Drug Repurposing for COVID-19: Current Status of Potential Therapeutics

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Review Article

ABSTRACT

The maneuver clinical investigation of an effective drug for coronavirus disease 2019 (COVID-19) is still ongoing and the milieu of a successful investigational drug with proven efficacy is still obscure. Drug repurposing is a method to identify new therapeutic uses for existing drugs, which include approved, delayed, withdrawn, and investigational drugs and drug candidates. Indeed, the cost of the standard drug discovery and development process amounts to more than a billion dollars, and the investigations are expected to last 10–15 years. Notably, repurposing existing approved drugs is a potential, effective, and profitable approach as it significantly reduces the cost and time of developing a new drug. Owing to the established safety, pharmacokinetic, and pharmacodynamic profiles of potential drug candidates, drug repurposing may allow scientists to skip or shorten some

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critical steps of the traditional drug discovery and development process. Prospectively, advanced approaches could be harnessed to conduct proof-of-concept trials that would accelerate the clinical evaluation of repurposed drugs. Drawing lessons from repurposing efforts for COVID-19 therapeutics, the present review briefly summarizes the current status of various potential drugs that have been clinically evaluated for repurposing platforms as well as that could maximize safety, efficacy, and possible therapeutic benefits, both alone or in combination, and clinical outcomes in patients with COVID-19.

Keywords: COVID-19; coronavirus; drug development; drug discovery; drug repurposing; antibiotics; antivirals.

1. INTRODUCTION

"Drug repurposing is the method of identifying the new uses for existing medicines and is considered an effective and profitable approach, which comprises approved, delayed, withdrawn, and investigational medicines. Repurposing is also known as re-profiling, re-tasking, repositioning, and deliverance of drugs" [1,2]. "Repurposing of drugs serves as a valuable strategy to reuse the drugs that have been tested formerly in humans with favorable safety and therapeutic effects. Rapid repurposing of several drugs including antivirals is initiated all over the world to combat severe complications caused by coronavirus" [3]. "Presently, potentially effective agents from preclinical trials are undergoing clinical investigation, and preventive or therapeutic agents are yet to be developed for COVID-19 patients" [4,5]. "At the beginning of the recent pandemic, there was no reliable cure or suitable therapies for COVID-19, only the emergency use authorization (EUA) by the US Food and Drug Administration (FDA) has been in practice with the approval of several drugs, including old antiviral medicines" [5]. "Moreover, the cost of the new drug and vaccine development process amounts to more than a million dollars, and investigations are extended for a duration of 10-15 years with a success rate of only 2.01%" [6-8]. Therefore, in the absence of effective agents, the scientific community has rationally considered the drug repurposing approach for the development of anti-COVID-19 drugs.

Given the urgent need for effective treatments for COVID-19, many researchers have been exploring the possibility of repurposing existing drugs to combat the disease. This approach has several advantages over developing new drugs, including lower costs and shorter development timelines. By drawing on experience gained from the previous successful repurposing approaches and existing knowledge and data, researchers can make more robustly and quickly identify drugs that may be effective against acute respiratory pattern coronavirus 2 (SARS-CoV-2) with less risk [2,9]. However, repurposing drugs is not without its challenges. Existing drugs may have unintended side effects or interactions when used to treat a new disease, and determining the appropriate dose and treatment regimen can be difficult. Nonetheless, many researchers are exploring this approach as a potential avenue for addressing the current pandemic [10]. "When repurposing medicine, researchers typically rely on two principles. The first is that a single drug can interact with multiple targets, which allows scientists to search for new sites of action for the compound" [2,11,12]. The second principle is that the therapeutic targets associated with a particular disease often play a role in multiple biological processes involved in pathogenesis. This can lead to the identification of new indications for drugs that target these common pathways [2,9,13]. "Drugs that act through these principles not only have the potential to be useful for the pharmacological management of disease that was originally intended but also for various diseases of different etiologies. The drug repurposing approach has gained a lot of advantages because one out of three drug approvals were related to existing approved therapeutic indications that generate a profit for the pharmaceutical industry. Prior knowledge of the repurposed candidates, such as safety, tolerability, manufacturing, pharmacodynamic, and pharmacokinetic data, helps to shorten the long drug development timeline and limit the cost of development" [11-14]. "Existing detailed information on human pharmacology and toxicology details of approved drugs helps to enable rapid clinical trials and regulatory review for repurposing" [15].

2. CORONAVIRUS AND COVID-19

"Coronaviruses (CoVs) are pleomorphic, enveloped, and positive single-stranded sense with a genome of nearly 30,000 nucleotides and 26 – 32 kb large RNA viruses with typical crown-shape glycoprotein spikes (peplomers) that cause respiratory and enteric diseases in humans and other creatures" [16]. "They're enveloped and have a non-segmented, single-stranded, positive-sense ribonucleic acid (ssRNA) as their nuclear material. The CoVs belong to the family Coronaviridae, subfamily Coronaviridae, and the order Nidovirales. They are genetically distributed into four important genera the alpha coronavirus, beta coronavirus, gamma coronavirus, and delta coronavirus. The former two genera generally infect bats, rodents, and mammals whereas the latter two mostly infect avian species. SARS-CoV- 2 was also found to be nearly related to the genus Betacoronavirus and was noted to be a distinct clade in lineage B of the subgenus Sarbecovirus" [17-19]. "The genome sequence of SARS-CoV2 showed 79.5 similarity with SARS-CoV and interestingly, 96.2 similarity with bat coronavirus RaTG13, suggesting its origin from a bat virus" [20]. "After bat-nCov, strains of SARS-CoV-2 have shown high similarity to pangolin-nCoV. Thus, the pangolin is suspected as an intermediate host" [20,21]. "The coronavirus genome contains four important structural proteins: the spike glycoprotein (S), membrane (M), envelope (E), and nucleocapsid (N) protein, which covers RNA and are encoded within the 3' end of the genome" [22]. "This virus entry is caused by attachment and membrane fusion of viral spike (S) protein with the host cell receptor, which is the key step in viral infection and pathogenesis. The N protein is a structural protein that binds to the RNA genome and is also involved in virus transcription, assembly, and budding. The membrane protein is the most abundant protein and defines the viral envelope shape. The E protein is the smallest protein and involve in viral assembly and budding" [22,23]. "The entry of all coronaviruses into host cells is intermediated by spike glycoprotein that gives coronaviruses a crown-like appearance by forming spikes on their surface. S- proteins consist of S1 and S2 domains that belong to class 1 fusion proteins" [24]. "Spike glycoprotein consists of a large ectodomain amino acid sequence, a short c terminal intracellular tail, and a single-pass transmembrane anchor. The ectodomain contains a receptor-binding unit S1 and a membrane-fusion unit S2, virus enters the host cell, via its receptor-binding domain (RBD) of S1 binds to angiotensin-converting enzyme 2 (ACE2) cell surface receptor, and S2 fuses the host cell and viral membranes, enabling the entry of viral genomes into host cells" [25,26]. The outbreak of COVID-19, caused by the new and largely contagious SARS-CoV- 2, represents a great pandemic to global health.

"COVID-19 presents a wide variety of clinical manifestations ranging from asymptomatic cases to multi-organ dysfunction and septic shock" [27]. "COVID-19 is classified into mild, moderate, severe, and critical based on the severity of the symptoms. Patients present with common symptoms that include fever, muscle soreness, fatigue, dry cough, and diarrhea. Mild disease patients present with symptoms of an upper respiratory tract viral infection, such as dry cough, nasal congestion, sore throat, headache, and malaise. Moderate disease patients have respiratory symptoms of cough, shortness of breath, and tachypnea. Moreover, COVID-19 patients are complicated with severe pneumonia, acute respiratory distress syndrome (ARDS), septic shock, or sepsis" [27-29]. "Clinical symptoms presentation comprises the presence of respiratory distress, severe dyspnea, tachypnea (respiratory rate> 30/ minute), SpO2 ≤ 93, PaO2 / FiO2< 300, and/ or more than 50 lung infiltrates within 24 to 48 hours. Indeed, in severe forms of the disease, fever can be absent or moderate. The risk of death from COVID-19 is increased among geriatric patients and among those with chronic medical conditions, such as cardiovascular disease, cancer, diabetes, lung disease, and obesity" [28-29]. "Some patients may have only mild fever, fatigue, or even no symptoms" [30]. "In addition, a multisystem inflammatory syndrome in children (MIS-C), also known as pediatric inflammatory multisystem syndrome is reportedly temporally associated with SARS-CoV-2. Though MIS-C is relatively uncommon, with an estimated incidence of 2 per 100,000 individuals less than 21 years old, it is a serious complication of SARS-CoV-2 infection in children and adolescents that generally occurs 2–6 weeks after SARS-CoV-2 infection" [31]. "it is hypothesized that the pathogenesis of MIS-C involves a dysregulated immune response to a recent SARS-CoV-2 infection, and host genetics might alter susceptibility to developing MIS-C. The majority of these children have presented skin rash, abdominal pain, diarrhea, vomiting, conjunctival injection, and hypotension. In addition, MIS-C evolved as a post-infectious severe inflammatory condition associated with

abnormal immune function and has evidence of shock, coronary artery aneurysms, atrioventricular block, left ventricular cardiac dysfunction, acute kidney injury, and clinical deterioration of multiorgan function" [31,32].

"The World Health Organization (WHO) has classified SARS-CoV-2 variants into three orders, namely variants of concern (VOCs), variants of interest (VOIs), and variants under monitoring (VUMs). The former four VOCs include nascence (B.1.1.7), Beta (B.1.351), Gamma (P. 1), and Delta (B.1.617.2). They all resulted in a new wave of epidemic and thousands of deaths in more than one country and area, and indeed across the whole world. The WHO named the fifth VOC as Omicron (B.1.1.529), which immediately raised global concerns in the year 2021 on November 26" [33]. "Notably, four common coronavirus types (alpha, beta, gamma, and delta) have been well distinguished, among them alpha and beta types are known to cause respiratory tract infections in humans. Indeed, SARS-CoV-2 belongs to the beta coronaviruses cause COVID-19 and affect respiratory, gastrointestinal, and neurological diseases. On 26 November 2021, the WHO classified this mutant as a variant of concern and named it Omicron (B.1.1.529). This new variant had endured significant mutations when compared to its former variants. The Delta variant (B.1.617.2) has eight mutations whereas Omicron (B.1.1.529) had endured 32 mutations of the S protein. In 2020, the Delta variant created havoc in India and other countries with these eight mutations" [34]. "These mutations, substantially on the spike protein of the virus, lead to slightly modified copies of the virus called "variants", resulting in the strain of the virus having unique properties such as altered transmission and severity of disease, thereby leading to increased rates of transmission, morbidity, and mortality" [35,36]. "Globally, as of 2 November 2023, a total of 771,679,618 confirmed cases of COVID-19, including 6,977,023 deaths, were reported to the WHO. Further, as of 23 October 2023, a total of 13,534,457,273 vaccine doses have been administered" [37].

3. DRUG REPURPOSING FOR COVID-19: POTENTIAL THERAPEUTICS AND PROMISING DRUG CANDIDATES

At the time of writing, there are no drugs or therapeutic vaccines that treat coronavirus. Numerous COVID-19 vaccines have been developed and approved for global vaccination for preventive measures [7,8]. However, approaches to manage the infection with monoclonal antibodies, oligonucleotides, interferon-based therapies, peptides, and small molecule drugs have been explored. To prevent the disease, the discovery of drugs and therapeutic vaccines may take several years. Crystallography data has been featured to control or overt rising SARS-CoV-2 infection. Moreover, protein structural data indicate that medicine-binding pockets in viral enzymes are conserved across SARS-CoV-2, SARS, and Middle East Respiratory Syndrome (MERS) [38]. Therefore, several investigators have been attempting to investigate the repurposing of existing drugs for MERS and SARS [39].

4. REPURPOSING OF ANTIBIOTICS

The repurposing of antibiotics is one of the most important therapeutic strategies employed for COVID-19 treatment. Antibiotics were used as a prophylactic therapy for infections co-existing with COVID-19 and some of the antibiotics exploit their antiviral properties [40].

4.1 Macrolides (Azithromycin and Clarithromycin)

Macrolides are broad-spectrum antibiotics used to treat systemic and local infections. Indeed, azithromycin, clarithromycin, and erythromycin have been shown to possess antiviral activities. Azithromycin is the most used antibiotic against COVID-19 and has also shown antiviral activity against Zika virus and Ebola Virus [41]. It has great tissue penetration. It is used alone and as an add-in therapy with hydroxychloroquine at the early stage before the onset of complications [41,42]. Furthermore, immunomodulation by azithromycin has improved clinical outcomes in severe COVID-19 owing to its ability to reduce cytokine production, maintain epithelial integrity, and prevent lung fibrosis, which are characteristics of the hyperinflammatory stage of COVID-19 [43,44]. It has been proposed that azithromycin may inhibit the acidification of endosomes during viral replication and infection that are required for the multiplication of viruses and causing viral infection. Another possible target for azithromycin is inhibiting the removal of virus capsid and release of the viral genomic nucleic acid [45]. The second macrolide antibiotic proposed for the treatment of COVID-19 patients is clarithromycin. It has anti-inflammatory, antiviral, and immunomodulatory effects and was

repurposed for COVID-19 to use as a single agent or in combination with hydroxychloroquine [46,47].

4.2 Glycopeptide (Teicoplanin)

Teicoplanin, a glycopeptide antibiotic, potentially blocks the virus entry of SARS-CoV-2 by inhibiting the enzymatic activity of cathepsin L, which is involved in the proteolysis of the S protein. Priming of the S protein is done by cathepsin L, furin, trypsin, and transmembrane serine proteases 2 (TMPRSS2) [48,49]. Teicoplanin is used to treat bacterial infections and was found to be active *in vitro* against SARS-CoV [50]. However, its efficacy in humans has yet to be established.

4.3 Cephalosporins (Cefuroxime)

Cefuroxime, a second-generation cephalosporin antibiotic treats a variety of bacterial infections with broad-spectrum activity. It was observed that cefuroxime acts against SARS-CoV-2 proteins, including the main protease, ACE2-Spike complex, and RNA-dependent RNA polymerase (RdRp). However, there was no evidence to support the data as no human clinical trial was conducted [40,51].

4.4 Aminoglycosides (Amikacin)

Aminoglycosides exert bactericidal activity against Gram-positive, and Gram-negative bacteria and exert antiviral properties. Aminoglycosides have a role against SARS-CoV-2 by the production of retrocyclin peptides, which inhibits cellular fusion and aggregation of SARS-CoV-2 [52]. It is reported that the main protease (Mpro) of SARS-CoV-2 is significant for cleaving nascent polypeptide chains. This led us to evaluate aminoglycosides (paramomycin, gentamycin, neomycin, streptomycin, amikacin, and tobramycin) against Mpro. Overall, amikacin was found to be the most potent inhibitor of Mpro among all these aminoglycosides that interacted with crucial residues by binding to the substrate-binding site of Mpro [53]. Besides, amikacin and non-antibiotic aminoglycosides are under investigation for potential clinical efficacy against coronavirus.

4.5 Fluoroquinolones (Ciprofloxacin, Levofloxacin, Moxifloxacin)

Fluoroquinolones are broad-spectrum synthetic antibiotics that act against Gram-negative and Gram-positive bacteria, mycobacteria, and anaerobes bacteria. Notably, respiratory fluoroquinolones, such as levofloxacin and moxifloxacin, constitute first-line therapeutic agents for the management of severe community-acquired pneumonia. Of particular interest, fluoroquinolones have shown various immunomodulatory actions and attenuated inflammatory responses by inhibiting the release of pro-inflammatory cytokines. In addition, favorable pharmacokinetic properties, achievable higher concentrations in the lungs, and an excellent safety profile are advantages over macrolides and beta-lactams [54]. Moxifloxacin and ciprofloxacin are involved in the inhibition of SARS-CoV-2 replication by inhibiting SARS-CoV-2 3CLpro [55]. Indeed, antiviral activity was seen with fluoroquinolones in the treatment of SARS-CoV-2 infection [54,55]. In particular, levofloxacin, moxifloxacin, and ciprofloxacin are indicated for the treatment of SARS-CoV-2-associated pneumonia and community-acquired pneumonia in COVID-19 patients [56-58].

4.6 Tetracyclines (Doxycycline, Minocycline, Eravacycline)

Tetracyclines, both the first and second generations, have bacteriostatic activity against both Gram-positive and Gram-negative bacteria, however, their lipophilic nature and high tissue penetration allow them to inhibit viral replication in the lungs [57-59]. These are used to treat the hyper-inflammation and cytokine storm caused by the complication of SARS-CoV-2-induced pneumonia. A computational model revealed that doxycycline is a potential drug candidate for SARS-CoV-2 owing to its inhibitory effect on the SARS-CoV-2 main proteinase (Mpro), also known as 3-chymotrypsin like protease (3CLpro) [40,60]. Moreover, several clinical studies reported their potential in COVID-19 patients but showed no additional benefit in patients with mild symptoms [61,62]. Tetracyclines definitely provide an effective and safe repurposing strategy for severe COVID-19 owing to their scientific support, and their unique combination of pharmacological activities in preventing fibrotic sequelae.

5. REPURPOSING OF ANTIVIRAL DRUGS

5.1 Drugs that Inhibit Viral Entry by Membrane Fusion and Endocytosis

SARS-CoV-2 enters the host cells by membrane fusion and endocytosis. Aloxistatin is a potential cysteine protease inhibitor for cathepsins and

calpains and has an important regulatory role in neurodegenerative diseases and muscular dystrophy. Cathepsin B and L are considered potential biomarkers for cancer. The catalytic activity of these two proteases leads them to serve as cell regulatory enzymes [4,63]. Indeed, aloxistatin reduced cellular entry of the virus by binding to Cathepsin L, which is a necessary factor for SARS-CoV-2 cell entry [63,64]. Another structural analysis indicated that aloxistatin interacts with membrane-permeable nonstructural protein (NSP) and with the active site of the SARS-CoV-2 main protease (Mpro). Interestingly, it also binds to papain-like proteases with lower specificity [65,66].

5.2 Drugs that Attack SARS-CoV-2 Viral Entry by Membrane Fusion

Nelfinavir mesylate was initially developed to treat human immunodeficiency virus (HIV) infection and has been reported as a small-molecule fusion inhibitor to inhibit SARS replication and cytopathic effects in cell culture [67]. Owing to its pleiotropic effects on cellular processes, including the induction of apoptosis and necrosis, the induction of cytoprotective mechanisms, including cell cycle retardation, and the unfolded protein response resulted in additional beneficial effects [68]. Nelfinavir mesylate also inhibits the function of TMPRSS2, which is involved in the activation of the S protein and prevents syncytia formation in Vero E6 cells [69,70]. Moreover, it has shown antiviral efficacy and therapeutic benefits in the rhesus macaque model and in COVID-19 patients [71]. Altogether, nelfinavir is a highly promising antiviral agent for the treatment of COVID-19 owing to its well-established safety profile in all patients, including during pregnancy.

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5.3 Drugs that Block Viral RNA Replication and Translation

Viral RNA is released into the cytoplasm, and translation of genomic RNA yields a very large polypeptide by translation upon release into the cytoplasm of a host cell, which undergoes proteolysis to generate RdRp. Importantly, structural proteins of the coronavirus, such as S, M, E, and N proteins are made through the action of RNA polymerase [66,70].

5.3.1 B-D-N4-hydroxycytidine (NHC, EIDD-1931) – Molnupiravir, prodrug of NHC

NHC is an orally bioavailable ribonucleoside analog shown to inhibit multiple viruses, including

chikungunya virus, norovirus, hepatitis C virus, influenza A and B, Ebola virus, and respiratory syncytial virus (RSV) [72]. NHC is promiscuously incorporated by viral RdRp, thereby it shows broad antiviral activity against all coronaviruses tested, including SARS-CoV-2. Molnupiravir is a prodrug form of NHC and is active in a lung humanized mouse model of SARS-COV2 by reducing disease infection by lethal mutagenesis [73]. Previous studies suggest that characteristics, such as the increased introduction of transition mutations in viral genomes and genetic barriers to resistance are helpful for the treatment of coronavirus. NHC inhibits viral replication by mutagenesis-D-N4-hydroxycytidine (NHC), which is a broad spectrum ribonucleoside. NHC has potential activity by acting against divergent-CoVs like MHV and MERS-CoV, SARS-CoV, and HCoV-NL. Through novel interaction between a nucleoside analog inhibitor and the enzyme SARS-CoV-2 replicase, the viral proofreading activity does not improve sensitivity to NHC inhibition [72,73]. In the presence of further passage, it generates only a low level of resistance due to the accumulation of multiple potentially deleterious transition mutations. Indeed, NHC inhibits virion release and interferes with RNA secondary structure [73,74]. Evidence from *in vitro* and *in vivo* studies, and clinical trials revealed the efficacy of molnupiravir against SARS-CoV-2 by inducing viral RNA mutagenesis, which promotes mutated complementary RNA strands that generate non-functional viruses [74-76]. Together, the data suggest promising antiviral activity and favorable prophylactic efficacy of molnupiravir that might be attributed to its mutagenic property of disrupting viral replication.

5.3.2 Remdesivir

Remdesivir is a nucleotide analog or nucleoside prodrug and acts against multiple viruses including pneumoviruses, filovirus, paramyxoviruses, and CoVs. It targets RdRp enzyme and has shown good efficacy against coronavirus, SARS, MERS, and CoVs by inhibition of viral replication [39,77]. It evades proofreading as coronaviruses have an exoribonuclease, a proofreading enzyme, that corrects errors in the RNA sequence. Remdesivir acquires resistance through viral mutation but mutant viruses are less infective [78]. In May 2020, the US FDA gave EUA to remdesivir for patients hospitalized with severe COVID-19 [79]. Accumulating data indicates that remdesivir has

little or no effect in individuals with moderate to severe COVID-19, however, it lowered the necessity for oxygen support among all patient subgroups [80]. It is reported that the use of remdesivir improved the risk of mortality, recovery, and need for oxygen support in AnyO2 and LFO2 among hospitalized patients with COVID-19 requiring supplemental oxygen at baseline [80,81]. Adding to this, several structural analogs of remdesivir are chemically reactive, highly interactive, non-carcinogenic, and stable with the target proteins [81]. It is highly essential to conduct additional studies to collect data on the safety and efficacy of remdesivir, particularly for different population subgroups of COVID-19 patients.

5.3.3 Favipiravir

Favipiravir was originally developed to treat Ebola, Yellow fever, chikungunya, norovirus, enterovirus, influenza virus, and avian virus [82]. Further, it may inhibit the replication of several other RNA viruses, including arenaviruses, phleboviruses, flaviviruses, and hantavirus [83]. It is a nucleotide analog that effectively inhibits RdRp by converting to T-705- ribofuranosyl 5′-triphosphate by host enzymes thereby preventing replication and transcription of the viral genome or causing lethal mutagenesis upon incorporation without affecting mammalian cells [83,84]. It also inhibits the SARSCoV-2 infection in Vero E6 cells (ATCC-1586) within a safe therapeutic dose and has been tried to treat mild to moderate COVID-19 [85]. Conversely, there are no primary or secondary outcome measures that did not differ between favipiravir, hydroxychloroquine, and standard therapy for mild to moderate COVID-19 disease [86]. Despite this, favipiravir treatment appeared safe and increased viral clearance, but there was no superior therapeutic utility [87].

5.3.4 Ribavarin

Ribavirin (RBV) is a guanosine analog and a broad-spectrum antiviral drug approved for the treatment of several viral infectious diseases like chronic hepatitis C and RSV infection in children. It interferes with the replication of RNA and DNA viruses and has shown activity against hepatitis B virus (HBV), Influenza A and B, Lassa fever, MERS-CoV, and SARS CoV-1 [88]. It inhibits the RdRp enzyme and causes exhaustion of the intracellular GTP pool by inhibiting the host inosine monophosphate dehydrogenase (IMPDH) enzyme that controls intracellular guanosine triphosphate (GTP) pools. In particular, RBV triphosphate binds to the nucleotide-binding pocket of the enzyme and inhibits the synthesis of viral mRNA polymerase, which leads to a decrease in the viral load. In addition, it inhibits mRNA capping that causes a mutation in the viral replication [88,89]. In clinical trials, it was well tolerated and did not show significant adverse effects [89,90]. Owing to these beneficial activities, RBV is a potential drug candidate in the management of COVID-19.

5.3.5 Umifenovir

Umifenovir is a broad spectrum and multitarget antiviral drug used to treat a wide range of enveloped and non-enveloped viral infections like influenza virus, parainfluenza virus, and coxsackie virus and has shown activity by preventing endosome membrane fusion to virus particles [91]. It interfered with SARS-CoV-2 binding and intracellular vesicle trafficking in Vero E6 cells and is considered for COVID-19 therapy in combination with protease inhibitors [92,93]. In addition, it is a highly selective haemagglutinin inhibitor and thereby suppresses SARS-CoV. It is able to target HA fusion machinery and prevents the COVs virus from absorbing cell surface and entering the cells. Recent studies showed that it improved CoVs infection without effect on the hospitalization rate [94]. Umfenovir treatment coupled with lopinavir/ritonavir is reckoned to retard the development of pulmonary lesions concurrently reducing the respiratory and gastrointestinal COVID-19 viral load thus lowering the transmission [1,93].

5.3.6 Oseltamavir

Oseltamivir, a neuraminidase inhibitor, was originally approved for prophylaxis of infection due to influenza viruses A and B and has no documented *in vitro* activity against SARS-CoV-2 [95]. Recently, it was administered in COVID-19-suspected outpatients without hypoxia. It was found that early administration of oseltamivir prevented the development of olfactory and taste disorders in COVID-19 patients. Intriguingly, it is one of the most widely used drugs for the management of MERS-CoV and SARSCoV-2 in Japan, Korea, and China during the early phase of the COVID-19 pandemic [95,96]. Accumulating data indicates that it had no effect on survival time, however, markedly reduced the duration of hospitalization in COVID-19 patients. Despite not having favorable effects on the laboratory, virological, and radiological findings, it

has shown an improved effect on the electrocardiographic safety parameters in COVID-19 patients [95-97]. However, more randomized clinical trials (RCT) are required to establish evidence on the safety and efficacy as well as effectiveness of oseltamivir use for treating COVID-19 in hospitalized patients.

6. REPURPOSING OF IMMUNOMODULA-TORS AND IMMUNOSUPPRESSANTS

SARS-CoV-2 infects alveolar epithelial cells, macrophages, and vascular endothelial cells. Cytokine storm is a complication in COVID-19 patients, which leads to aggressive inflammation with increased secretion of several interleukins (IL) and interferons (INF). Recently, several drugs that act by inhibiting various inflammatory responses have been evaluated for clinical and therapeutic benefit in COVID-19 patients [19,26].

6.1 Fingolimod and Siponimod

Following the invasion of coronavirus, a series of events, including recruitment of immune cells, cytokine storm, and hyperinflammation, induces uncontrollable endothelial cell damage in patients with COVID-19. Indeed, endothelial integrity is maintained by sphingosine 1-phosphate (S1P) signaling and reduction in serum S1P level is a predictor of clinical severity in COVID-19. Fingolimod and siponimod bind to S1P receptors expressed on lymphocytes and reduce the progress of autoreactive T-lymphocytes and their naive progenitors from secondary lymphoid organs into the circulation [98]. Fingolimod is an approved drug for multiple sclerosis (MS) and acts as an S1P modulator that binds to the endothelium, and improves the integrity of the endothelial barrier. Though it had no effect on intubation and/or mortality rate in patients with moderate COVID-19, evidence exists that fingolimod increased hemoglobin levels and reduced re-admission rate in COVID-19 patients after hospitalization [99]. Intriguingly, it inhibits lymphocytes entry to the inflamed organs and alveolar space and stabilizes pulmonary endothelial integrity by decreasing cytokine storm in COVID-19 patients [99,100]. It is reported that the use of fingolimod or siponimod showed no additional benefit in mild to moderate COVID-19 patients and MS patients with COVID-19 [79]. Recent studies revealed that siponimod did not affect humoral immune responses in COVID-19-vaccinated MS patients [101].

6.2 Colchicine

Colchicine is a lipid-soluble drug used for the treatment of gout, pericarditis, and cancer and now it has been repurposed to treat coronavirus [102]. It acts by interfering with the chemotaxis of neutrophils and monocytes, which are inflammatory cells that have been observed in the lungs of people with severe COVID-19. It disrupts the nod-like receptor protein 3 (NLRP3) inflammasome activation, the most characteristic process triggered by viroporin E, a SARS-CoV-2 component. The colchicine-cytoskeletal proteins (tubulin) complex may block viral entry and replication [103]. In particular, it acts by suppressing the release of IL-1β and IL-18, cytokines associated with COVID-19 severity [103,104]. However, it had no effect on the reduction of mortality and length of hospital stay [105,106]. Moreover, results from the clinical trials do not support its prophylactic use and have no effect on reducing the risk of contracting COVID-19 and such evidence is insufficient to recommend its use in patients with COVID-19.

6.3 Anakinra

IL-1β and cytokine release syndrome (CRS) play a vital role in the progression of SARS-CoV-2-induced ARDS and multiple organ failure [19,26]. Anakinra is used for the treatment of rheumatoid arthritis and was repurposed in the management of COVID-19. It was the first recombinant IL-1β receptor antagonist used as an off-label indication for COVID-19 for patients with elevated soluble urokinase plasminogen activator receptor (suPAR) [107]. In the early stages of the recent pandemic, anakinra was used in combination with corticosteroids to get maximum effect [108]. In clinical trials, comparison to standard care, anakinra did not show any additional benefit in adult hospitalized COVID-19 patients in reducing mortality, safety, clinical improvement, and not worsening severity [109,110]. Several approved anti-inflammatory interleukin modulating monoclonal antibodies, such as canakinumab, siltuximab, sarilumab, risankizumab, ustekinumab, secukinumab, and ixekizumab as well as TNF-α mudulators, such as Infliximab and adalimumab have shown activity against SARS-CoV2 and efficacy in COVID-19 patients and clinical evaluation is still undergoing [111].

6.4 Tocilizumab and Sarilumab

IL-6, a key inflammatory cytokine, is highly elevated in severely ill COVID-19 patients and

the IL6/IL-6 receptor (IL-6R) signaling pathway is a promising therapeutic target for alleviating inflammatory symptoms. Tocilizumab, a recombinant humanized anti-IL-6 receptor monoclonal antibody used to treat rheumatological disorders blocks the assembling of the activated complex with the transmembrane protein (gp130-IL-6-sILr) in suppressing the JAK-STAT signaling pathway and downregulating the downstream inflammatory molecules [111-113]. Preliminary data suggested that tocilizumab controlled the hyper-inflammatory state of CRS induced by chimeric antigen receptor T cells and markedly lowered the risk of mortality and requirement of mechanical ventilation in COVID-19 patients [113,114]. Prospectively, it may be effective in reducing mortality, particularly among critical COVID-19 patients, and could be a potential target for COVID-19. Though its use showed a reduction of 45% in the hazard of death, notably, its use is frequently associated with superinfections. Moreover, the fatality rate was not remarkable between tocilizumab patients with or without superinfections [115]. Sarilumab is a fully human monoclonal antibody used to treat rheumatoid arthritis by inhibiting the binding of IL-6 to its α receptor. It was repurposed to treat respiratory failure caused by cytokine storm in COVID-19 and have shown beneficial effects by inhibiting both soluble and membrane-bound forms potentially by suppressing the pulmonary epithelial and immune cells [116,117]. However, sarilumab treatment did not produce survival benefits in patients with severe COVID-19 at 28 days [118]. In addition, a clinical trial assessing the efficacy and survival benefit was terminated owing to no beneficial effect on clinical outcomes [119].

6.5 Methylprednisolone and Dexamethasone

Corticosteroids, such as dexamethasone, prednisone, methylprednisolone, and hydrocortisone have anti-inflammatory and anti-fibrotic effects and have been repurposed in COVID-19 as they regulate immune-mediated lung injury, reduce the severity of cytokine release syndrome, and decrease the development to respiratory failure and death [120]. It has been reported that appropriate application of corticosteroids could avoid the need for invasive mechanical ventilation and improve the outcomes of critical patients with COVID-19 [121]. Methylprednisolone exerts multiple phenotypic expressions and suppresses cell-mediated immunologic responses of lymphocytes and its safety features make this drug an ideal choice for children with acute respiratory conditions [121,122]. Notably, its use reduced the mortality rate and extended the survival period [123]. It is the first drug that showed maximum efficacy, recovery, and improved survival in COVID-19 patients. Of particular note, dexamethasone reduces the production of pro-inflammatory cytokines, such as vascular endothelial growth factor (VEGF), tumor necrosis factor–alpha (TNF-α), IFN–γ, interleukin IL-1β, IL-2, IL-6, and IL-8. Of these, five cytokines are linked to SARS-CoV-2 severity [123,124]. Indeed, two drugs, dexamethasone and methylprednisolone, have been shown to reduce the duration of mechanical ventilation, improve alveolar-capillary membrane permeability, decrease inflammation, and promote tissue repair. It is reported that methylprednisolone appeared to have lower mortality and benefitted from corticosteroid use in patients above the age of 60 [123-125]. Some preliminary trials showed promising results with the use of dexamethasone and methylprednisolone in the severe form of COVID-19 [123-126]. A growing body of evidence indicates that early on administration of dexamethasone markedly reduced mortality and discharge to hospice in those requiring supplemental oxygen [121,125,127]. These data strongly support the use of systemic dexamethasone in hospitalized COVID-19 patients.

7. REPURPOSING OF ANTIParasitic Agents

7.1 Emetine

Emetine is an antiprotozoal drug and a protein inhibitor once used to treat amoebiasis, dengue, cytomegalovirus, and herpes simplex virus. It has now repurposed for SARS-CoV and MERS as an antiviral showing its activity against RNA and DNA virus [39,128]. Emetine blocks viral invasion and inhibits viral replication so the drug can be enriched in vero cells of lung tissue. Owing to their mechanism of action, antiviral and anti-inflammatory activities, as well as safety profile, several alkaloids, including emetine, cephaeline, and papaverine have been evaluated for their use in the treatment of COVID-19. It is reported that emetine has a high potential to inhibit SARS-CoV-2 [129-131]. Additionally, emetine was found to have synergistic activity against other antivirals like remdesivir [39]. Prospectively, Acer Therapeutics has partnered with the National

Center for Advancing Translational Sciences to evaluate emetine for the potential treatment of COVID-19 patients [132].

7.2 Nitazoxanide

Nitazoxanide (NTZ) shows antiparasitic activity against *Giardia lamblia* and *Cryptosporidium parvum*. It is a broad-spectrum antiviral drug used to treat coronavirus, such as SARS-CoV-1, SARS-CoV-2, MERS-CoV, and murine coronavirus through modulation of host innate immune responses [133]. It may be used alone or in combination with remdesivir, umifenovir, and amodiaquine exhibiting synergistic activity [134,135]. It targets endosomal and fusion into the host cells by intensification of the IFN pathway, depletion of ATP-sensitive Ca^{2+} store, augmentation of cytoplasmic RNA sensing, impairment of viral replications, phosphorylation of protein kinase, and inhibition of cellular translation thus causing reduction in COVID-19 [136]. An interim analysis of the currently undergoing clinical trial of nitazoxanide showed a greater reduction in viral load compared to the placebo and the final results awaiting [137]. An RCT has been undergoing to evaluate the safety and efficacy of favipiravir and/or nitazoxanide as early therapy in COVID-19 [138].

8. REPURPOSING OF ANTICANCER DRUGS

Owing to similarities of clinical characteristics between the pathogenesis of cancer and SARS-CoV-2 infection, such as inflammation, immune dysfunction, and coagulopathy, repurposing provides a biological rationale for evaluating immunosuppressive anticancer agents to reduce the course and/or alleviate symptoms of COVID-19. Several anticancer drugs, such as interferon, bicalutamide, and pembrolizumab have already been clinically tested for repurposing, alone or in combination [139-142]. Valrubicin has an antiangiogenic function that can bind and inhibit SARS-CoV-2 Mpro and proteases which are required for replication [139]. Therefore, it is a good candidate drug for COVID-19. Clinical studies reported that early administration of interferon β-1a as well as a combination of pembrolizumab and tocilizumab effectively reduced the duration of hospital stay and early discharges without any complications compared to the standard care in COVID-19 patients [142,143]. A recent molecular docking study demonstrated that tucatinib, irinotecan, selinexor, dacomitinib, olaparib, lapatinib, ibrutinib, and pazopanib act most effectively as potential inhibitors against Mpro, the main protease of COVID-19, which regulates the spread of this infectious disease [144]. Based on the results from *in silico* approach, further *in vitro, in vivo* studies, and human trials will evaluate the efficacy of these drugs against COVID-19.

9. REPURPOSING OF BRADYKININ 2 RECEPTOR ANTAGONISTS

9.1 Icatibant

Icatibant, a bradykinin type 2-receptor antagonist, showed safety and effectiveness against hereditary angioedema attacks and pulmonary edema in COVID-19 patients. It is due to activation of B1 and B2 receptors in the lungs and may be beneficial for COVID-19 patients by inhibiting bradykinin's action on endothelial cells and by inhibiting the SARS-CoV-2 M protease [145]. ACE2 catalyzes the inactivation of angiotensin II (Ang II), and its putative inhibition by SARS-CoV-2 could result in increased systemic levels of Ang II. The risk of renal, circulatory, and electrolytic abnormalities was noticed in hypertensive and diabetes patients because of abnormality in the renin-angiotensin-aldosterone system, which further complicates the severity of COVID-19 [146]. Pulmonary edema in COVID-19 is inhibited by icatibant which blocks the increase in vascular permeability mediated by bradykinin [147]. A recent proof-of-concept study reported that the addition of icatibant to the standard care of COVID-19 was safe and improved both COVID-19 pneumonia and mortality [148]. Further, RCTs are necessary to establish the clinical value and therapeutic benefit of this treatment.

10. REPURPOSING OF MONOCLONAL ANTIBODIES

Evidence established that COVID-19–related hospitalization and death can be prevented prophylactically by giving immediate passive humoral immunotherapy with neutralizing monoclonal antibodies like bamlanivimab and etesevimab which were isolated from two separate patients who recovered from COVID-19 in North America and China. These antibodies inhibit viral entry into host cells by targeting the S protein of SARS-CoV-2 [149,150]. The FDA granted EUA to neutralizing antibody bamlanivimab as a treatment for mild-to-moderate COVID-19 in adults and youths ages 12 years and older [150]. Further, the

administration of bamlanivimab lowered nasopharyngeal viral levels and faster reductions in inflammatory markers and viral decay in hospitalized COVID-19 patients whereas it did not reduce the symptom duration in non-hospitalized adults with early variants of SARS-CoV-2 [151]. Blocking viral attachment and cell entry with SARS-CoV-2 neutralizing antibodies (BLAZE-1) clinical trial showed that bamlanivimab monotherapy and combination therapy bamlanivimab with etesevimab were efficacious in reducing the risk of COVID-19–related hospitalization and progression to severe disease [152,153]. Though the FDA revoked the EUA due to poor efficacy, it is still available as a combination therapy [150]. On the other hand, the development of resistance to monoclonal antibodies stopped the progression of the clinical trial. This combination may be repurposed as a cocktail regimen for managing COVID variants.

11. REPURPOSING OF JAK-STAT INHIBITORS

11.1 Baricitinib

Baricitinib, a small molecule JAK1 and JAK2 inhibitor used in the treatment of rheumatoid arthritis, effectively reduced SARS-CoV-2 viral infection by inhibiting clathrin-mediated endocytosis [154,155]. One of SARS-CoV-2's key virulence factors is its ability to downregulate ACE2 expression after cell entry, thereby thwarting ACE2 lung-protective effects [155]. Interruption of AP2-associated protein kinase 1 (AAK1) an important regulator in endocytosis might inhibit the passage of virus into cells and the intracellular assembly of virus particles [154]. Accumulating clinical data suggests that baricitinib when used as an add-on to standard therapy, either alone or in combination with other drugs, has shown clinical benefit and improved COVID-19 pneumonia in hospitalized patients with moderate to severe COVID-19. Recently, the US FDA approved baricitinib, and is the first immunomodulatory treatment for COVID-19 [156]. Ruxolitinib is another selective JAK-1 and JAK-2 Inhibitor approved for the treatment of myelofibrosis, polycythemia vera, graft-versus-host disease, and hemophagocytic lymphohistiocytosis**.** Ruxolitinib shows anti-inflammatory effect in COVID-19 by decreasing the production of inflammatory cytokines such as transforming growth factor-beta (TGF-β), IL-10, IL-12, and IL-23 [157]. One clinical trial was prematurely terminated for generating external evidence and therefore it is difficult to correlate favorable effects of baricitinib in severe COVID-19 [158]. Adding to this, a combination of ruxolitinib with simvastatin had no impact on the clinical outcome and survival benefits of COVID-19 [159].

11.2 Camostat Mesylate

Camostat mesylate is a promising repurposed drug against COVID-19 that inhibits many of the serine proteases that SARS-CoV and SARS-CoV-2 use for virus-to-host cell membrane fusion, viral particle entry, and possibly inflammation [160]. ACE2 is the target for SARS-CoV-2 as its cell entry receptor to infect human cells. This mechanism utilizes the human epithelial cell (respiratory, gastrointestinal tracts) surface-expressed Transmembrane Serine Protease 2 (TMPRSS2). Camostat and nafamostat potently inhibit SARS-CoV-2 and MERS-CoV infection in cultured human airway epithelia; nafamostat was a more attractive candidate to prevent COVID-19 lung disease as it exhibited greater potency than camostat in reducing SARSCoV-2 infection. Nafamostat inhibited SARS-CoV-2 infection and improved disease outcomes. These serine protease inhibitors (camostat and nafamostat) markedly reduce SARS-CoV-2 and MERS-CoV infections in primary cultures of airway epithelia by inhibiting the activity of cell surface serine proteases (TMPRSS2) [161,162]. Together, the safety of camostat was established in the management of COVID-19, however, this study did not reveal therapeutic benefits in mild to moderate COVID-19 [163]. In several clinical trials, camostat mesylate did not reduce the time to viral clearance and had not shown efficacy as an antiviral drug against SARS-CoV-2 [163,164].

12. CONCLUSION

COVID-19 has been a historic pandemic that affected millions of lives. Healthcare professionals have been in a struggle to find the right drug and rapid cure for the disease. Among various available approaches, drug repurposing is the most beneficial approach considering both the time and cost of development and clinical evaluation of new drugs. Various therapeutic classes, such as antibiotics, antivirals, antiparasitics, immunomodulatory and immunosuppressants as well as biological monoclonal antibodies were repurposed. In this process, few drugs have been found to be effective in decreasing the severity of symptoms while others have been withdrawn from use

because of unfavorable and unintended effects. The favorable therapeutic benefits and clinical outcomes of evaluated drugs resulted in the emergency use authorization of a few successful drugs in view of the effective management of COVID-19 in hospitalized patients during the unprecedented time. A deep understanding of the virus, experience gained from previous epidemics, genomic database of variants of the virus as well as novel approaches and robust technologies have made it possible to modulate viral replication, and inflammatory cascades, and identify numerous therapeutic targets in the attempt to drug repurposing. These continuous efforts of drug repurposing and application of novel therapeutic modalities in the management of this infectious disease would accelerate and strengthen the global preparedness for the next crisis.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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