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Drug repositioning approach to target viral and host cells in terms of COVID-19 treatment: A review of in vivo experiments and clinical studies

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Abstract

While the COVID-19 pandemic is expanding at an alarming rate, there is currently no treatment option for this disease. Therefore, it is necessary to find an effective treatment special for hospitalized COVID-19 patients at the earliest possible time. One of the promising options which should be investigated is the possible effects of old drugs or drug repositioning. This strategy has less risk with more economic advantages and can benefit the long-term control of this pandemic. Our study aimed to give an overview, update the current status of drug candidates (both virus-targeting and host-targeting drugs) for repurposing in COVID-19 infection, and assess the possible mechanism of their effect, in vivo antiviral efficacy, and clinical studies.

Keywords: COVID-19, Drug repurposing, therapeutic, pandemics.

1. Introduction

Ribonucleic acid (RNA) viruses are the most infected pathogens that can spread very fast for their capability of zoonotic potential, evolvability, and enhanced virulence (1, 2). Despite advances in technologies to study these viruses in the last two decades, it has been impossible to stop the rapid evolution of these viruses, leading to pandemics (3). The prevalent coronavirus strains that can infect humans include HCoV-OC43, HCoV-NL63, HCoV-229E, and HCoVHKU, with the capability of mild respiratory illness (4, 5). In the twenty-first century, the first outbreak of human coronavirus was the severe acute respiratory syndrome (SARS-CoV) in China, and this fatal respiratory illness killed around 750 people (6-8). The second coronavirus outbreak occurred in the Middle East countries, named Middle East respiratory syndrome coronavirus (MERS-CoV), and led to the death of 866 people (9, 10). The most extensive human coronavirus outbreak started in Wuhan in China's Hubei Province in December 2019 (11). This human coronavirus, known as coronavirus disease 2019 (COVID-19), spread quickly worldwide and was announced a pandemic in March 2020 (10-15).

Sudden and fast outbreaks of COVID-19 caused a unique challenge in choosing proper treatments within the short time available for drug analysis and development for healthcare professionals. Although there is no particular medicine against COVID-19, more than 80 clinical trials have been developed to test therapeutic approaches for COVID-19, including drug repurposing or repositioning (16). Some clinical trial steps, especially phases I and II, might not be required in the drug repositioning strategy. Existing pharmaceutical supply chains are available for formulation and distribution in drug repositioning, and new mechanisms of action for old drugs and new classes of medicines may be discovered. Therefore, this medical strategy has lower costs (17, 18). This study aimed to collect and summarize all clinical and in vivo findings related to the old drugs–COVID19 disease, and assess the mechanism of action to introduce a suitable therapy for this infectious disease.

2. Research Method

This study involved articles and relevant data investigating the antiviral activity of available drugs in clinical and preclinical phases (in vivo), published until October 3, 2021. We collected information by searching in Google Scholar, PubMed/MEDLINE, Scopus, Cochrane Library, clinicaltrials.gov website, and valid encyclopedia. We combined the keywords "Drug repositioning", OR "Drug

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repurposing", and "clinical future" with the keywords "SARS-CoV-2" OR "COVID-19" as search terms. We removed the in silico and in vitro studies. We did not restrict the search regarding the type and language of studies. We included all kinds of published research projects, reviews, comments, letters, editorials, and eBooks and used Google Translate software to review studies written in the English language.

3. Result

3.1. Classification of candidate drug targets

Potential drug targets must be selected from among several viral and host molecules to achieve a successful drug treatment of COVID-19 (Figure 1). The macro-molecule such as RNA/DNA and proteins participating in vital processes of the virus infection cycle, such as replication, cell entry, host metabolic pathways, and immune response, can be regarded in this case (19). This study comprehensively reviewed the drug repositioning used in COVID-19 in two categories: Virus targets and host drugs.

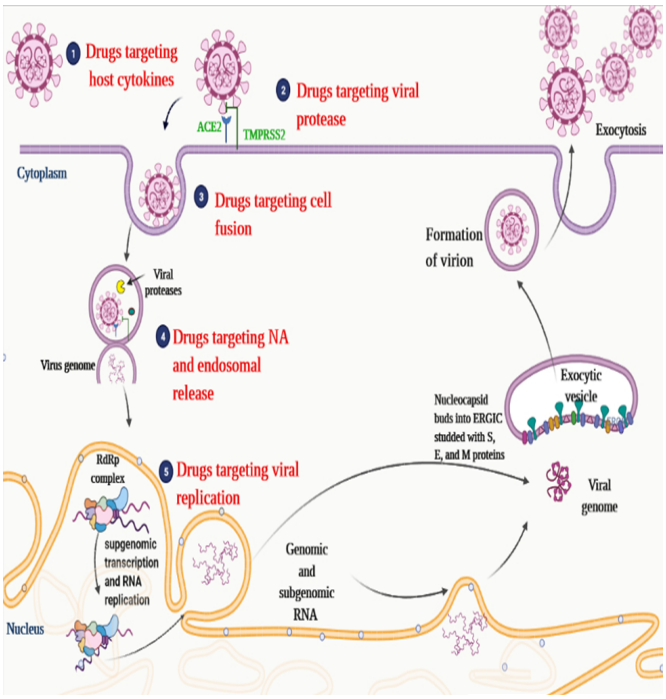

Fig. 1. Therapeutic targets for the drug repositioning to combat COVID-19 based on the virus life cycle

1: Drugs that suppress coronaviruses by enhancing host immune system activity and release interferons

2: The fusion of the viral spike proteins with the cellular ACE2 receptor causes the entrance of the virus to the host cell. Then, the ACE2 is downregulated. Therefore, the drugs targeting viral protease or enhancer ACE2 expressions, such as Angiotensin-converting enzyme inhibitors (ACEIs) and Angiotensin receptor blockers (ARBs), may have efficacy in this condition

3: After endocytosis of the virus, the drugs can disturb viral endosteal conditions, such as reducing endosomal pH and helping lysis viral structural proteins

4: The drugs that can suppress viral nucleic acid (NA) and translation of the viral proteins by host ribosomes may have antiviral activity

5: Drugs that can inhibit RNA-dependent RNA polymerase (RDRP) as the main viral protease enzyme making functional proteins to stop viral replication in the host cell

3.2. Virus based drug repositioning

3.2.1. Drug repositioning that targets viral replication

The key enzymes in the replication of the COVID-19 virus (e.g., protease and polymerase) are highly conserved, with 96% and 97% overall identity (GISAID,2020). Therefore, drugs that could bind protease or polymerase sites of the SARS virus may also be good therapeutic candidates against the COVID-19 virus (Table1).

3.2.1.1. Remdesivir

One of the novel RNA polymerase (RdRp) inhibitor drugs that have been developed against the Ebola virus for the first time is remdesivir. Remdesivir is the only FDA-approved drug for treating COVID-19 patients (20, 21). From a mechanistic point of view in the coronavirus, remdesivir in the cells is metabolized to remdesivir triphosphate (RTP), an active NTP analog (22). The RTP can be used as a substrate by the RdRp resulting in remdesivir Monophosphate (RMP) merging into the growing RNA product (23, 24). A cohort study observed clinical improvement in 36 of 53 patients (68%) with severe COVID-19 who received remdesivir (25). Similar results were also reported by other studies (26) (27) (20). On the other hand, one study reported that there was not a significant difference in clinical benefits after ten days of remdesivir prescription in hospitalized COVID-19 patients at ten hospitals in China (28). Several clinical trial studies in China and USA (NCT04252664, NCT04292899, and NCT04257656) reported that patients with COVID-19 could tolerate remdesivir prescription (28, 29). Most meta analysis studies evinced that a 5-day course remdesivir administration to severe COVID-19 patients might have more positive effects and decreased mortality with lower drug costs than a 10-day course (30-33). However, other meta analysis studies stated stronger evidence about the need to administer remdesivir to severe COVID-19 patients. (34, 35), while one meta analysis study showed that remdesivir administration should not be recommended for use especially in countries with low inclome (36).

3.2.1.2. Favipiravir

Favipiravir (approved in Japan for influenza since 2014) is a small purine analog, transformed into its active ribofuranosyl 5'-triphosphate metabolite in the cell, and can be linked to the growing RNA strand (37). Since the antiviral activity of favipiravir in clinical trials may be more potent than in vitro, this drug is being conducted in several randomized trials against COVID-19 in combination with other drugs (38-42). The prescription dose of favipiravir for COVID-19 patients is i.e. 53 mg/kg/day. Favipiravir oral bioavailability is close to 100% (43). This antiviral drug acts dose-dependent and has a short half-life of 2–5.5 h (43-45). Some studies demonstrated that favipiravir could improve clinical conditions and decrease the median time to viral clearance in mild to moderate COVID-19 patients (39). However, this was not reported for severe COVID-19 (46). Evidence from a meta-

analysis study showed that favipiravir might not decrease mortality in patients with mild to moderate COVID-19 (47). On the other hand, another meta-analysis study reported that favipiravir leads to the clearance of the virus by seven days, takes part in clinical improvement within 14 days, and can decrease the mortality rate by more than 30% (48).

Table 1. List of drug repositionings that have the potential to target the virus and may be used against COVID-19 infection.

Drug name	Drug Indication	Target	Effect	Invivo test	Clinical trials	References
emdesivir	Antiviral (Ebola and Marburg)	RdRp	viral replication inhibitor	Rhesus macaques, mouse	NCT04292730- Phase 3 NCT04292899- Phase 3 NCT04257656 Phase 3 NCT04401579- Phase 3	(20, 28, 29, 185, 186)
avipiravir	AntiRNA viral (influenza, Rhino, and Respiratory Syncytial Virus)	RdRp	viral replication inhibitor	Hamster	NCT04358549- Phase 2 NCT04346628- Phase 2 NCT04303299- Phase 3	(38-42, 187, 188)
ibavirin	Antiviral	RdRP, Inosine monophosphate dehydrogenase	viral replication inhibitor	N/A	NCT04276688- Phase 2 CTOROTSADTOC IRCT20200324046850N2- Phase 2 NCT04392427- Phase 3	(55-58)
ofosbuvir	AntiRNA viral (flaviviridae, HCV)	RdRp	viral replication inhibitor	N/A	IRCT20200624047908N1- Phase 3 IRCT20200128046294N2- Phase 3 IRCT20130812014333N145- Phase 3 IRCT20100228003449N29- Phase 2–3	(63-65)
Tenofovir/ Emtricitabine	Antiviral (HIV-1)	NRT	viral replication inhibitor	N/A	NCT04685512- Phase 2 NCT04519125- Phase2 NCT04334928-Phase 3 NCT04405271- Phase 3	(68, 69, 71, 72)
Azvudine	Antiviral (HIV-1, HBV, HCV)	NRT	viral replication inhibitor	N/A	ChiCTR2000029853 NCT04668235- Phase 3 NCT04425772- Phase 3	(74-76)
vermectin	Anti-parasit	Nuclear transport activity	viral replication inhibitor	Hamster, Mous	NCT04646109- Phase 3 NCT04381884- Phase 2 NCT04739410- Phase 4	(99, 102-105, 189)
olnupiravir	AntiRNA viral (influenza)	RNA replication	viral replication inhibitor	Hamster	NCT04405570- Phase 2	(107, 108)
arunavir	Anti-retroviral (HIV-1)	Protease	viral entery inhibitor	N/A	NCT04425382 NCT04252274- Phase 3 NCT04303299- Phase 3	(27, 80, 190), (, https :// www.sd.china news. com/2/2020/0205/ 70145.html)
Lopinavir-ritonavir	Anti-retroviral (HIV-1)	Protease	viral entry inhibitor	Ferrets	NCT04330690- Phase 2 NCT04372628- Phase 2 NCT04276688- Phase 2	(57, 86-88, 90, 91, 142, 191)
afamostat	Anticoagulant	Protease	viral entery inhibitor	Mous	NCT04418128- Phase 2,3 NCT04352400- Phase 2,3	(94-96)
Proxalutamide And 5-alpha-reductase inhibitors	Antiandrogen	Protease	viral entery inhibitor	N/A	NCT04728802-Phase 3 NCT04870606- Phase 3 NCT05009732- Phase 3 NCT04853927- Phase 3	(109, 115, 116, 118)

3.2.1.3. Ribavirin

Ribavirin is a guanosine analog causing a disturbance in virus genome replication. This antivirus drug interferes with polymerases and can disturb RNA capping, depending on natural guanosine to stop RNA degradation. In addition, ribavirin can inhibit natural guanosine generation in the virus by directly inhibiting inosine monophosphate dehydrogenase in a critical pathway of transforming guanine precursor to guanosine (49, 50). Although there is no in vivo study on the effect of ribavirin on COVID-19, a previous in vivo study on the effect of ribavirin on SARS and MERS-CoV infected mice reported that this drug could not increase the survival rate (51, 52). Moreover, monotherapy of ribavirin is insufficient to inhibit coronavirus, and combinatorial therapies with LPV/r and IFN-a for MERS-CoV (53) and with LPV/r viral protease inhibitors for SARS-CoV are recommended (54). The clinical trials' efficacy of ribavirin in treating COVID-19 patients is being tested. The oral prescription of this drug (400 mg per day) combined with another drug such as interferon-alpha or lopinavir/ritonavir could improve symptoms in mild to moderate COVID-19 (55-58).

3.2.1.4. Sofosbuvir

Sofosbuvir is a uridine nucleotide analog prodrug that causes RNA chain termination in RNA virus HCV and competitively blocks HCV NS5B polymerase (59). Since COVID-19 and HCV are both positive-sense RNA viruses, sofosbuvir as an RNA polymerase inhibitor drug is expected to be effective for COVID-19 (60, 61). Although sofosbuvir alone could not inhibit COVID-19 in Vero cells, it can do so in hepatoma Huh-7 cells (EC50= 6.2 mM, SI= 61) and human lung adenocarcinoma Calu-3 cells (EC50= 9.5 mM, SI= 54) (62). Meanwhile, a drug combination of daclatasvir and sofosbuvir could inhibit COVID-19 in all three cell lines (EC50= 0.6~1.1 mM, SI= 34~47) (60). Several clinical trial studies were carried out to assess the use of sofosbuvir/daclatasvir in COVID-19 patients. Oral prescription of sofosbuvir/daclatasvir (60-400 mg per day) or sofosbuvir/velpatasvir in moderate to severe hospitalized COVID-19 patients had improved clinical outcomes (63-65).

3.2.1.5. Tenofovir/emtricitabine

Tenofovir and emtricitabine are the analogs of adenosine 5′-monophosphate and cytidine that can inhibit nucleoside reverse transcriptase in HIV-1 (66, 67). The coadministration of these drugs is used as a backbone of antiretroviral therapies. The clinical finding showed that the use of tenofovir/emtricitabine in non-severe COVID-19 patients (68) is suitable, but the significant effect of prophylactic efficacy of tenofovir/emtricitabine against COVID-19 was not observed (69, 70). Two ongoing clinical trial studies on this subject are about the prophylactic efficacy of tenofovir/emtricitabine against COVID-19 in Healthcare Workers from Argentina and Colombia (71, 72).

3.2.1.6. Azvudine

Azvudine is a cytidine analog that can act as the chain terminator in proviral genome biosynthesis in various types of viruses (73). Several clinical studies have been carried out to assess the positive effect of this drug in COVID-19 patients (74-76). A randomized, open-label, controlled clinical trial showed that oral administration of Azvudine in mild COVID-19 patients could shorten the nucleic acid negative conversion (NANC) time compared to the control group (74).

3.2.2. Drug repositioning that targets viral protease

The RNA of the virus is converted into polypeptide through translation and then packed into virions after the cleavage by the main viral proteases (11). Since protease in COVID-19 has a 96% overall similarity with SARS-CoV (77), the use of some protease inhibitors prescribed in HIV and SARS-CoV therapy may be effective against COVID-19 (77, 78).

3.2.2.1. Darunavir

Darunavir is a non-peptide protease inhibitor against HIV-1, has more inhibitor potential than the other protease, enhances binding affinity, and reduces dissociation rate (79). Although there is no in vivo and preclinical evidence, several clinical news reports evinced that oral prescription of darunavir (600 mg tablet every 12 h) with other antiviral drugs and supportive therapy could be effective in COVID-19 patients (27). However, a randomized open-label controlled trial in China (NCT04252274) reported no improved symptoms in mild COVID-19 patients after 5-day Darunavir/Cobicistat treatment (80).

3.2.2.2. Paxlovid

Paxlovid is traditionally used to fight HIV (81). According to the last reports, this drug could bind to the COVID-19 3CL-like protease and disturb the virus's function, host cell entry, and reproduction (81, 82). The interim analysis of the clinical phases in 1219 COVID-19 adults patients that received paxlovid after three days of covid-19 symptoms showed the risk of hospital admission or death in COVID-19 patients treated with paxlovid was 89% lower than that in the placebo group (82).

3.2.2.3.Lopinavir/ritonavir

Currently, the combination of these two drugs is used to treat and prevent HIV infection. Lopinavir can make uncleavable peptidomimetic of the linkage peptide in HIV gag-pol polyprotein that inhibits HIV protease activity by binding to it (83, 84). Regarding the host proteases' rapid degradation of lopinavir in the body, a lower dose of ritonavir (a protease inhibitor) must be used to inhibit CYP3A4 and help lopinavir remain active for a longer time (85). Despite the differences in the main proteases of HIV and coronavirus, the use of nonspecific protease inhibitors in HIV therapy (Lopinavir/ritonavir) has more clinically positive effects than the control group in clinical studies of SARS-CoV patients (54). Some clinical studies reported that lopinavir and ritonavir therapy could reduce the viral load (86-88). WHO uses the prescription of lopinavir/ritonavir alone or in combination with interferon-beta (INF-β) as an option for a "solidarity" clinical trial for COVID-19 patients (89, 90). Moreover, the combination of ritonavir-lopinavir and umifenovir in COVID19-patients could substantially halt the progression of lung damage (91).

3.2.2.4. Nafamostat

This drug is a synthetic serine protease inhibitor and an anticoagulant in nature. This drug could inhibit COVID-19 in the Vero E6 cells at a 50% effective concentration of 22.50 μM (92). Nafamostat has high efficiency in inhibiting the entry of the COVID-19 virus into host cells (93). The in vivo observation showed that the mice treated with nafamostat before COVID-19 infection had less virus-induced weight loss, viral replication, and mortality than the untreated control mice (94). Several clinical trials are studying these drugs (95-97).

3.2.2.5. Ivermectin

Ivermectin is commonly used as an anti-parasitic drug that has recently exhibited efficacy against some viral infections. Although the exact antiviral mechanism of ivermectin is unknown, a recent study suggested that this drug may inhibit

the importin (IMP) α/β1-mediated nuclear import of viral proteins (98). This drug may prevent clinical deterioration due to its immunomodulatory activities through the cholinergic anti-inflammatory pathway (99). The combination of ivermectin and hydroxychloroquine may inhibit both entry and replication of COVID-19 and thus has a synergistic effect. Therefore, combination therapy for the prophylaxis or treatment of COVID-19 was suggested (100). The main problem with administering ivermectin is the need for a high dosage to achieve antiviral activity (101). The ivermectin therapy (150 mcg/Kg) for COVID-19 patients in a case-controlled study decreased the mortality rate and the duration of hospital stay (102). Some clinical studies reported an improvement in the symptoms of severe COVID-19 after the treatment (103-105).

3.2.2.6. Molnupiravir

Molnupiravir is the newest experimental antiviral drug for treating influenza and disrupts viral RNA replication (106). The in vivo study on the combined effect of molnupiravir and favipiravir on infected hamsters with COVID-19 showed strong antiviral activity and reduced transmission of the virus to uninfected contact sentinels (107). Although molnupiravir administration for COVID-19 is only just beginning to go through the first clinical trials, this drug is known as the first oral and direct-acting antiviral that has been highly effective against COVID-19. This drug has a favorable safety and tolerability profile and can reduce the nasopharyngeal COVID-19 infectious virus (108).

3.2.2.7. Proxalutamide and 5-alpha-reductase inhibitors

5-alpha-reductase inhibitors are a group of anti-androgen drugs used to treat prostate gland hyperplasia and male pattern hair loss. Proxalutamide has androgen antagonism action and downregulates androgen expression, which was developed to treat prostate and breast cancer (109). In COVID-19 infectivity, androgen signaling has a critical role. The serine 2 (TMPRSS2), androgen-promoted enzyme, and transmembrane protease in the host cell help virus entry mediated by viral spike proteins (110). The TMPRSS2 could modify viral spike proteins and, therefore, increase the virus's binding to angiotensin-converting enzyme 2 (ACE2) and viral entry into host cells (111). Some epidemiologic and clinical evidence demonstrated that the severity of COVID-19 disease is related to the androgen-mediated phenotype androgenetic alopecia (AGA) (112, 113). Therefore, COVID-19 in male patients with more advanced AGA is more likely to need more care or die (114). The newest clinical reports showed significant clinical symptoms of COVID-19 infection and a lower mortality rate in men patients undergoing androgen deprivation therapy (ADT) (109, 115-117). A recent finding showed that Proxalutamide could help nonhospitalized COVID-19 patients with mild to moderate symptoms to clear the virus much faster than those given a placebo (110, 118). Therefore, proxalutamide could be a good candidate in the global fight against COVID-19. Nevertheless, more detailed studies are needed to make more accurate comments.

3.2.2.8. Casirivimab and imdevimab

Casirivimab/imdevimab is a combinational medicine consisting of two human monoclonal antibodies that can be bound to different sites on the receptor-binding domain of the spike protein of COVID-19 and can block its attachment to the human ACE2 receptor (119). Primary clinical studies reported that administration of casirivimab and imdevimab can prevent symptomatic infection, reduce overall infection, and decrease viral load and duration of viral RNA detection in COVID-19 (120). These antibodies in high-risk patients with mild to moderate COVID-19 infection could significantly reduce hospitalization rates (121, 122). In contrast, another study reported that using bamlanivimab/etesevimab in patients infected by the Gamma variant of COVID-19 could enhance the risk of hospitalization or death (123). Therefore, knowing which COVID-19 variant infection is in question may allow more appropriate use of these drugs.

3.3. Drug repositioning targeting host cell

3.3.1. Drug repositioning targeting cell fusion

The drugs inhibiting the fusion can prevent the fusion process during viral entry into the host cells (Table 2). Therefore, they prevent the virus entry into the host cell (124, 125).

3.3.1.1. Arbidol (umifenovir)

Arbidol, also called umifenovir, is a small indole-derivative molecule, showing activity against a wide range of enveloped and nonenveloped viruses (126). This drug has an approved therapeutic effect on prophylaxis and influenza virus infection (127). Arbidol can hinder the hemagglutinin fusion machinery by inhibiting viral membrane fusion and blocking virus entry into the cell (127). According to clinical studies, arbidol treatment coupled with lopinavir/ritonavir could reduce the development of pulmonary lesions and viral load, lowering the transmission of mild to severe COVID-19 patients (90, 91, 128, 129). However, some clinical trial studies reported that the administration of arbidol and lopinavir/ritonavir monotherapies in mild/moderate COVID-19 patients had no significant effect on the viral negative conversion rate and symptom improvement (130, 131).

3.3.1.2. Baricitinib and ruxolitinib

Like other viruses, receptor-mediated endocytosis has a vital role in the COVID-19 virus's entrance into the host cells. Regulation of the process of endocytosis is undertaken by AP2-associated protein kinase 1 (AAK1). Thus, the drugs targeting AAK1 block the viral entry and the intracellular viral assembly (132). Baricitinib and ruxolitinib are Janus kinase (JAK) inhibitors with a high potential to bind to and inhibit AAK1 (133, 134). Suppression of inflammation through inhibiting the production of cytokines and chemokines by macrophage and neutrophil recruitment was observed in baricitinib-treated infected animals (135). Clinical trials on baricitinib and ruxolitinib considered the effect of these drugs on the control of cytokine storms in

severe COVID-19 patients (136, 137).

Table 2. List of drug repositionings that have the potential to target the host cell and may be used against COVID-19 infection

Drug name	Drug Indication	Target	Effect	Invivo test	Clinical trials	References
Arbidol (Umifenovir)	Antiviral (influenza A and B)	Spike glycoprotein	viral entry and post-entry inhibitor	Hamsters, Mouse, Rat	ChiCTR2000029592 NCT04286503- Phase IV NCT04260594- Phase IV NCT04255017- Phase IV	(90, 91, 128-131, 192-194)
Baricitinib	kinase inhibitors.	Janus-kinase 1/2	Cytokine storm inhibitor	Rhesus macaques	NCT04640168- Phase III NCT04693026- Phase III NCT04358614- Phase II, III	(135, 195-197)
Ruxolitinib	kinase inhibitors.	Janus-kinase 1/2	Cytokine storm inhibitor	N/A	NCT04362137-Phase III NCT04334044- Phase I, II NCT04338958- Phase I, II	(136, 137, 198, 199)
Chloroquine and hydroxychloroquine	Anti-malarial	Glycosylation of the host receptor for the virus, Change in endosomal pH, angiotensin converting enzyme 2	Viral entry inhibitor and Post-entry Inhibitor	Mous, Ferrets, Hamsters, Rhesus macaques	NCT04353336- Phase II, III NCT04331600- Phase IV NCT04334148-Phase III NCT04355026- Phase IV	(27, 143-146, 200)
Angiotensin Receptor Blockers and renin-angiotensin-aldosterone system (RAAS) inhibitors	Using treat high blood pressure and heart failure	Angiotensin converting enzyme	Viral entry inhibitor	N/A	NCT04335123- Phase I NCT04312009- Phase II NCT04428268- Phase II	(153-155)
Azithromycin	Antibiotic	Change in cytokines and endosomal pH (Not conclusive)	Inhibits IL-6 production	N/A	NCT04622891 NCT04349592 NCT04381962- Phase III NCT04332107- Phase III NCT04334382- Phase III	(158-163, 201)
Tocilizumab	Using treat rheumatoid arthritis	IL-6 receptor	Inhibits IL-6 release	N/A	NCT04445272- Phase II NCT04730323- Phase IV NCT04479358- Phase II NCT04331795- Phase II	(166, 167, 202-205)
Dexamethasone and Methylprednisolone	Corticosteroid	Inflammatory cells	Inhibits release of cytokines	Mous	NCT04325061- Phase IV NCT04395105- Phase III NCT04347980- Phase III	(168, 170, 171, 206)
Interferons (pegylated IFNα-2a and pegylated IFNα-2b)	Antiviral	B cells through a host interferon receptor, IFNAR1 signalling	Enhanced immune response against viral infections	N/A	NCT04349410- Phase III NCT04273581- Phase II NCT04379518 -- Phase I, II	(42, 176, 207)
Statins	lipid-lower	Angiotensin converting enzyme 2	Improve endothelial dysfunction	N/A	NCT04486508-Phase III NCT04380402- Phase II IRCT20190727044343N2-Phase II–III NCT04390074	(183, 184)

3.3.1.3. Chloroquine and hydroxychloroquine

Chloroquine and its derivative hydroxychloroquine, known for its antimalarial actions, can also interfere with the endosome-mediated viral entry in the host cell and the late stages of viral replication in an acidic environment (138). Therefore, these drugs have exhibited broad-spectrum antiviral activities (138). The in vivo antiviral effect of these drugs against COVID-19 was highly controversial. Hydroxychloroquine did not have antiviral activity in hamsters and macaques (139-141). In addition, it decreased the clinical scores in ferrets but did not affect the viral titers (142). Although large-scale clinical trials have not yet confirmed the efficacy of chloroquine and hydroxychloroquine against COVID-19, these drugs have been considered in several recent clinical studies to combat COVID-19. Nowadays, the answer to the question of "whether the administration of these antimalarial drugs can be repurposed for the treatment of COVID-19" has sparked much interest globally. Some clinical trial studies reported prophylactic and therapeutic efficacy of chloroquine and hydroxychloroquine against COVID-19 (27, 143-146). However, the use of chloroquine against COVID-19 needs a high dose, leading to an overdose of chloroquine and,

consequently, poisoning and death (147, 148). Although hydroxychloroquine is less toxic in animal models (149), this drug has shown side effects such as prolonged heart failure and QT interval. WHO recently stopped the hydroxychloroquine arm of the Solidarity Trial conducted to find an effective COVID-19 treatment.

3.3.2. Drug repositioning targeting host cytokines

3.3.2.1. Angiotensin receptor blockers

COVID-19, like other coronaviruses, binds to the ACE2 receptors (150). There is a significant relationship between COVID-19 infection and the process of chronological aging due to the presence of two host receptors, CD26 and ACE2, associated with senescence (151). The Angiotensin receptor blockers (ARBs) drugs inhibit the action of ACE, an isoform of ACE2 that can enhance the expression of ACE2 (152). Some clinical studies showed that ACEI/ARB drugs did not decrease the mortality rate of COVID-19 patients with cardiovascular diseases (153), while others reported that ACEIs/ARB drugs decreased the mortality of COVID-19 patients more than the control group (154). This drug can decrease the peak of viral load and level of IL-6 in peripheral blood through the increment of CD3 and CD8 T cell counts in peripheral blood. This process may positively affect the clinical condition of COVID-19 patients (154). Nevertheless, clinical studies on the effect of ACEIs/ARB drugs on COVID-19 patients are ongoing (155).

3.3.2.2. Azithromycin

Azithromycin has anti-inflammatory and antiviral properties with potential activity against COVID-19 (156). The immunomodulatory activity of azithromycin through the regulation of cellular processes involved inhibits a variety of pro-inflammatory pathways and also exhibits immunomodulatory properties (157). Some clinical evidence showed that a single oral dose of azithromycin has a positive effect on preventing COVID-19 (158, 159). However, no supportive evidence could be found for using azithromycin in COVID-19 treatment in hospitalized COVID-19 patients (160). To date, more than 100 clinical trials have been performed on the effect of azithromycin alone or combined with other drugs (such as clarithromycin and hidroxicloroquin) to control COVID-19 symptoms in mild to severe patients (161-163). However, more comprehensive studies are needed for better conclusions.

3.3.2.3. Tocilizumab

Tocilizumab is an antihuman monoclonal antibody belonging to the immunoglobulin G1k subclass responsible for binding to the human IL-6 receptor and inhibiting its signal transduction pathway (164). Tocilizumab is used against rheumatoid arthritis and cytokine release syndrome/systemic inflammatory response syndrome (165). After COVID-19 infection, the use of this drug may reduce the cytokine response of the host. The clinical study with successful treatment confirmed this hypothesis. However, the recovery of the normal T cells and the COVID-19 patient may be due to a rebound phenomenon of IL-6 level (166). Clinical studies suggest that tocilizumab is a good candidate for treating COVID-19 in patients with the risk of cytokine storms, especially in immunocompromised patients. (166, 167).

3.3.2.4. Dexamethasone and methylprednisolone

Dexamethasone and methylprednisolone are corticosteroids with anti-inflammatory, vasoconstrictive, and antifibrotic activities. This drug has been one of the conflicting treatment choices since the emergence of COVID-19. The preliminary results of the RECOVERY trial showed that the administration of dexamethasone (6 mg once daily for up to 10 days) could improve the recovery and decrease the rate of mortality in COVID-19 patients (168). However, choosing the correct steroid and its dose in the initial phase of the disease to the severe phase of COVID-19 patients and during treatment is still under study and controversy (169-171).

3.3.2.5. Interferons

The interferons (IFNs) are antiviral molecules divided into two classes: type I (IFNα, IFNβ, IFNω, and IFNτ) and type II (IFNγ). Previous research demonstrated that IFNα contributes to innate immunity against the virus, leading to its use against viral infections. The interferon alfacon-1 is recombinant of IFNα.The pegylated IFNα-2a and pegylated IFNα-2b are pegylated types (172). The Pegylated interferon alfa-2b can fight against viral infections by activating interferon receptors in host B cells and enhancing immune response (173). The in vitro study showed that the recombinant human IFNα-2b has antiviral activity, low toxicity, and a high therapeutic index against COVID-19 infection (174). Although studies in China and Iran reported that intranasal IFNα-2b combined with ribavirin showed antiviral activity in COVID-19 patients (42, 175, 176), more clinical trials are needed before using these drugs.

3.3.2.6. Statins

Statins have anti-inflammatory and immunomodulatory properties and can be used against the COVID-19 infection (177). They are commonly used to fight coronary artery diseases. They can increase the expression of the ACE2 (178). In a viral infection, stimulation of ACE2 by statins can help restore viral infection-induced endothelial dysfunction and maintain the homeostasis of the patients (179). In addition, statins showed antiviral activity by inhibiting viral protease (180). Therefore, the pleiotropic properties of this drug may be related to the therapeutic impact on COVID-19 patients through interfering with endothelial function and anti-thrombotic and anti-inflammatory effects (181, 182). Recent clinical studies reported that statin administration was associated with reduced mortality and reduced the risk of ICU admission in COVID-19 patients via modulation of cytokine overexpression (183, 184). Therefore, this drug can be an essential adjunctive substance in COVID-19 management. Further studies are required to confirm the higher observed

benefits.

4. Discussion

The COVID-19 infection as a global pandemic is a significant challenge to public health and national economies. Given that, no specific therapy has been approved to treat this infection, and repositioning existing drugs that target specific steps within the life cycle of the COVID-19 virus or host immune system could be a fast and alternative therapeutic strategy for dealing with this viral outbreak. To identify potential candidate drugs with promising antiviral activities, they should not only prove effective on animal models but be confirmed by previous human experience. In other words, although animal studies may help predict the drugs' effect in a more realistic scenario, the outcomes between animals and humans can be variable. It should be borne in mind that specific antivirals for the long-term benefit should be developed along with efficient use of repurposed drugs for COVID-19 therapy. Although the introduction and advancement of specific antivirals therapy with different targets in the life cycle of COVID-19 and the use of combination therapy may have more potential to prevent severe disease progression by reducing viral load, results indicate that symptomatic control of this infection (by targeting the host cells) has more positive outcomes compared to current antivirals (which effect the virus directly).

Drug repurposing is a promising strategy that can elevate the effectiveness of the therapy via a simplified pharmacokinetic and pharmacodynamic profile. In addition, these strategies can reduce drawbacks associated with conventional new drugs, such as drug-drug interaction and drug resistance. Optimizing drug repurposing can be done by data available on many public platforms, such as CheEMBL, PubChem, DrugBank, DrugCentral, STITCH, PHAROS, SEA, SuperTarget, TTD, along with others. that can help organize a correlation between chemical and physical properties of multiple drugs, through integrating in silico prediction and in vitro validation. The use of available drugs that can target specific steps within the life cycle of SARS-CoV-2 may be a strong alternative therapeutic strategy for dealing with this pandemic and similar future virus pandemics. To improve the success rate of drug repurposing in the clinical trial, it is recommended to personalize drug repurposing, taking into account the gene expression profile as an effective approach. Using new in silico methods and AI integrated with big data, it is possible to progress in the drug repurposing field and provide support for taking decisions for the therapeutic benefits of drugs against COVID-19. The preliminary screening of old drugs in the face of new virus diseases such as COVID-19 using the newest graph convolutional network models can help medical staff screen out potential treatments for COVID-19 in the shortest time.

Moreover, some items such as the inclusion criteria, administration route, treatment assignment, co-existing treatments, and endpoints should be carefully considered in the design and interpretation of clinical data of COVID-19 drug reposting studies. Among all of the drugs reviewed in this article, some antivirals (such as molnupiravir, lopinavir/ritonavir, paxlovid) and a few other medicines (such as corticosteroids, casirivimab/imdevimab) have more scientific evidence along with more reliable clinical trials showing anti-covid efficacy. In summary, In sum, twe want to underscore here the critical point that there are no promised pharmacotherapy guidelines to be a definite treatment for this pandemic yet. Subsequently, prescribing unnecessary medicines for infected patients, especially antibiotics (such as azithromycin -antibiotic resistance development-) and corticosteroids (if prescribed extraordinary, especially before the inflammatory phase -mucormycosis-) can expose the globe to more health-related challenges. In light of all the above, from our standpoint, complete vaccination of the majority of the worldwide population within a limited duration (to avoid further mutation of SARS-CoV-19) is the golden key to controlling and overcoming the pandemic.

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Conflict of interest

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