Received: 22 June 2020 | Revised: 21 July 2020 | Accepted: 12 August 2020

DOI: 10.1002/med.21728

MINI REVIEW

WILEY

COVID-19 drug repurposing: A review of computational screening methods, clinical trials, and protein interaction assays

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Funding information

NIH/NIGMS, Grant/Award Number: R35-GM133346

Abstract

The situation of coronavirus disease 2019 (COVID-19) pandemic is rapidly evolving, and medical researchers around the globe are dedicated to finding cures for the disease. Drug repurposing, as an efficient way for drug development, has received a lot of attention. However, the huge amount of studies makes it challenging to keep up to date with the literature on COVID-19 therapeutic development. This review addresses this challenge by grouping the COVID-19 drug repurposing research into three large groups, including clinical trials, computational research, and in vitro protein-binding experiments. Particularly, to facilitate future drug discovery and the creation of effective drug combinations, drugs are organized by their mechanisms of action and reviewed by their efficacy measured by clinical trials. Providing this subtyping information, we hope this review would serve the scientists, clinicians, and the pharmaceutical industry who are looking at the new therapeutics for COVID-19 treatment.

KEYWORDS

clinical trial, computational research, COVID-19, drug repurposing, in vitro protein interaction assay

1 | INTRODUCTION

COVID-19 is an acute respiratory disease caused by the RNA virus SARS-CoV-2. Since its first outbreak in Wuhan, China, the disease has rapidly spread to more than 180 countries around the world. The World Health Organization (WHO) declared it as a public health emergency on Jan 30, 2020, and assessed it as a pandemic

on Mar 11, 2020. The situation of the COVID-19 pandemic is continuously evolving. According to the WHO COVID-19 situation report No. 134 published on Jun 2, 2020, there have been 6.19 million confirmed cases worldwide, and the disease has taken 376,320 lives. Effective treatments are in urgent need, but currently, no drug with stable performance has been found for COVID-19.

Medical researchers around the globe are dedicated to understanding and finding cures for the disease. By the time this review is written, there are 3153 COVID-19 related studies listed on the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP), which include studies from countries other than the United States, and 1963 studies listed on http://ClinicalTrials.gov, which include the US clinical trials only. Among the studies in the United States with their study phases documented, most of them are in Phases 2 or 3, and more than 600 drug interventions are included in these trials. Drug repurposing, defined as finding new indications for existing drugs,[1] is of particular interest for coping with the COVID-19 urgency. Compared with developing drugs de novo, which was estimated to cost 10 to 17 years and 800 million USD,[1] drug repurposing significantly reduces both the time and money needed as the lengthy and costly ADMET (absorption, distribution, metabolism, elimination, toxicity) evaluation can be avoided. If succeeded, this would result in readily available and comparatively affordable medical treatments for COVID-19. Repurposing existing drugs to treat COVID-19 is biologically feasible as SARS-CoV-2 shares some similarities with other coronaviruses such as SARS-CoV and MERS-CoV,[2] and there are many successful precedents in repurposing antivirals for new virus targets.[3] Actually, most of the drugs currently in clinical trials for COVID-19 are repurposed from approved antiviral drugs. Additionally, with the help of advancing computational methods and mature protein interaction assays, finding potential drug repurposing targets from currently approved drugs or drug candidates.

As a global emergency, the COVID-19 pandemic leads to an explosion of publications, and the research situation is largely unorganized and unstructured: The results of large-scale controlled clinical trials are still on the way, though the results of smaller-scale clinical trials usually contradict with each other. Inevitably, overlapping or similar works exist in computational studies. The amount and complexity of current studies make it hard to keep up to date with the literature on COVID-19 therapeutic development. In the hope to help reduce double efforts, in this review, we grouped the COVID-19 drug repurposing research into three large categories, including clinical trials, computational research, and in vitro experimental studies (Figure 1). In the clinical trial group, drugs are organized and reviewed by their mechanisms of action, which we hope is informative to the discovery of drugs of similar mechanisms and the creation of combinatory treatment. In the computational research group, methods are sorted by their target proteins, and proposed drugs are listed out to prevent duplicated efforts.

2 | DRUGS IN CLINICAL TRIALS FOR COVID-19

To facilitate the completeness of this review, we hand-curated the drugs currently on clinical trials by mapping the Food and Drug Administration's (FDA) drug database and PubChem repository. Then, for each identified drug, we screened through literature that reported clinical trial results on PubMed using the drug name plus "COVID-19." We also searched for ongoing clinical trials for each drug on NIH ClinicalTrials website using the same searching phrases. Of note, trials suspended, withdrawn, terminated, and completed are not included as ongoing trials. For this section, the drugs are organized and reviewed based on their molecular mechanisms. A summary of the type, cohort, drug doses, and outcome of the clinical trials mentioned in this section is presented in Table 1.

2.1 | RNA mutagens: Remdesivir, favipiravir and ribavirin

As the replication of SARS-CoV-2 depends on the virus protein RNA-dependent RNA polymerase (RdRp), molecules that interfere with the function of RdRp could be potential treatments of COVID-19 by inducing mutations

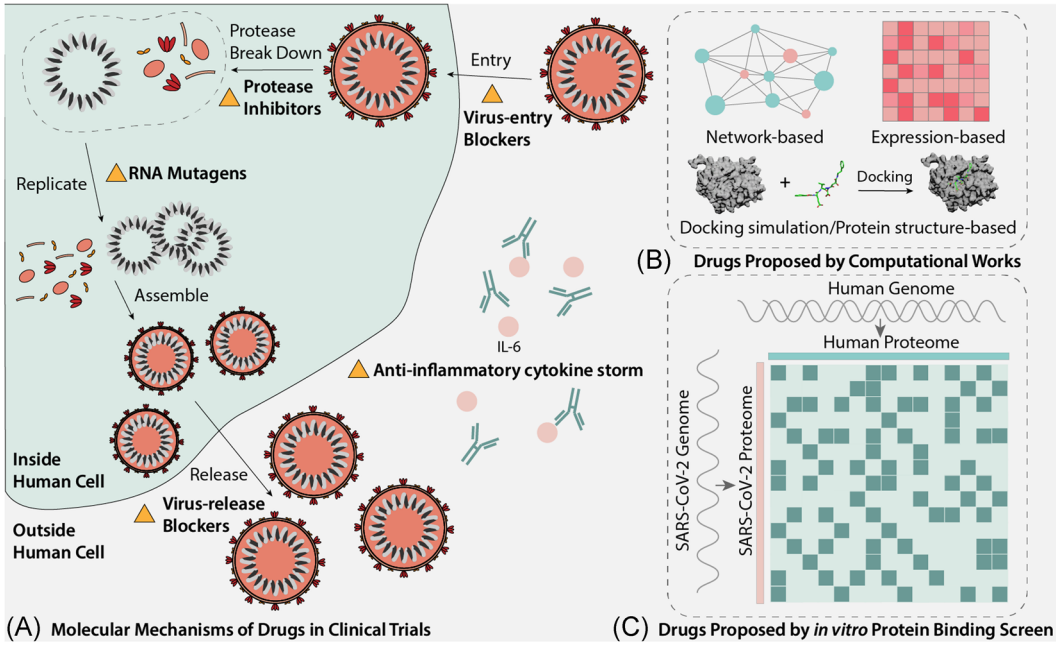

FIGURE 1 Overview of the review. A, Molecular mechanisms of drugs in clinical trials. B, Drugs proposed by computational works (Molecular docking figure credits to Wikipedia Docking [molecular] webpage; https://en.wikipedia.org/wiki/Docking_(molecular)). C, Drugs proposed by in vitro protein-binding screen [Color figure can be viewed at wileyonlinelibrary.com]

into the virus and blocking virus replication.[28] Remdesivir, favipiravir, and ribavirin are typical drugs that fall into this category, and the clinical trials about these drugs are reviewed below. Other potential drugs in this category include fluorouracil and acyclovir. However, clinical trials have not yet been conducted to test their efficacy.

2.1.1 | Remdesivir

Remdesivir, a 1′-cyano-substituted adenosine nucleotide analogue prodrug,[29] is proposed to have the potential to treat COVID-19 by inducing RNA mutation in SARS-CoV-2. The theoretical evidence of this argument lies in that remdesivir triphosphate can compete with adenosine triphosphate (ATP) for incorporation in Ebola virus, resulting in early termination of the RNA chain.[30] It is also found to be able to inhibit the replication of SARS-CoV, MERS-CoV, and a wide spectrum of other CoVs in in vitro systems.[31] A recent study has also demonstrated its ability to control infection of COVID-19 in vitro.[32] A number of clinical trials have been carried out to test remdesivir's effectiveness on COVID-19. A study treated a cohort of 53 patients with severe COVID-19 with compassionate-use remdesivir for 10 days, 200 mg intravenously on day 1 and 100 mg for the following 9 days. The results show that during a median follow-up of 18 days after the first dose of remdesivir, 68% of the patients showed clinical improvements in terms of oxygen support.[4] However, a randomized, double-blinded, placebo-controlled clinical trial carried out in 10 hospitals in Hubei, China looked into remdesivir's efficacy in a cohort of 237 adults, and the results show that remdesivir is not statistically significantly associated with clinical benefits, whereas the statistically insignificant reduction in time to clinical improvement in patients within 10 days of symptom onset requires further confirmation in larger cohorts.[33] Another smaller-scale study in Italy administered compassionate-use remdesivir for 10 days to a cohort of 35 patients with severe COVID-19 in both ICU and the infectious diseases ward, and the results indicate that remdesivir benefits patients outside ICU.[5] By far, the largest-scale study on remdesivir is a

TABLE 1 Summary of clinical trials

Author	Type of study	Cohort	Drugs and doses	Results
Remdesivir				
Grein et al.[4]	Compassionate	61 patients, oxygen saturation ≤ 94% or receiving oxygen support	A 10-d course of remdesivir treatment, 200 mg intravenously on day 1, 100 mg for next 9 d	During a median follow up of 18 d, 36 of 53 (68%) patients improved in terms of the oxygen support class
Wang et al.[33]	Randomized, double-blind, placebo-controlled, multicenter	237 patients, age ≥ 18, symptom onset ≤ 12 d, oxygen saturation ≤ 94%, radiologically confirmed pneumonia	A 10-d course of remdesivir treatment, 200 mg intravenously on day 1, 100 mg for next 9 d vs. the same amount of placebo	Remdesivir use was not associated with a difference in time to clinical improvement; Patients whose symptom onset ≤ 10 d treated with remdesivir showed a numerically faster time to clinical improvement compared to placebo (not significant)
Antinori et al.[5]	Compassionate	35 patients, 18 in ICU and 17 in the normal ward, age ≥ 18, oxygen saturation ≤ 94% or NEWS2 ≥ 4 or receiving oxygen support	A 10-day course of remdesivir treatment, 200 mg intravenously on day 1, 100 mg for next 9 d; existing treatments including HCQ was continued, but LPV/r was discontinued	On day 28, 14 patients from the normal ward were discharged, two still hospitalized and one died, but six patients in ICU were discharged, three still hospitalized, and eight died.
Beigel et al.[6]	Randomized, double-blind, placebo-controlled, multicenter	1063 patients, age ≥ 18, oxygen saturation ≤ 94% or radiologically confirmed pneumonia or receiving oxygen support	A 10-day course of remdesivir treatment, 200 mg intravenously on day 1, 100 mg for next 9 d vs. the same amount of placebo	Patients with remdesivir had a median to recovery time of 11 d, whereas patients with placebo had a median to recovery time of 15 d ($p < .001$)
Favipiravir				
Cai et al.[7]	Open-label, nonrandomized, controlled	80 patients, age 16–75, disease onset ≤ 7 d, no severe clinical condition	FPV: Oral FPV, 14-d course of treatment, 1600 mg on day 1, twice daily; 600 mg on days 2–14, twice daily; plus interferon (IFN)-a by aerosol inhalation (5 million U twice daily) LPV/r (control): 14-day course of treatment, 400mg/100mg on day 1-14,	FPV group showed shorter viral clearance time (4[2.5-9] d compared to 11[8–13] d; $p < .001$) FPV group showed improvement in chest imaging (improvement rate of 91.43% compared to 62.22%; $p = .004$)

TABLE 1 (Continued)

Author	Type of study	Cohort	Drugs and doses	Results
			twice daily; plus interferon (IFN)-a by aerosol inhalation (5 million U twice daily)	
Chen et al.[8]	Prospective, randomized, controlled, open-label, multicenter	240 patients, age ≥ 18, initial symptoms ≤ 12 d	FPV: 1200 mg × 2 on day 1 and 600 mg × 2 for day 2–10 + conventional therapy	No statistically significant difference in clinical recovery rate on day 7 (71 of 116 compared to 62 of 120; $p = .1396$)
			Arbidol (control): 200 mg × 3/d for 10 d + conventional therapy	FPV led to shorter latencies to the relief of pyrexia and cough ($p < .0001$)
Ribavirin				
Yuan et al.[9]	Retrospective (analysis of electronic medical reports)	94 patients	IFN-α, LPV/r, ribavirin, arbidol, FPV, human γ globulin, glucocorticoid	IFN-α + LPV/r and IFN-α + LPV/r + ribavirin-treated patients showed a positive correlation between messenger RNA clearance rate and length of hospital stay
Hung et al.[10]	Prospective, open-label, randomized, multicenter, phase 2	127 patients, age ≥ 18, NEWS2 ≥ 1, symptom onset ≤ 14	Combination group: LPV/r 400 mg/100 mg every 12 h + ribavirin 400 mg every 12 h + IFN-β1b 8 million U every alternate day for 14 days	Combination group had shorter time from the beginning of treatment to negative nasopharyngeal swab (7[5–11] compared to 12[8–15]; $p = .0010$)
			Control group: LPV/r 400 mg/100 mg every 12 h for 14 d	
Ritonavir-lopinavir				
Yan et al.[11]	Retrospective	120 patients	LPV/r: Oral, 400 mg/100 mg, twice daily	Older age and lack of LPV/r treatment lead to prolonged viral shedding independently
				Early administration (onset time ≤ 10 days) of LPV/r can shorten viral shedding ($p < .001$)

(Continues)

TABLE 1 (Continued)

Author	Type of study	Cohort	Drugs and doses	Results
Ye et al.[12]	Controlled, non-randomized	47 patients, age 5–68	Test group: LPV/r 400 mg/100 mg twice daily or 800 mg/200 mg once a day with food + adjuvant drugs Control group: Adjuvant drugs including interferon aerosol inhalation and arbidol tablets	Body temperature decreased faster in the test group (not significant) The abnormal proportion of WBC, lymphocytes, CRP and PLT in the test group was lower than the control group after three treatments The test group had a shorter time before RNA test turns negative ($p = .0219$)
Cao et al.[13]	Randomized, controlled, open-label	199 patients, age ≥ 18, oxygen saturation ≤ 94%	Test group: LPV/r 400 mg/100 mg twice daily for 14 d + standard care Control group: Standard care	Time to clinical improvement, mortality rate at day 28, and percentage of patients with positive RNA test at multiple time points were similar in two groups
Wen et al.[14] (full-text not accessible)	Retrospective	178 patients	LPV/r group Arbidol group Combination group Control group: Conventional treatment	No significant difference in the rate of negative conversion, clinical improvement, and CT improvement among the four groups Significant difference in the proportion of changing from mild/moderate to severe/critical on day 7 ($p = .017$), LPV/r and control group had a smaller proportion of deterioration changing
Deng et al.[15]	Retrospective	33 patients, age ≥ 18, without invasive ventilation	Combination group: Arbidol 200 mg every 8 h, LPV/r 400 mg/100 mg every 12 h; Monotherapy group: LPV/r 400 mg/100 mg every 12 h; Until RNA test negative for three times (5–21 d)	Combination group had higher viral clearance rate on day 7 ($p < .05$) and day 14 ($p < .05$); Combination group had higher chest image improving rate at day 7 ($p < .05$)

TABLE 1 (Continued)

Author	Type of study	Cohort	Drugs and doses	Results
Zhu et al.[16]	Retrospective	50 patients, no severe pneumonia or ARDS	LPV/r group: LPV/r 400 mg/100 mg twice daily for 7 d Arbidol group: 0.2 g arbidol, three times daily for 7 days All patients received conventional therapy	No difference in fever duration ($p = .61$) Arbidol group had less viral load on day 14 (0% compared to 44.1%) Arbidol group had shorter RNA test positive duration ($p < .01$)
Chloroquine				
Gao et al.[17]	Not declared	More than 100 patients	Not declared	Chloroquine treatment is superior to control treatment in CT improvement and shortening the disease course (No details described)
Huang et al.[18]	Controlled, randomized	22 patients, age ≥ 18	Chloroquine: 500 mg daily for 10 d LPV/r (control): 400mg/100mg orally twice daily for 10 days	Chloroquine group had shorter time for RNA test to turn negative, faster CT improvement, and shorter time to discharge from hospital
Hydroxychloroquine				
Chen et al.[19]	Randomized, parallel-group	62 patients, age ≥ 18, oxygen saturation > 93%, no severe or critical illness	HCQ: 400 mg/d for 5 days + standard treatment Control: Standard treatment only	HCQ group showed faster fever and cough remission, a larger proportion of patients with clinical improvement, less progression to severe illness
Gautret et al.[20]	observational	80 patients, mildly infected	HCQ: 200 mg orally, three times/d for 10 days; Azithromycin: 500 mg on day 1 and 250 mg on days 2–5; Some patients (with pneumonia, NEWS >= 5) also received ceftriaxone	Clinical improvement and rapid fall of nasopharyngeal viral load were observed

(Continues)

TABLE 1 (Continued)

Author	Type of study	Cohort	Drugs and doses	Results
Molina et al.[21]	prospective	11 patients, severe disease, five with cancer, one with HIV, two obesity	HCQ: 600 mg/d for 10 d; Azithromycin: 500 mg on day 1 and 250 mg on days 2–5	No evidence for rapid viral clearance and clinical benefits
Tang et al.[22]	Randomized, controlled, open-label	150 patients, 148 mild to moderate disease and two severe disease	HCQ group: HCQ 1200 mg daily for days 1–3, 800 mg daily for the rest of treatment duration (2–3 wk according to patient condition) + standard care Control group: standard care	HCQ did not result in a higher proportion of negative conversion
Mahévas et al.[23]	Observational	181 patients, age 18-80, require oxygen but not intensive care	HCQ group: HCQ 600 mg/d, started treatment 48 h after admission; Control group: no HCQ treatment	Similar survival rate and clinical improvement in two groups
Arbidol				
Chen et al.[8]	Prospective, randomized, controlled, open-label, multicenter	240 patients, age ≥ 18, initial symptoms ≤ 12 days	FPV: 1200 mg × 2 on day 1 and 600 mg × 2 for day 2–10 + conventional therapy arbidol (control): 200 mg × 3/d for 10 d + conventional therapy	No statistically significant difference in clinical recovery rate on day 7 (71/116 compared to 62/120; $p = .1396$) FPV led to shorter latencies to the relief of pyrexia and cough ($p < .0001$)
Wen et al.[14] (full text not accessible)	Retrospective	178 patients	LPV/r group Arbidol group Combination group Control group: Conventional treatment	No significant difference in the rate of negative conversion, clinical improvement, and CT improvement among the four groups Significant difference in the proportion of changing from mild/moderate to severe/critical on day 7 ($p = .017$), LPV/r and control group had a smaller proportion of deterioration changing

TABLE 1 (Continued)

Author	Type of study	Cohort	Drugs and doses	Results
Deng et al.[15]	Retrospective	33 patients, age ≥ 18, without invasive ventilation	Combination group: Arbidol 200 mg every 8 h, LPV/r 400 mg/100 mg every 12 h;	Combination group had higher viral clearance rate on day 7 ($p < .05$) and day 14 ($p < .05$)
			Monotherapy group: LPV/r 400 mg/100 mg every 12 h;	Combination group had higher chest image improving rate at day 7 ($p < .05$)
			Until RNA test negative for three times (5–21 d)	
Zhu et al.[16]	Retrospective	50 patients, no severe pneumonia or ARDS	LPV/r group: LPV/r 400 mg/100 mg twice daily for 7 d	No difference in fever duration ($p = .61$)
			Arbidol group: 0.2 g arbidol, three times daily for 7 d	Arbidol group had a less viral load on day 14 (0% compared to 44.1%)
			All patients received conventional therapy	Arbidol group had shorter RNA test positive duration ($p < .01$)
Xu et al.[24]	Retrospective, multicenter	141 patients, age ≥ 18, without ventilation	Combined group: Arbidol 200–mg, oral, three times daily for 7–10 d; IFN-α2β, inhale, twice daily, 5 × 10(5) IU for 10–14 d	No significant differences between the two groups in terms of viral clearance
			Monotherapy group: Inhale IFN-α2β, twice daily, 5 × 10(5) IU for 10–14 d	Faster CT improvement in the combined therapy group
Tocilizumab				
Xu et al.[25]	Observational	21 patients, severe or critical disease	Tocilizumab: 4–8 mg/kg body weight	Quick and significant clinical improvements were observed, all patients discharged with a mean of 15.1 d after given tocilizumab
			Standard treatment: LPV/r 400 mg/100 mg twice daily; IFN-α, inhale, twice daily, 5 million U; ribavirin, 500 mg two to three times daily	

(Continues)

TABLE 1 (Continued)

Author	Type of study	Cohort	Drugs and doses	Results
Luo et al.[26]	Retrospective	15 patients, two moderately ill, six severely ill, seven critically ill	Different for each patient, see Table 1 in paper	Tocilizumab ameliorated increased CRP rapidly in all patients treatment failed for four patients, three dead and ine aggravated
Dexamethasone				
RECOVERY Collaborative Group[27]	Randomized, controlled, open-label	6425 patients, anyone hospitalized and confirmed with COVID-19 and without risky medical histories, including children under 18 and pregnant or breastfeeding women	dexamethasone 6 mg once daily for 10 d compared with usual care	28-d mortality reduced one-third of patients need invasive ventilation, one-fifth of patients need oxygen support but not invasive ventilation, no reduction in patients without oxygen support

Abbreviations: ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; FPV, favipiravir; HCQ, hydroxychloroquine; ICU, intensive care unit; LPV/r, lopinavir/ritonavir.

recently published double-blind, randomized, controlled study on a cohort of 1059 participants from 10 countries. The results indicate that remdesivir significantly reduced the time to recovery of COVID-19.[6] Although the clinical trial results of remdesivir are promising, FDA still has not approved it as a drug against COVID-19 by the time this review is written.[34] Besides literature reports, there are 17 ongoing clinical trials on remdesivir's clinical effect on COVID-19 documented by NIH ClinicalTrials by the time of May 15, 2020.[35]

2.1.2 | Favipiravir

Favipiravir-triphosphate can also mimic ATP and GTP for incorporation with RdRp,[36] however, not as effective as remdesivir.[37] In an open-labeled nonrandom controlled study, the effects of favipiravir and ritonavir-lopinavir on SARS-CoV-2 treatment were compared. The favipiravir group exhibited significantly shorter virus clearance time, improved chest imaging, and fewer adverse reactions.[7] Another retrospective, randomized, controlled study compared the effect of favipiravir and arbidol in a cohort of 240 patients, and found that there are no differences in the recovery rate in the two groups at day 7.[8] However, favipiravir led to significantly accelerated relief of symptoms including pyrexia and cough.[8] Besides literature reports, there are 16 ongoing clinical trials on favipiravir's clinical effect on COVID-19 documented by NIH ClinicalTrials by the time of May 20, 2020.[35]

2.1.3 | Ribavirin

Ribavirin's mechanism is similar to that of favipiravir, which also mimics ATP and GTP to incorporate with RdRp.[37] A study on a cohort of 94 patients showed that a combination of IFN-α, lopinavir/ritonavir, and ribavirin may be beneficial to patients with SARS-CoV-2 infection.[9] Another open-label, randomized, phase-2 trial assessed the efficacy of a combination of IFN-β-1b, lopinavir/ritonavir, and ribavirin on treating SARS-CoV-2 infected patients. The study demonstrated that triple therapy was superior to only using lopinavir/ritonavir in terms of treating patients with mild or moderate SARS-CoV-2 infection.[10] However, there aren't clinical trials that directly assess the efficacy of ribavirin by the time this review is written. Besides literature reports, there is another ongoing clinical trial on the treatment of COVID-19 by a combination of nitazoxanide, ribavirin, and ivermectin.[35]

2.2 | Protease inhibitors: Ritonavir-lopinavir and darunavir

As the CoVs' gene expression and replication processes require proteolytic processing of polypeptides into non-structural proteins, it is reasonable to use protease inhibitors to block these processes.[38,39] Representative drugs in this category include ritonavir-lopinavir and darunavir.

2.2.1 | Ritonavir-lopinavir

Ritonavir-lopinavir is originally a combination medication for AIDS by inhibiting the protease of HIV.[40] A number of clinical trials have been carried out to test whether it is also effective in treating COVID-19. A retrospective study including 120 patients shows that early administration of ritonavir-lopinavir could shorten the time of virus shedding.[11] A controlled study involving 47 patients with COVID-19 infection indicated that a combination of ritonavir-lopinavir and adjuvant drugs significantly decreased the number of days for virus clearance compared to adjuvant drugs alone.[12] However, a randomized, controlled, open-label trial on 199 patients with SARS-CoV-2 suggested that no additional benefits were observed for the ritonavir-lopinavir treatment.[13] But the result of this

study is controversial as there are arguments that it is premature to abandon ritonavir-lopinavir treatment only based on this trial since it is statistically underpowered to show a better improvement, and that the secondary outcomes of the trial suggested that ritonavir-lopinavir has the potential to reduce overall severe-disease and mortality risk.[41] Another set of studies investigated ritonavir-lopinavir's effectiveness compared to or in combination with the antiviral drug arbidol, and the results are not in favor of ritonavir-lopinavir. A retrospective cohort study with 178 patients diagnosed with COVID-19 suggests that no evidence proved that ritonavir-lopinavir or ritonavir-lopinavir combined with arbidol can shorten the disease course.[14] A retrospective study with a cohort of 33 patients shows that a combination of arbidol and ritonavir-lopinavir achieved better clinical response compared to using ritonavir-lopinavir only.[15] In another retrospective cohort study, 50 patients were divided into ritonavir-lopinavir group and arbidol group and compared to the ritonavir-lopinavir group, viral clearance is faster in patients in the arbidol group.[16] The most common side effects of ritonavir-lopinavir are mild to moderate gastrointestinal adverse effects such as diarrhea, nausea, and vomiting.[40] Besides these published trials, there are 31 ongoing clinical trials on ritonavir-lopinavir's clinical effect on COVID-19 documented by NIH ClinicalTrials at the time of May 20, 2020.[35]

2.2.2 | Darunavir

Darunavir is also a protease inhibitor originally used for HIV.[42] There are not clinical trials concerning the SARS-CoV-2 treatment effectiveness of darunavir. On the basis of the case studies of three HIV-positive patients infected with SARS-CoV-2, Riva et al.[43] suggests that according to these preliminary evidence, darunavir at a dosage of 800 mg does not prevent HIV patients from COVID-19 infection, and also may not protect HIV patients from worsening of respiratory function caused by SARS-CoV-2. There is one ongoing clinical trial (NCT04252274) that assesses the efficacy and safety of darunavir.[35]

2.3 | Virus-entry blockers: Chloroquine, hydroxychloroquine, arbidol, and antibodies against spike (S) protein

SARS-CoV-2 enters the human cell by binding to plasma membrane receptors. Therefore, interfering with this process would block virus entry and thus has the potential to fight virus infection. Drugs in this category include arbidol, and potentially, chloroquine and hydroxychloroquine, and the antibodies against virus spike (S) protein, including LY3819253, JS016, and REGN-COV2.

2.3.1 | Chloroquine

Chloroquine has been used as an antimalaria drug for many years. Its antiviral mechanism is not completely clear, whereas there are studies suggesting that it disrupts virus-receptor binding by interfering with glycosylation of the human cell membrane receptor angiotensin-converting enzyme 2 (ACE2).[44] A recent study proposed that the virus entrance process not only involves spike protein binding to ACE2 but also host gangliosides, and chloroquine interferes with this process by competing with the virus's spike protein to bind to gangliosides.[45] Gao et al.[17] reported in a letter that there are clinical trials that demonstrated that chloroquine performed better than control treatment in improving clinical outcomes of COVID-19 infected patients. However, the letter didn't give any details of the clinical trials. A controlled study in a cohort of 22 patients showed that compared to ritonavir-lopinavir treatment, chloroquine phosphate significantly reduced the disease duration.[18] However, large-scale studies are still in urgent need to determine the effectiveness of chloroquine.

2.3.2 | Hydroxychloroquine

Hydroxychloroquine is the hydroxylated form of chloroquine, and thus they share similar antiviral mechanisms. Some early small-scale trials found hydroxychloroquine effective for mild COVID-19 treatment. For example, a randomized controlled trial with 62 patients demonstrated that the use of hydroxychloroquine significantly shortened the disease course.[19] Another pilot observational study in a cohort of 80 mildly infected patients also shows that combined therapy using hydroxychloroquine and azithromycin may improve the situation of infected patients.[20] However, another study mentioned that they failed to observe strong clinical improvement when using the same drugs and doses to treat 11 patients severely infected with COVID-19.[21] The results of a series of larger-scale studies also cast doubt on the effectiveness of hydroxychloroquine. A recent randomized controlled study involving 150 mild to moderate patients concludes that no evidence suggests that hydroxychloroquine treatment performs better than standard patient care, and the adverse effect of hydroxychloroquine is higher.[22] Another recent observational study in 181 patients with SARS-CoV-2 who required oxygen but not intensive care also does not support the effectiveness of hydroxychloroquine.[23] Besides, it is reported that hydroxychloroquine add-on therapy to ritonavir-lopinavir may have many potential adverse effects including cardiac, metabolic, and neurological symptoms, and so forth, and should be used with caution.[46] FDA recently established a summary of safety issues brought by chloroquine and hydroxychloroquine, including severe heart rhythm problems, blood and lymph system disorders, kidney injuries, and liver problems and failure, and cautioned against the use of these drugs outside hospital settings.[47]

2.3.3 | Arbidol

Arbidol is a broad-spectrum antiviral. Previous studies on viruses such as HCV, influenza virus, and so forth. demonstrated that it interferes with various steps of the virus life-cycle, including virus entry, endocytosis, endosomal trafficking, and so forth.[48] There is a lack of clinical trials that directly measure the efficacy of arbidol in treating COVID-19. Most of the clinical trials related to arbidol use it as a control group or in combination with other drugs. As mentioned in the ritonavir-lopinavir section, there are clinical studies suggesting that arbidol monotherapy[16] and arbidol combined with ritonavir-lopinavir[15] perform better at shortening the duration of the disease compared to ritonavir-lopinavir only. However, there is another clinical trial stating that no evidence suggests that arbidol combined with ritonavir-lopinavir would shorten the disease course.[14] A randomized controlled study that compares the efficacy of arbidol and favipiravir in a cohort of 240 patients showed no significant difference in 7-day recovery rate between the two groups, whereas favipiravir led to an earlier improvement of symptoms including pyrexia and cough.[8] Recently, a retrospective cohort study involving 141 adult patients without ventilation suggests that there is almost no difference in clinical outcomes between arbidol monotherapy and arbidol combined with IFN-2b, and the study infers that combined therapy may be used to improve the situation of mild patients though it may not be able to accelerate virus clearance.[24] There are three ongoing clinical trials that evaluate the efficacy and safety of arbidol for COVID-19 infection treatment.[35]

2.3.4 | LY3819253

LY3819253, developed by the pharmaceutical company Eli Lilly, is the world's first neutralizing antibody that goes into clinical trials. It is a potent monoclonal antibody against the SARS-CoV-2 spike (S) protein. The current Phase 1 (NCT04411628, 40 participants) and Phase 2 (NCT04427501, 400 participants) are randomized, double-blind, placebo-controlled studies with mild or moderate infected participants, and both are anticipated to end in mid to late August, 2020.[35]

2.3.5 | JS016

JS016 is also a neutralizing antibody against the SARS-CoV-2 spike (S) protein. It is developed by the pharmaceutical Shanghai Junshi Bioscience and entered Phase 1 clinical trial in early June (NCT04441918). The randomized, double-blind, and placebo-controlled clinical trial aims at evaluating the safety of the product based on the experience of 40 healthy participants.[35] Studies in vitro and in rhesus monkeys show that JS016 (CB6) has the ability to inhibit SARS-CoV-2 infection.[49] The completion date of the trial is expected to be in mid-December 2020.

2.3.6 | REGN-COV2

REGN-COV2 is a combination therapy containing the antibodies REGN10933 and REGN10987, and is currently under Phase 1 clinical trial (NCT04426695).[35] The antibodies are generated from humanized mice and convalescent humans, both proved to be efficiently targeting the receptor-binding domain of the spike protein.[50] There are expected to be 1860 participants in the Phase 1 trial, and the study completion date is going to be in June 2021.

2.4 | Virus-release blockers: Oseltamivir

This category of medication inhibits the release of the virus from the infected cell, thus blocks virus transmission. A typical drug in this category is oseltamivir. Studies in influenza viruses show that it binds to and inhibits the virus neuraminidase enzyme, which facilitates virus release from the infected cell.[51] There are currently no completed clinical trials for oseltamivir's efficacy in treating COVID-19. Four ongoing clinical trials are dedicated to assess the efficacy and safety of oseltamivir.[35]

2.5 | Non-virus-targeting treatments: Tocilizumab, dexamethasone, CD24Fc, and dapagliflozin

Cytokine storm is a crucial factor that leads to acute respiratory distress syndrome and multiple organ failure, which would suddenly exacerbate the disease and finally lead to death. Therefore, inhibition of the cytokine storm is an important step in COVID-19 treatment.[52] Drugs in this category include interleukin-6 (IL-6) inhibitors (tocilizumab) and CD24Fc. Besides these treatments that directly target cytokines, metabolic modulators can also reduce adverse events brought by SARS-CoV-2 infection. These drugs include the corticosteroid drug dexamethasone and SGLT2 inhibitor dapagliflozin.

2.6 | Tocilizumab

IL-6 level is highly positively related to COVID-19 disease severity. The monoclonal antibody tocilizumab, an IL-6 receptor antagonist, is used in most cases of COVID-19 treatment where IL-6 is targeted. An observational study on 20 patients with severe or critical COVID-19 infection showed that the use of tocilizumab immediately improved clinical outcomes.[25] Another observational study in 15 patients, 13 of which are severely or critically ill, also demonstrated that tocilizumab may be a useful therapy, and the repeated dose is recommended for patients with elevated IL-6 level.[26] However, two cases with adverse effects are reported, and the author advised clinicians to be cautious about hypertriglyceridemia when using tocilizumab.[53]

2.7 | CD24Fc

CD24Fc, composed of the nonpolymorphic regions of CD24 attached to the Fc region of human IgG1, is an immunomodulator that can suppress the expression of multiple cytokines.[35] It is currently in Phase 2/Phase 3 clinical trial stage, and the current randomized, double-blind, placebo-controlled Phase 3 trial (NCT04317040) evaluates the safety efficacy of CD24Fc in treating COVID-19 in the cohort of 230 patients.[35] The study completion date is expected to be in December 2020.[35]

2.8 | Dexamethasone

Dexamethasone is an FDA approved synthetic corticosteroid that suppresses the immune system by inhibiting naive T cell proliferation and differentiation,[54] and is the first-line treatment for immune-related complications. A large-scale randomized, controlled, open-label trial involving 6425 patients observed that dexamethasone reduced the 28-day mortality rate by one-third in patients receiving invasive ventilation, and by one-fifth of patients receiving oxygen but not invasive ventilation.[27] It does not reduce the mortality rate in patients not requiring oxygen support.[27] Metabolic side effects of dexamethasone include a mild increase of blood glucose level,[55] ocular hypertension, and cataract,[56] neuropsychological side effects such as mood and behavior change,[57] and osteoporosis.[58] However, these adverse effects are mostly associated with long-term high-dose dexamethasone treatments, whereas its benefit-risk profile is favorable for short-term treatments.[59] WHO is in the process of adding dexamethasone into COVID-19 treatment guidelines.[59]

2.9 | Dapagliflozin

Dapagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor and is hypothesized to be able to prevent serious side effects caused by SARS-CoV-2 infection by preventing low PH in cells.[60] However, it is suggested to be carefully used together with insulin to prevent the side effect of euglycemic diabetic ketoacidosis.[60] A randomized, double-blind, placebo-controlled Phase 3 study (NCT04350593) is being carried out to evaluate the safety and efficacy of dapagliflozin in preventing adverse events in a cohort of 900 COVID-19 patients.[35] The completion date is expected to be in December 2020.[35]

Finally, it is worth noting that there are no drugs passed clinical trials and approved by FDA for COVID-19 by the time this review is written. Phase 3 trials compare a new drug to the standard-of-care drug, and Phase 4 trials test new drugs approved by the FDA for short-lived and long-lasting side effects and safety.[61] For the COVID-19 situation, drugs passed Phases 3 or 4 may be considered as passed clinical trials. There are currently nine completed Phase 3 trials and two completed Phase 4 trials concerning COVID-19 on the clinicaltrials. gov webpage, involving drugs such as remdesivir (positive), favipiravir (result not posted), hydroxychloroquine (unclear, larger data set needed; negative), baricitinib (result not posted), methylprednisolone therapy (result not posted), liposomal lactoferrin (result not posted), and danoprevir (result not posted).[35]

3 | DRUGS THAT HAVE BEEN PROPOSED BY COMPUTATIONAL WORKS

Significant efforts have been put into the computational works for prioritizing previous FDA-approved drugs for repurposing to treat COVID-19. In this section, we summarized the general categories of computational drug repurposing methods to help reduce duplicated works (Table 2).

TABLE 2 Drugs proposed by computational methods

Author	Protein in focus	Proposed drugs/molecules
Category 1. Network-based algorithms		
Zhou et al.[62]	119 proteins in the HCoV-host interactome network	Irbesartan, toremifene, camphor, equilin, mesalazine, mercaptopurine, paroxetine, sirolimus, carvedilol, colchicine, dactinomycin, melatonin, quinacrine, eplerenone, emodin, oxymetholone
Cava et al.[63]	Angiotensin-converting enzyme 2 (ACE2)	LMB-2, L-778123, didanosine, lomustine, fumarate, vatiquinone, lentinan, flutamide, photofrin, medroxyprogesterone acetate, dihydrokainate, letrozole, mesalamine, cerulenin, thiabendazole, trichostatin, nimesulide, fluticasone propionate, semapimod, iratumumab, ivacaftor, SGN-30, retinol, QBW251, lumacaftor, apigenin, NS-398, tezacaftor, naproxen, esflurbiprofen, mefenamic acid, VK-19911, alglucosidase alfa, ibutilide, fumarate, amiodarone, hydrochloride, venetoclax
Category 2. Expression-based algorithms		
He and Garmire[64]	ACE2	COL-3, CGP-60474
Category 3. Docking simulation or protein structure-based algorithms		
Wu et al.[65]	18 SARS-CoV-2 proteins and 2 human proteins: Nsp1, Nsp3, Nsp7-Nsp8, Nsp9-Nsp10, Nsp14-Nsp16, $3CL^{pro}$, E-channel (E protein), ORF7a, Spike, ACE2, C-terminal RNA binding domain (CRBD), N-terminal RNA binding domain (NRBD), helicase, RNA-dependent RNA polymerase (RdRp), TMPRSSS2	**Ribavirin**, valganciclovir, β-Thymidine, aspartame, oxprenolol, lymecycline, chlorhexidine, alfuzosin, cilastatin, famotidine, valganciclovir, ceftibuten, fenoterol, fludarabine, etc. (only listed part of the results)
Al-Khafaji et al.[66]	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	Saquinavir, **ritonavir**, **remdesivir**, delavirdine, cefuroxime axetil, **oseltamivir**, prevacid
Shah et al.[67]	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	**Lopinavir**, asunaprevir, **remdesivir**, CGP42112A, indinavir, **ritonavir**, ABT450, marboran (methisazone), galidesivir
Kandeel and Al-Nazawi[68]	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	Chromocarb, **ribavirin**, telbivudine, vitamin B12, aminophylline, nicotinamide, triflusal, and so forth (only listed part of the results)
Mahanta et al.[69]	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	Viomycin
Pant et al.[70]	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	Cobicistat, **ritonavir**, **lopinavir**, **darunavir**
Wang[71]	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	Carfilzomib, eravacycline, valrubicin, **lopinavir**, elbasvir
Odhar et al.[72]	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	Conivaptan, olaparib, loxapine, sonidegib, azelastine, idelalisib, tolvaptan, perampanel, suvorexant, ponatinib

TABLE 2 (Continued)

Author	Protein in focus	Proposed drugs/molecules
Mittal et al.[73]	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	Leupeptin, hemisulphate, pepstatin A, nelfinavir, birinapant, lypression, octreotide
Das et al.[74]	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	**Ritonavir**, emetine, **lopinavir**, indinavir (only listed part of the results)
Farag et al.[75]	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	**Darunavir**, mitoxantrone, nelfinavir, moexpril, daunorubicin, rosuvastatin, saquinavir, metamizole, bepotastine, benzonatate, atovaqoune
Gimeno et al.[76]	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	Perampanel, carprofen, celecoxib, alprazolam, trovafloxacin, sarafloxacin, ethyl biscoumacetate
Elfiky[77]	RdRp	**Ribavirin**, **remdesivir**, sofosbuvir, galidesivir, tenofovir, **hydroxychloroquine**, cefuroxime, **f**avipiravir, setrobuvir, YAK, IDX-184
Gupta et al.[78]	SARS-CoV-2 envelope (E) protein	Belachinal, macaflavanone E, vibsanol B
Beck et al.[79]	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$), RdRp, Helicase, 3′–5′ exonuclease, endoRNAse, 2′-O-ribose methyltransferase	Atazanavir, ganciclovir, **lopinavir**, **ritonavir**, **darunavir**, and so forth (only listed part of the results)
Elmezayen et al.[80]	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$), human transmembrane protease serine 2 (TMPRSS2)	Talampicillin, lurasidone, rubitecan, loprazolam (only listed part of the results)
Hall and Ji[81]	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$), Spike (S) protein	Cangrelor, NADH, flavin adenine dinucleotide (FAD) adeflavin, comeprol, Coenzyme A, tiludronate, zanamivir, bortezomib, saquinavir, cangrelor, carfilzomib, indinavir, **remdesivir**
Batra et al.[82]	Spike (S) protein or Spike (S) protein–ACE2 interface complex	Pemirolast, sulfamethoxazole, valaciclovir, sulfamerazine, tazobactam, nitrofurantoin
Oliveira et al.[83]	Spike (S) protein	Suramin sodium, 5-hydroxytrytophan, dihydroergocristine mesylate, quinupristin, nilotinib, dexamethasone-21-sulfobenzoate, tirilazad, selamectin, acetyldigitoxin, doramectin
Park et al.[84]	Spike (S) protein	CR3022 human antibody, F26G19 mouse antibody, D12 mouse antibody

Note: Bold words indicate drugs in clinical trials reviewed above.

3.1 | Network-based algorithms

Zhou et al.[62] integrated HCoV–host interactions, drug-target network and human protein interactome together and proposed 16-drug and three-drug combinations for SARS-CoV-2 infection treatment. In this study, CoV-associated host proteins were collected and based on these proteins, HCoV-host interactome was generated. Then, potential drugs are identified by measuring network proximity between the HCoV-specific network and the drug-target network in the human interactome.[62] Another study focused on the main cell receptor of SARS-CoV-2, the

angiotensin-converting enzyme 2 (ACE2).[63] A protein-protein interaction network containing genes coexpressed with ACE2 was constructed, and focus was placed on genes that were already associated with drugs. A total of 36 potential drugs were proposed by this method.[63]

3.2 | Expression-based algorithms

In an expression-based drug repurposing study, based on the statement that inhibition of the angiotensin-converting enzyme 2 (ACE2) may be the mechanism of lung injury induced by SARS-CoV-2, two potential repurposed drugs were proposed for COVID-19 treatment since they reversed the change of gene expression patterns caused by ACE2 inhibitor.[64]

3.3 | Docking simulation or protein structure-based drug design

There are a comparatively large number of studies under this category, which can be further divided into two subcategories:

(a) Docking simulation for small molecule treatment predictions: The general steps for this kind of drug design method are (1) predict target protein structures using homology modeling or retrieve established crystal structures from databases; (2) screen for molecules that can bind to the target proteins using virtual docking simulation; (3) validation of the most promising molecules using methods such as molecular dynamic simulation, and so forth (Figure 2). Differences between studies mainly lie in the choice of protein targets, the docking sites on the protein targets, the drug/molecule databases, and the virtual screening algorithms. Several viruses or host proteins that are crucial for virus invasion or replication are in focus for drug design. SARS-CoV-2 3C-like main protease ($3CL^{pro}$ or M^{pro}), as the first SARS-CoV-2 protein whose crystal structure has been discovered,[85] becomes the target of most molecular docking drug screening studies.[66–76,80,81] To highlight a few, Gimeno et al.[76] integrated the predictions of three molecular docking softwares (Glide, FRED, and AutoDock Vina), only selecting the drugs that are predicted to have high binding affinity to M^{pro} by all the three softwares.[76] Wang[71] and Mittal et al.[73] both used molecular dynamic simulation followed by binding free energy calculations to validate the top docking molecules. Other popular targets include RdRp,[77] spike (S) protein,[81,83] and spike (S) protein-human ACE2 interface.[82] Besides, several studies investigated relatively novel targets, such as cellular transmembrane protease serine 2 (TMPRSS2)[80] and SARS-CoV-2 envelope (E) protein.[78] Instead of focusing on only one or two proteins, there are some large-scale studies that focused on more than two protein targets. An early study carried out by Wu et al.[65] modeled and screened for drugs against 18 SARS-CoV-2 proteins and two host proteins.[65] And another study by Beck et al.[79] screened for drugs against five virus proteins using their own pretrained deep learning-based drug-target interaction model.[79] Finally, Shi et al.[86] developed a new molecular docking-based web server that facilitates protein structure-based drug screening. As the structure of RdRp) has been established very recently,[28] we forecast that more inhibitors may be proposed for this protein target.

(b) Docking simulation for antibodies treatment: The binding of SARS-CoV-2 spike (S) protein with human ACE2 protein is believed to facilitate SARS-CoV-2 to enter human cells,[87,88] making this process a good target. Using antibody-antigen docking simulation, Park et al.[84] proposed that the human antibody CR3022 may have a high affinity to SARS-CoV-2 spike protein, and thus, it may be a potential treatment of COVID-19.

Besides drug repurposing, computational methods are also used for vaccine design. Multiple in-silico studies have been carried out to design multiepitope vaccines against SARS-CoV-2.[89–91] General workflow of vaccine design includes the retrieval of antigenic protein sequences, predicting potential epitopes, construction of the vaccine, and validating the binding ability of the designed vaccine with TLR3 immune receptor using docking

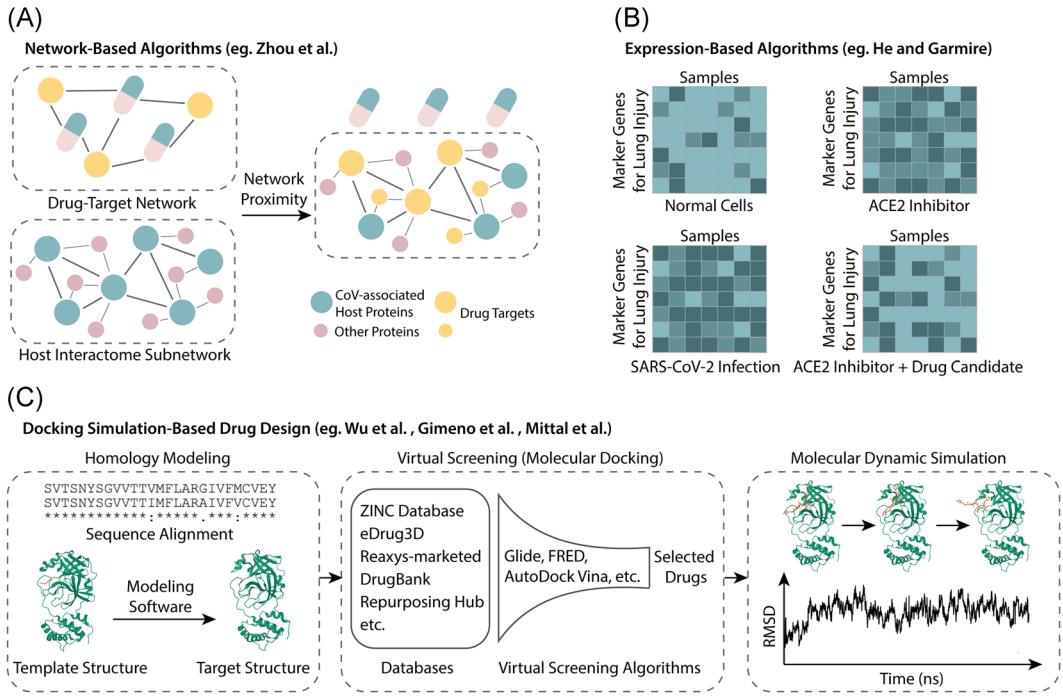

FIGURE 2 Illustration of computational drug repurposing methods. A, Network-based algorithms, using the work of Zhou et al.[62] as an example; B, Expression-based algorithms, using the work of He and Garmire[64] as an example; C, General pipeline of docking simulation-based drug design (Protein structures credit to RCSB PDB 3AW0 [https://www.rcsb.org/structure/3AW0] and 6LU7 [https://www.rcsb.org/structure/6LU7]. Sequence alignment performed by UniProt [https://www.uniprot.org/align/]). Note that the root mean standard deviation plot is only for illustration [Color figure can be viewed at wileyonlinelibrary.com]

simulation. Antigenic proteins used in these studies include SARS-CoV-2 spike glycoprotein,[89] nucleocapsid,[90] ORF3a, and nonstructural proteins.[91]

It is worth mentioning that for this part of the review, we mostly focused on the repurposing of currently approved drugs or drug candidates under clinical trials. There are a number of enlightening studies that focus on finding new drugs from plants or other natural products or designing new molecules[91] that are not included here since they are outside the scope of this review.

4 | DRUGS THAT HAVE BEEN PROPOSED BY IN VITRO PROTEIN-BINDING ASSAYS

Studies have been carried out for genome-wide in vitro binding screening of the virus proteins and human proteins, and drugs that directly target these proteins can thus be proposed.[85,93,94] In this section, we will review the methods and progress in this area (Table 3).

Gordon et al.[93] cloned, tagged, and expressed 26 of the SARS-CoV-2 proteins in human cells, and then identified 332 SARS-CoV-2-human protein interactions using affinity-purification mass spectrometry, among which 67 druggable proteins and 69 potential drugs are identified. Li et al.[94] first used SARS-CoV-2 genome-wide yeast-two hybrid and co-immunoprecipitations to identify the intra-viral protein-protein interactions. Then they cloned and overexpressed each of the virus genes and determined host-virus interactome using affinity-purification, liquid

TABLE 3 Drugs proposed by in vitro protein binding assays

Author	Main method	Proposed drugs/molecules
Gordon et al.[93]	AP-MS	Silmitasertib, valproic acid, haloperidol, entacapone, indomethacin, metformin, ponatinib, **ribavirin**, migalastat, and so forth (only listed part of the results)
Li et al.[94]	Y2H and co-IP, AP-LC-MS	Does not contain screening for drugs, only identified protein-protein interaction network
Jin et al.[85]	FRET	Ebselen, shikonin, tideglusib, PX-12, disulfiram, carmofur

Note: Bold words indicate drugs in clinical trials reviewed above.

Abbreviations: AP-LC-MS; affinity purification, liquid chromatography-mass spectrometry; FRET, fluorescence resonance energy transfer; co-IP, co-immunoprecipitation; Y2H, yeast-two hybrid.

chromatography and mass spectrometry (AP-LC-MS). Jin et al.[85] purified M^{pro} and then used fluorescence resonance energy transfer assay to screen through the M^{pro} binding ability of more than 10,000 compounds including approved drugs or drug candidates.[85]

5 | OUTLOOK

In this review, we summarized drugs against COVID-19 proposed by clinical trials, computational approaches and in vitro protein binding assays. From the clinical trials session, we conclude that there is not a single drug for which consistent positive response has been reported yet, and large-scale controlled trials are in urgent need. Additionally, the clinical trials reviewed in this study reveal that there are differences in drug efficacy between mild or moderate infected patients and severe or critical patients. Thus, analysis and reports taking into account these factors may be informative. From the computational study summary, we learned that some of the drugs proposed by computational methods have already been put into clinical use, which validates the methods in some way.

Current small-scale pilot trials point to the necessity for future large-scale, well-controlled trials to resolve a certain inconsistency in results, as disagreements in the reported drug response can root from differences in dosage, baseline biometrics and population groups. With more clinical trial results coming in, they will also enable meta-analysis to stratify these variables across centers and trials. Besides, an in-depth reflection on the causes and solutions of challenges faced by clinical trials, such as small sample sizes, result consistency, and efficiency of result delivery would be very helpful for future clinical trials.

With the effort of researchers around the world, a variety of unconventional drugs and treatments are explored. Synthetic peptide against COVID-19, for example, is one of the novel treatment options that deserve attention due to its relatively fast and inexpensive synthesis process and better safety. There are currently a handful of peptide treatments against COVID-19 under clinical trials, such as angiotensin peptide (1–7) (NCT04375124) and LSALT peptide (NCT04402957), and several suggested by studies and clinical trials, such as modified α-ketoamide inhibitors[95] and solnatide.[96] Future reviews may consider providing a more detailed summary of the development of peptide treatments.

Additionally, antibodies and vaccines play crucial roles in the battle against COVID-19. Future work may provide more complete and in-depth reviews focusing on the development of antibodies and vaccines against COVID-19.

ACKNOWLEDGMENTS

Scientific editing by Amanda Hargrove. This study is supported by NIH R35-GM133346.

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How to cite this article: Wang X, Guan Y. COVID-19 drug repurposing: a review of computational screening methods, clinical trials, and protein interaction assays. *Med Res Rev*. 2021;41:5-28. https://doi.org/10.1002/med.21728