming screenings during their development for the treatment of other diseases are being focused upon. According to the Austrian Institute of Health Technology Assessment, the majority of the 155 drugs in the pipeline for COVID-19 are those developed for the treatment of other diseases.

WHO is coordinating some efforts aimed at finding a cure for COVID-19, although many countries are carrying them out on their own. The Solidarity Trial is one such Clinical Trial effort announced by the WHO on 18 March 2020, with anticipated participation of over 100 countries. As on 2 June 2020, 35 countries with over 400 hospitals had recruited more than 3500 COVID-19 patients. The trial aims to cut down multiple small trials and accomplish rapid worldwide comparison of various unproven but potential treatments for the disease. The Randomized Evaluation of COVID-19 therapy trial (RECOVERY) is the UK's large clinical trial of promising coronavirus treatments. The University of Oxford and the Nuffield Department of Population Health are coordinating the effort.

Given the pandemic situation, drug regulators from all over the world, including India, are ready to push the bar lower by waiving off data on animal and toxicity studies, ensuring speedy clearance for the clinical trials and approval of manufacturing license within days if convinced of the potential of the drug. For example, Gilead Sciences initiated phase II studies of the Ebola drug remdesivir against COVID-19 at the end of February 2020, in the US, Asia and Europe and in May 2020 the US Food and Drug Administration (FDI) granted the drug Emergency Use Authorization (EUA).

Unfortunately, we are also witnessing developments like the publication of researches on COVID-19 without peer review by reputed journals (between January and May 2020 over 30,000 works were published, a large fraction of which were not peer-reviewed), retraction of the publication even by the most reputed journals like *The Lancet* and *British Medical Journal*, endorsement of drugs with unproven efficacy by practitioners of indigenous medicines and heads of states, recruitment of a large number of COVID-19 patients for hurriedly planned clinical trials and granting/withdrawal of permissions for emergency uses of anti-COVID-19 drugs by drug regulatory authorities all over the world.

Repurposing of Drugs

Employment of a drug, previously developed for the treatment of a specific disease, for new therapeutic purposes, constitutes drug repurposing (also termed repositioning, retracking and

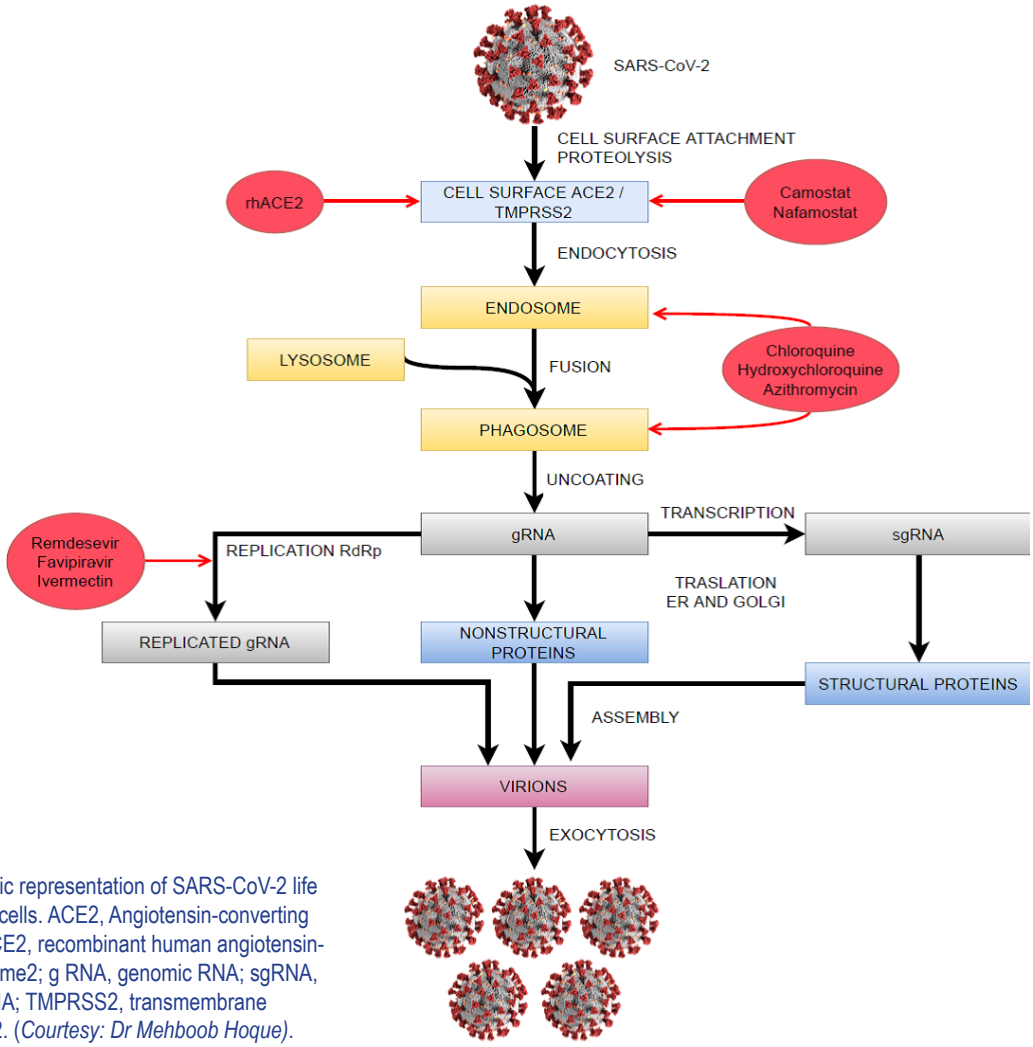

Fig. 1. Schematic representation of SARS-CoV-2 life cycle in human cells. ACE2, Angiotensin-converting enzyme 2; rhACE2, recombinant human angiotensin-converting enzyme2; g RNA, genomic RNA; sgRNA, subgenomic RNA; TMPRSS2, transmembrane proteaseserine2. (*Courtesy: Dr Mehboob Hoque*).

therapeutic switching). Repurposing if successful cuts short the time and resources required for drug development, by doing away with most toxicity studies and animal experimentation as these were done before the drug received the original approval. For repurposing an approved drug, scientists can directly investigate the effects in patients of the new disease i.e. to stage II or III clinical screening (see box *What are Clinical Trials* for details).

Repurposing additionally facilitates convenient formulation and distribution of the drug by the pharmaceutical companies already familiar with the task. While it is true that a drug developed for a specific disease rarely proves effective against an unrelated ailment, some remarkable success stories do exist. Viagra (sildenafil), originally developed by Pfizer for heart-related chest pain, turned out to be extremely popular for the treatment of erectile dysfunction in men and pulmonary arterial hypertension two decades after its marketing. Similarly, thalidomide promoted as a drug for anxiety, disturbed sleep and morning sickness later emerged effective against multiple myeloma and some drug-resistant forms of TB.

To develop a treatment for COVID-19, initially, researchers looked at drugs developed for the treatment of other viral diseases. According to the US National Institute of Health Ecology chief Vincent Munster, "The general genomic layout, general replication kinetics and biology of MERS, SARS and SARS-CoV-2 viruses are similar, so testing drugs which target relatively generic part of coronavirus is a logical step." The search, however, has been extended to other drugs not related to viral treatment. Taking into account the known details of the structure of SARS-CoV-2 proteins computer modelling and artificial intelligence are also being applied for the development of anti-COVID-19 drugs.

SARS-CoV-2 Virus & Anti-COVID-19 drugs

SARS-CoV-2, like other coronaviruses, contains single-stranded RNA as the genetic material. The now-famous structure of the virus shows a lipid membrane surrounded spherical entity (125 nm diameter) dotted on the surface with several proteins including the spike glycoprotein. The endocytic entry of the virus is facilitated by the binding of the spike protein to the human cell surface Angiotensin-Converting Enzyme-2 (ACE-2), that induces endocytosis.

The resulting endosomes may fuse with the lysosome and the resulting

Table I. Some drugs undergoing clinical trials for their anti-COVID-19 efficacy

Drug	Approved as	Mode of action	Lead for anti-COVID-19 screening	Developed by
Hydroxychloroquine Chloroquine	Antimalarial Immunomodulator	Acidifies endosomes, lysosomes	In vitro studies on coronaviruses	Bayer Laboratories
Remdesivir	Anti-Ebola Anti-SARS-CoV	Restricts viral RNA replication	Blocks growth of coronaviruses *in vitro*	Gilead
Dexamethasone	Anti-inflammatory, anti-arthritic, anti-cancer	Restricts WBC from reaching areas of swelling, promotes apoptosis	Stops anti-cytokine storm	Recovery trials, Government of UK Generic drug
Favipiravir (Avigan) Avifavir	Anti-influenza	Inhibits RdRp	In vitro studies on coronaviruses	Toyama Chemical (Fuji film group) Generic drug
Tocilizumab/ Atlizumab (Actemra)	Immunosuppressive Anti-rheumatoid arthritis	Binds to interleukin-6 receptor (IL6R)	Preliminary studies on human subjects	Hoffmann-La Roche/Chugai
Itolizumab/ (Alzumab)	Psoriasis	Lowers circulating interleukin (IL)-6 and C-reactive protein	Preliminary studies on humans	Biocon India
Lopinavir, Ritonavir	Anti-HIV/AIDS	Inhibits chymotrypsin-like protease $3CL^{pro}$	*In vitro* anti-SARS-CoV-2 activity, anti-MERS	Developed by Abbott
Ivermectin	Broad spectrum anti-parasitic	Blocks Cl^- channels, inhibits SARS-CoV-2 in vitro	A preliminary study on COVID-19 patients in Bangladesh (also given Doxycycline)	Merck Institute of Pharmaceutical Research, USA
Nafamostat	Anticoagulant for chronic pancreatitis, post-operative gastric reflux	Inhibits TMPRSS2, interferes with virus entry	Blocks SARS-CoV-2 cellular entry *in vitro*	Japan Toba Co, Ono Pharmaceuticals, Japan
Recombinant human ACE-2 (APNO1)	Drug for acute lung injury, pulmonary arterial hypertension	Competes with virus for cell surface ACE-2	Protects against influenza (H7N9), inhibits SARS-CoV-2 in vitro	APEIRON Biologics AG
Famotidine (pepsid)	Antacid	Binds to a protease involved in entry of SARS-CoV-2 entry	COVID-19 patients previously on famotidine showed better recovery	Developed by Yamanouchi Pharmaceutical Co, Japan
Azithromycin	Antibiotic	Inhibits translation of bacterial mRNA; Blocks autophagosome clearance	*In vitro* active against Zika and Ebola viruses	Plivad.o.o., Croatia
Haloperidol	Anti-psychotic-Schizophrenia	Blocks dopamine and serotonin type 2 receptors	*In vitro* activity against SARS-COV-2	Janssen Pharmaceuticals, Belgium
Acalabrutinib (Calquence)	Non-Hodgkin lymphoma Leukemia	Inhibits Bruton tyrosine kinase BTK	Preliminary studies on COVID-19 patients	Astra Zeneca
AQCH	Anti-dengue		*In vitro* inhibition of SARS-CoV-2	Sun Pharma
Ashwagandha (plant extract)	Ayurvedic medicines	Overall health improvement, immunity booster	Withanone, a constituent blocks *in vitro* SARS-C0V-2 replication	Ministry of Ayush, ICMR, CSIR, UGC

acidification and proteolysis by cathepsin L lead to the fusion of viral envelope with the lysosomal membrane. Post fusion, the nucleocapsid passes into the cytoplasm and the viral genome is released. The released single-stranded RNA acts as mRNA and two-thirds of the genome is translated into two large protein complexes which in turn are cleaved into 16 non-structural proteins. Important among these are the RNA dependent RNA polymerase (RdRp), helicase and an Exoribonuclease (EXON). The RdRp is directly involved in the replication and transcription of RNA from the viral genomic RNA. Translation of the coat and structural proteins takes place in the ER and Golgi apparatus and a large number of virions are assembled using the synthesized mRNA proteins and lipids before they are released out the cell by exocytosis (Figure 1).

During the early infection phase, SARS-CoV-2 multiplies inside the body and induces symptoms resembling common cold/flu. This is followed by the pulmonary phase in which the host immune system is challenged resulting in respiratory symptoms including cough, breathlessness and blood clot formation. The third phase described as hyperinflammatory phase is characterised by a "cytokine storm" in which a hyped immune system attacks the body's own tissues causing serious harm to heart, lung, kidney and other organs. This results in Acute Respiratory Distress Syndrome (ARDS) that accounts for a significant number of deaths among COVID-19 patients. As of today, there are no approved drugs available to contain COVID-19. Table 1 shows a list of some potential anti-COVID-19 drugs, which have received EUA from the US FDA and similar agencies in several other countries and are undergoing clinical trials. These include drugs approved earlier for the treatment of various bacterial infections, malaria, rheumatoid arthritis, HIV, diarrhoea, heartburn and cancers. In the rush to find out a cure for COVID-19 and availability of a large number of patients, weak evidences and even anecdotal supports have been in some instances adequate to obtain the permission of drug regulators for the conduct of clinical trials in some countries.

What Are Clinical Trials?

Development of drugs is a lengthy, complex and expensive process, full of failures and risks. The journey of a drug candidate from its discovery to the market requires about a decade and currently costs about 2.5 billion US$. This involves exhaustive studies in the laboratory, on experimental animals, and finally on human subjects that constitute the clinical trials. Only companies with huge resources can, therefore, undertake the endeavour.

The US Food and Drug Administration (FDA) and similar agencies in other countries lay down norms for the conduct of clinical trials of drugs, scrutinize them and once satisfied, approve their marketing. The Drug Controller General of India (DCGI) under the Ministry of Health and Family Welfare, approves licenses of drugs in India. In order to conduct clinical trials, companies in the USA are required to file Investigational New Drug application (IND) listing all details of the drug including its structure, investigations in the laboratory and on experimental animals showing its efficacy and safety. The FDA model, which is widely followed by drug regulatory agencies in most other countries, has three major phases of clinical trials.

In phase I, studies are done on a small number (< 100) of healthy volunteers in order to primarily assess the safety of the drug candidate. The studies also examine how the human body processes the drug (pharmacokinetics) and the impact of the drug on various body functions (pharmacodynamics). In addition, assessment of safe drug dosages and side effects, if any, are also made.

In phase II, studies are conducted on larger cohorts (100-500) of patient volunteers. Effect of the drug candidate is compared with other available drugs for the treatment of the disease as well as placebo (placebo is a substance that is designed to possess no therapeutic value). Optimization of drug dosage and schedule of administration as well as investigation of short-term side effects on patient volunteers are undertaken.

In phase III, large numbers of patient volunteers (1,000-5,000) are included from across trial sites around the world. Fine details of efficacy safety of the drug in patients and overall risk-benefit ratios are examined.

Some studies continue after a drug is marketed. Those that delineate risks, benefits and optimal use after making the drug available in the market constitute phase IV.

Remdesivir is an antiviral agent originally developed for the treatment of Ebola infection against which it was not highly effective. It is however used as an anti-influenza drug in some parts of the world. Remdesivir inhibits synthesis of viral (MERS-CoV and SARS-CoV) RNA by the RdRp, hence the multiplication of the SARS-CoV-2. Remdesivir also inhibits the 3',5'-exoribonuclease, the proofreading enzyme which removes any wrong bases accidentally incorporated into the RNA. *In vivo* mouse models of the viruses and rhesus monkey model have shown the impressive anti-viral and prophylactic effect of the drug.

A clinical trial that showed that hospitalized COVID-19 patients recover faster earned remdesivir EUA from the US FDA for its use outside clinical trials. Remdesivir, however, did not impact mortality. Clinical trials continue although remdesivir has been approved for use on serious patients of COVID-19 in several countries including India. Indian pharmaceutical companies Cipla and Hetero Pharmaceuticals have received permission from Gilead Pharma to manufacture the drug in the country. Cipla will market the drug under the brand name Cipremi, while Hetero Pharma will sell its product as Covifor. Remdesivir is recommended to be used for serious hospitalized patients on oxygen and its use as prophylactic is not recommended.

Two potential plant sources of anti-COVID-19 drugs. (Left, the broom creeper (*Cocculus hirsutus*) and right, Ashwagandha (*Withania somnifera)*

Favipiravir (Avigan) has approval as an anti-flu drug in Japan and recently received EUA in several countries including India. It also inhibits the RdRp of the viruses. Glenmark Pharmaceuticals Ltd. will sell the drug under the name FabiFlu and undertake phase III clinical trials of a combination of other drugs. Favipiravir is recommended for mild to moderately ill COVID-19 patients but not as a prophylactic or for pregnant and lactating women.

Dexamethasone is a widely used anti-inflammatory steroidal drug. Dexamethasone has been shown to exhibit life-saving potential in critically ill patients according to a study conducted in the UK. This is the first drug shown to have the potential to cut down death by about 30 per cent, according to the lone UK clinical trial on 21,000 participants. The drug has already been approved in the UK and WHO has recommended further studies on the extremely inexpensive drug that is produced in many countries for the treatment of other diseases. The UK Government has authorized the drug use on hospitalized patients, those that require oxygen and are on ventilators. In June end the drug received approval for use on COVID-19 patients in India. The impact of the UK work as anti-SARS-CoV-2 is so strong that the WHO fears hoarding of the drug and speculative procurement may lead to global scarcity.

Several in vitro studies suggest that chloroquine/hydroxychloroquine interfere with entry, virus-endosome fusion, uncoating, assembly of the viruses including the coronaviruses. It also inhibits the replication of coronaviruses including SARS-CoV-2 in cell cultures. WHO suspended its clinical trial on HCQ under its solidarity program because of the potential toxic effects on cardiac function. The decision to suspend trials was triggered by a study published in the journal *Lancet* that HCQ or HCQ with the antibiotic azithromycin has no beneficial effects for COVID-19 patients. However, in the face of worldwide criticism from the scientific community, the study published in the journal was withdrawn and the WHO decided to reconsider its decision to suspend the trials.

The antibiotic azithromycin showed some promise as an anti-COVID-19 drug but has since been dropped from studies in several countries including India.

Tocilizumab marketed as Actemra by Roche is a monoclonal antibody that blocks a cytokine interleukin-6 receptor. High levels of IL-6 portends respiratory failure and deaths. Itolizumab, developed by Biocon India, is also a monoclonal antibody and like tocilizumab interferes with the induction of cytokine storm. After infection by SARS-CoV-2 inflammation and cytokine storm begin from the second week and experts advise administration of tocilizumab and similar drugs that fight cytokine storm after eight days of infection.

The anti-HIV/AIDS medication lopinavir/ritonavir in spite of promising *in vitro* studies have not so far yielded encouraging results in clinical trials on COVID-19 patients.

AQCH is a phytopharmaceutical derived from the tropical climber *Cocculus hirsutus*, developed for dengue but has broad anti-viral effects. ACQH has been developed by CSIR-Indian Institute of Integrative Medicine (CSIR-IIIM), Jammu and DBT-ICGEB and is active against all four subtypes of dengue virus. This is the first phytopharmaceutical to receive the approval by the DCGI for EUA against COVID-19. AQCH has inhibitory action against SARS-CoV-2 *in vitro*.

The other plant-based drug that is being investigated for anti-COVID-19 role is Ashwagandha (*Withania somnifera*), a plant that is widely used in Ayurvedic system of medicine in India. The ministry of Ayush and CSIR (India) are initiating clinical trials on four Ayush formulations – Ashwagandha, Yashtimadhu (Mulethi), Gaduchi +pippali (giloy) and Ayush-64 developed as an anti-malarial.

It is true that the exponentially increasing cases of COVID-19 with millions of human lives at stake warrant fast-tracking of the search for remedies, but it is important not to abandon scientific reasoning. At the time of the outbreak of EBOLA pandemic, WHO recommended that "it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention keeping in view no vaccine or antivirals were available."

Major economic and political gains, however, prompt the promotion of drugs with questionable efficacy and safety, risking millions of innocent lives. While it is the duty of governments to ensure that this does not happen, some governments and heads of states, unfortunately, themselves become a party. Madagascar's President Andry Rajoelina has recently promoted a herbal tea consisting of the extract of sweet wormwood, *Artemisia annua* and other components being marketed as COVID-Organics which the country is offering as preventive to all citizens including school children. Scientists and the WHO are concerned that COVID-Organics has not gone through the laid down norms of clinical trials. Nearly all countries have traditional systems of medicine. But these should not be promoted as cures for COVID-19 without adequate screening essential to establish efficacy and lack of toxicity.

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