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COVID-19 Drug Repurposing: a review of computational screening methods, clinical trials, and protein interaction assays

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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, in order 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

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

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 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 3,153 COVID-19 related studies

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listed on the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP), which include studies from countries other than the US, and 1,963 studies listed on ClinicalTrials.gov, which include the US clinical trials only. Among the studies in the US with their study phases documented, most of them are in Phase 2 or Phase 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 10–17 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 since 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, while 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.

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 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.

RNA mutagens: remdesivir, favipiravir and ribavirin—Since 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 into the virus and blocking virus replication [4]. 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.

Remdesivir: Remdesivir, a 1′-cyano-substituted adenosine nucleotide analogue prodrug [5], 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 [6]. 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 [7]. A recent study has also demonstrated its ability to control infection of COVID-19 *in vitro* [8]. 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, 200mg intravenously on day 1 and 100mg 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 [9]. However, a randomized, double-blinded, placebo-controlled clinical trial carried out in ten 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, while the statistically insignificant reduction in time to clinical improvement in patients within 10 days of symptom onset requires further confirmation in larger cohorts [10]. 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 [11]. By far, the largest-scale study on remdesivir is a 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 [12]. 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 [13]. 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 [14].

Favipiravir: Favipiravir-triphosphate can also mimic ATP and GTP for incorporation with RdRp [15], however not as effective as remdesivir [16]. 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 [17]. 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 [18]. However, favipiravir led to significantly accelerated relief of symptoms including pyrexia

and cough [18]. 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 [14].

Ribavirin: Ribavirin's mechanism is similar to that of favipiravir, which also mimics ATP and GTP to incorporate with RdRp [16]. 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 [19]. 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 [20]. 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. [14].

Protease inhibitors: ritonavir-lopinavir and darunavir—Since 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 [21,22]. Representative drugs in this category include ritonavir-lopinavir and darunavir.

Ritonavir-lopinavir: Ritonavir-lopinavir is originally a combination medication for AIDS by inhibiting the protease of HIV [23]. 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 [24]. 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 [25]. 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 [26]. But the result of this study is controversial, since 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 [27]. 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 [28]. 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 [29]. 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 [30]. The most common side effects of ritonavir-lopinavir are mild to moderate gastrointestinal adverse effects such as diarrhea, nausea, and vomiting [23]. 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 [14].

Darunavir: Darunavir is also a protease inhibitor originally used for HIV [31]. There are not clinical trials concerning the SARS-CoV-2 treatment effectiveness of darunavir. Based on case studies of three HIV positive patients infected with SARS-CoV-2, Riva et al. suggests that according to these preliminary evidence, darunavir at a dosage of 800mg 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 [32]. There is one ongoing clinical trial (NCT04252274) that assesses the efficacy and safety of darunavir [14].

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.

Chloroquine: Chloroquine has been used as an anti-malaria drug for many years. It's antiviral mechanism is not completely clear, while 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) [33]. 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 [34]. Gao et al. 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 [35]. 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 [36]. However, large-scale studies are still in urgent need to determine the effectiveness of chloroquine.

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 [37]. 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 [38]. 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 [39]. 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 [40]. 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 [41]. Besides, it is reported that hydroxychloroquine add-on therapy to ritonavir-lopinavir may have many potential adverse effects including cardiac, metabolic and neurological symptoms etc., and should be used with caution [42]. 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 use of these drugs outside hospital settings [43].

Arbidol: Arbidol is a broad-spectrum antiviral. Previous studies on viruses such as HCV, influenza virus etc. demonstrated that it interferes with various steps of the virus life-cycle, including virus entry, endocytosis, endosomal trafficking etc. [44]. 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 [30] and arbidol combined with ritonavir-lopinavir [29] 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 [28]. 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, while favipiravir led to earlier improvement of symptoms including pyrexia and cough [18]. 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 while it may not be able to accelerate virus clearance [45]. There are three ongoing clinical trials that evaluate the efficacy and safety of arbidol for COVID-19 infection treatment [14].

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 [14].

JS016: JS016 is also a neutralizing antibody against 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 [14]. Studies in vitro and in rhesus monkeys show that JS016 (CB6) has the ability to inhibit SARS-CoV-2 infection [46]. The completion date of the trial is expected to be in mid December, 2020.

REGN-COV2: REGN-COV2 is a combination therapy containing the antibodies REGN10933 and REGN10987, and is currently under Phase 1 clinical trial (NCT04426695) [14]. The antibodies are generated from humanized mice and convalescent humans, both proved to be efficiently targeting the receptor-binding domain of the spike protein [47]. There are expected to be 1860 participants in the Phase 1 trail, and the study completion date is going to be in June 2021.

Virus-release blockers: oseltamivir—This category of medication inhibits the release of 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 [48]. 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 [14].

Non-virus-targeting treatments: tocilizumab, dexamethasone, CD24Fc and dapagliflozin—Cytokine storm is a crucial factor that leads to the acute respiratory distress syndrome (ARDS) 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 [49]. Drugs in this category include 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.

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 [50]. Another observational study in 15 patients, 13 of which are severely or critically ill, also demonstrated that tocilizumab may be a useful therapy, and repeated dose is recommended for patients with elevated IL-6 level [51]. However, two cases with adverse effects are reported, and the author advised clinicians to be cautious about hypertriglyceridemia when using tocilizumab [52].

CD24Fc: CD24Fc, composed of the non-polymorphic regions of CD24 attached to the Fc region of human IgG1, is an immunomodulator that can suppress the expression of multiple cytokines [14]. 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 [14]. The study completion date is expected to be in December 2020 [14].

Dexamethasone: Dexamethasone is an FDA approved synthetic corticosteroid that suppresses the immune system by inhibiting naive T cell proliferation and differentiation [53], 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 28-day mortality rate by one-third in patients receiving invasive ventilation, and by one-fifth in patients receiving oxygen but not invasive ventilation [54]. It does not reduce mortality rate

in patients not requiring oxygen support [54]. 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, while 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].

Dapagliflozin: Dapagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor, and is hypothesised 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 [14]. The completion date is expected to be in December 2020 [14].

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 Phase 3 or Phase 4 may be considered as passed clinical trials. There are currently 9 completed Phase 3 trials and 2 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 dataset needed; negative), baricitinib (result not posted), methylprednisolone therapy (result not posted), liposomal lactoferrin (result not posted), and danoprevir (result not posted) [14].

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).

Network-based algorithms—Zhou et al. integrated HCoV-host interactions, drug-target network and human protein interactome together and proposed 16 drugs and 3 drug combinations for SARS-CoV-2 infection treatment [62]. 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 HCoV-specific network and 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 co-expressed 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].

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].

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 sub-categories:

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 etc. (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 virus 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 [65], becomes the target of most molecular docking drug screening studies [66–77]. To highlight a few, Gimeno et al. integrated the predictions of 3 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. [74] both used molecular dynamic simulation followed by binding free energy calculations to validate the top docking molecules. Other popular targets include RNA-dependent RNA polymerase (RdRp) [78], spike (S) protein [7977], and spike (S) protein-human ACE2 interface [80]. Besides, several studies investigated relatively novel targets, such as cellular transmembrane protease serine 2 (TMPRSS2) [72] and SARS-CoV-2 envelope (E) protein [81]. 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. modeled and screened for drugs against 18 SARS-CoV-2 proteins and 2 host proteins [82]. And another study by Beck et al. screened for drugs against 5 virus proteins using their own pre-trained deep learning-based drug-target interaction model [83]. Finally, Shi et al. developed a new molecular docking-based web server that facilitates protein structure-based drug screening [84]. As the structure of RNA dependent RNA-polymerase (RdRp) has been established very recently [4], 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 [85,86], making this process a good target. Using antibody-antigen docking simulation, Park et al. proposed that the human antibody

CR3022 may have high affinity to SARS-CoV-2 spike protein and thus it may be a potential treatment of COVID-19 [87].

Besides drug repurposing, computational methods are also used for vaccine design. Multiple *in-silico* studies have been carried out to design multi-epitope vaccines against SARS-CoV-2 [88–90]. 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 simulation. Antigenic proteins used in these studies include SARS-CoV-2 spike glycoprotein[88], nucleocapsid[89], ORF3a[89], and non-structural proteins [90].

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 trial. 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.

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 [92,93,65]. In this section, we will review the methods and progress in this area (Table 3).

Gordon et al. 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 [92]. Li et al. first used SARS-CoV-2 genome-wide yeast-two hybrid (Y2H) and co-immunoprecipitations (co-IP) 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 chromatography and mass spectrometry (AP-LC-MS) [93]. Jin et al. purified M^{pro}, and then used fluorescence resonance energy transfer (FRET) assay to screen through the M^{pro} binding ability of more than 10,000 compounds including approved drugs or drug candidates [65].

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 work 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 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 [94] and Solnatide [95]. 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.

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Biosketches

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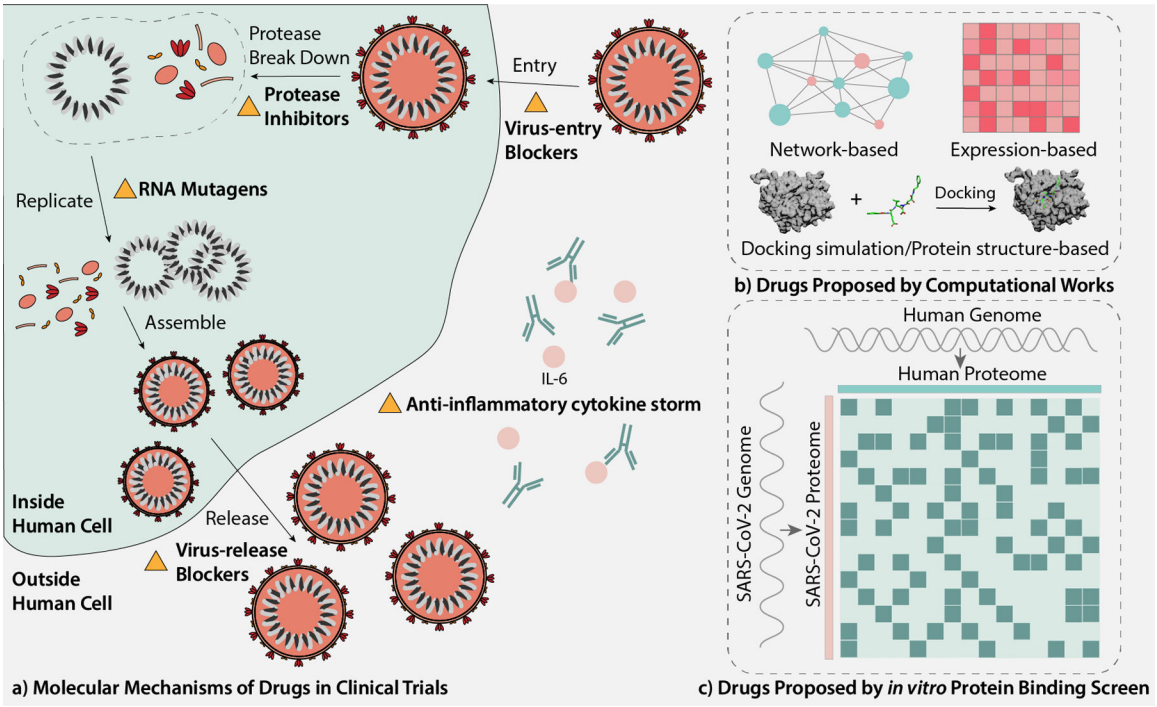

Figure 1.

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.

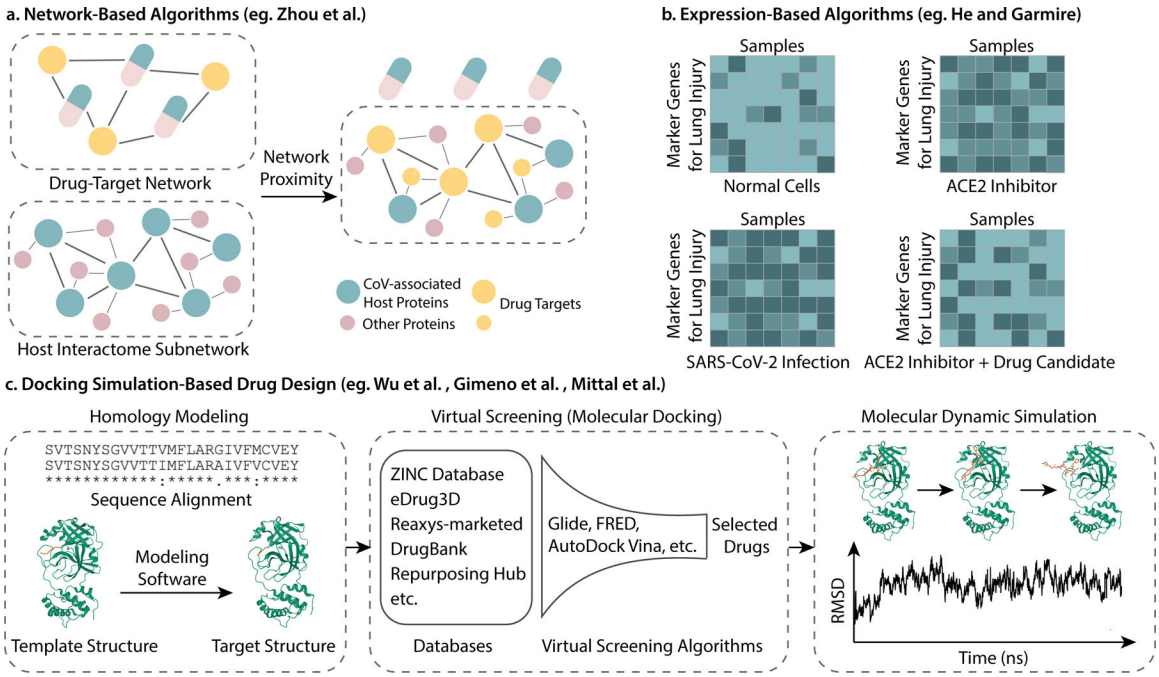

Figure 2.

Illustration of computational drug repurposing methods. (a) Network-based algorithms, using the work of Zhou et al. as an example; (b) Expression-based algorithms, using the work of He and Garmire 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 RMSD plot in the figure is only for illustration.)

Table 1.

Summary of clinical trials

Author	Type of Study	Cohort	Drugs and Doses	Results
remdesivir				
Grein et al.	Compassionate	61 patients, oxygen saturation <= 94% or receiving oxygen support	A 10-day course of remdesivir treatment, 200mg intravenously on day 1, 100mg for next 9 days	During a median follow up of 18 days, 36 of 53 (68%) patients improved in terms of the oxygen support class
Wang et al.	Randomized, double-blind, placebo-controlled, multicenter	237 patients, age >= 18, symptom onset <= 12 days, oxygen saturation <= 94%, radiologically confirmed pneumonia	A 10-day course of remdesivir treatment, 200mg intravenously on day 1, 100mg for next 9 days vs. the same amount of placebo	Remdesivir use was not associated with a difference in time to clinical improvement; Patients whose symptom onset <=10 days treated with remdesivir showed a numerically faster time to clinical improvement compared to placebo (not significant)
Antinori et al.	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, 200mg intravenously on day 1, 100mg for next 9 days; existing treatments including HCQ was continued, but LPV/r was discontinued	On day 28, 14 patients from the normal ward were discharged, 2 still hospitalized and 1 died, while 6 patients in ICU were discharged, 3 still hospitalized and 8 died.
Beigel et al.	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, 200mg intravenously on day 1, 100mg for next 9 days vs. the same amount of placebo	Patients with remdesivir had a median to recovery time of 11 days, while patients with placebo had a median to recovery time of 15 days ($p<0.001$)
favipiravir				
Cai et al.	Open-label, nonrandomized,controlled	80 patients, age 16–75, disease onset <= 7 days, no severe clinical condition	FPV: oral FPV, 14-day course of treatment, 1600 mg on day 1, twice daily; 600 mg on day 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, twice daily; plus interferon (IFN)-a by aerosol inhalation (5 million U twice daily)	FPV group showed shorter viral clearance time (4(2.5–9) days compared to 11(8–13) days, $p < 0.001$); FPV group showed improvement in chest imaging (improvement rate of 91.43% compared to 62.22%, $p = 0.004$)
Chen et al.	Prospective, randomized, controlled, open-label, multicenter	240 patients, age >= 18, initial symptoms <= 12 days	FPV: 1200mg * 2 on day 1 and 600mg * 2 for day 2–10 + conventional therapy Arbidol (control): 200mg * 3/day for 10 days + conventional therapy	No statistically significant difference in clinical recovery rate on day 7 (71/116 compared to 62/120, $p = 0.1396$); FPV led to shorter latencies to the relief of pyrexia and cough ($p < 0.0001$)
ribavirin				
Yuan et al.	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 mRNA clearance rate and length of hospital stay
Hung et al.	Prospective, open-label, randomized, multicenter, phase 2	127 patients, age >= 18, NEWS2 >= 1,	Combination group: LPV/r 400mg/100mg every 12h + ribavirin 400mg every 12h +	Combination group had shorter time from the beginning of treatment to negative

Author	Type of Study	Cohort	Drugs and Doses	Results
		symptom onset <= 14	IFN-β1b 8 million U every alternate day for 14 days Control group: LPV/r 400mg/100mg every 12h for 14 days	nasopharyngeal swab (7(5–11) compared to 12(8–15), p = 0.0010)
ritonavir-lopinavir				
Yan et al.	Retrospective	120 patients	LPV/r: oral, 400mg/100mg, 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<0.001)
Ye and Luo et al.	Controlled, non-randomized	47 patients, age 5–68	Test group: LPV/r 400mg/100mg twice daily or 800mg/200mg 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 3 treatments; The test group had a shorter time before RNA test turns negative (p=0.0219)
Cao et al.	Randomized, controlled, open-label	199 patients, age >= 18, oxygen saturation <= 94%	Test group: LPV/r 400mg/100mg twice daily for 14 days + 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. (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 4 groups; Significant difference in the proportion of changing from mild/moderate to severe/critical on day 7 (p=0.017), LPV/r and control group had a smaller proportion of deterioration changing
Deng et al.	Retrospective	33 patients, age>=18, without invasive ventilation	Combination group: arbidol 200mg every 8h, LPV/r 400mg/100mg every 12h; Monotherapy group: LPV/r 400mg/100mg every 12h; Until RNA test negative for 3 times (5–21 days)	Combination group had higher viral clearance rate on day 7 (p<0.05) and day 14 (p<0.05); Combination group had higher chest image improving rate at day 7 (p<0.05)
Zhu et al.	Retrospective	50 patients, no severe pneumonia or ARDS	LPV/r group: LPV/r 400mg/100mg twice daily for 7 days Arbidol group: 0.2g arbidol, 3 times daily for 7 days All patients received conventional therapy	No difference in fever duration (p=0.61); arbidol group had less viral load on day 14 (0% compared to 44.1%); arbidol group had shorter RNA test positive duration (p<0.01)
Chloroquine				
Gao et al.	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.	Controlled, randomized	22 patients, age >= 18	Chloroquine: 500mg orally twice daily for 10 days; 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

Author	Type of Study	Cohort	Drugs and Doses	Results
				shorter time to discharge from hospital
Hydroxychloroquine				
Chen et al.	Randomized, parallel-group	62 patients, age >= 18, oxygen saturation > 93%, no severe or critical illness	HCQ: 400mg/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.	observational	80 patients, mildly infected	HCQ: 200mg orally, 3 times per day for 10 days; Azithromycin: 500mg on day 1 and 250mg on day 2–5; Some patients (with pneumonia, NEWS>=5) also received ceftriaxone	Clinical improvement and rapid fall of nasopharyngeal viral load were observed
Molina et al.	prospective	11 patients, severe disease, 5 with cancer, 1 with HIV, 2 obesity	HCQ: 600mg per day for 10 days; Azithromycin: 500mg on day 1 and 250mg on day 2–5;	No evidence for rapid viral clearance and clinical benefits
Tang et al.	Randomized, controlled, open-label	150 patients, 148 mild to moderate disease and 2 severe disease	HCQ group: HCQ 1200mg daily for day 1–3, 800mg daily for the rest of treatment duration (2–3 weeks according to patient condition) + standard care Control group: standard care	HCQ did not result in a higher proportion of negative conversion
Mahevas et al.	Observational	181 patients, age = 18–80, require oxygen but not intensive care	HCQ group: HCQ 600mg/day, started treatment 48 hours after admission; Control group: no HCQ treatment	Similar survival rate and clinical improvement in two groups
arbidol				
Chen et al.	Prospective, randomized, controlled, open-label, multicenter	240 patients, age >= 18, initial symptoms <= 12 days	FPV: 1200mg * 2 on day 1 and 600mg * 2 for day 2–10 + conventional therapy arbidol (control): 200mg * 3/day for 10 days + conventional therapy	No statistically significant difference in clinical recovery rate on day 7 (71/116 compared to 62/120, p = 0.1396); FPV led to shorter latencies to the relief of pyrexia and cough (p < 0.0001)
Wen et al. (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 4 groups; Significant difference in the proportion of changing from mild/moderate to severe/critical on day 7 (p=0.017), LPV/r and control group had a smaller proportion of deterioration changing
Deng et al.	Retrospective	33 patients, age>=18, without invasive ventilation	Combination group: arbidol 200mg every 8h, LPV/r 400mg/100mg every 12h; Monotherapy group: LPV/r 400mg/100mg every 12h; Until RNA test negative for 3 times (5–21 days)	Combination group had higher viral clearance rate on day 7 (p<0.05) and day 14 (p<0.05); Combination group had higher chest image improving rate at day 7 (p<0.05)
Zhu et al.	Retrospective	50 patients, no severe pneumonia or ARDS	LPV/r group: LPV/r 400mg/100mg twice daily for 7 days Arbidol group: 0.2g arbidol, 3 times daily for 7 days All patients received conventional therapy	No difference in fever duration (p=0.61); arbidol group had less viral load on day 14 (0% compared to 44.1%);

Author	Type of Study	Cohort	Drugs and Doses	Results
				arbidol group had shorter RNA test positive duration ($p<0.01$)
Xu et al.	Retrospective, multicenter	141 patients, age>=18, without ventilation	Combined group: arbidol 200mg, oral, 3 times daily for 7–10 days; IFN-α2β, inhale, twice daily, 5 × 10(5) IU for 10–14 days Monotherapy group: inhale IFN-α2β, twice daily, 5 × 10(5) IU for 10–14 days	No significant differences between the two groups in terms of viral clearance; Faster CT improvement in the combined therapy group
tocilizumab				
Xu et al.	Observational	21 patients, severe or critical disease	Tocilizumab: 4–8mg/kg body weight Standard treatment: LPV/r 400mg/100mg twice daily; IFN-α, inhale, twice daily, 5 million U; ribavirin, 500mg 2–3 times daily	Quick and significant clinical improvements were observed, all patients discharged with a mean of 15.1 days after given tocilizumab
Luo et al.	Retrospective	15 patients, 2 moderately ill, 6 severely ill, 7 critically ill	Different for each patient, see Table 1 in paper	TCZ ameliorated increased CRP rapidly in all patients; treatment failed for 4 patients, 3 dead and 1 aggravated
dexamethasone				
RECOVERY Collaborative Group	Randomized, controlled, open-label	6425 patients, anyone hospitalized and confirmed with COVID-19 and without risky medical histories, including children < 18 and pregnant or breastfeeding women	dexamethasone 6 mg once daily for 10 days compared with usual care	28-day mortality reduced one-third in patients need invasive ventilation, one-fifth in patients need oxygen support but not invasive ventilation, no reduction in patients without oxygen support

Table 2.

Drugs proposed by computational methods
(bold words indicate drugs in clinical trials reviewed above)

Author	Protein in focus	Proposed drugs/molecules (bold words indicate drugs in clinical trials reviewed above)
Category 1. Network-based algorithms		
Zhou et al.	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.	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	Angiotensin converting enzyme 2 (ACE2)	COL-3, CGP-60474
Category 3. Docking simulation or protein structure based algorithms		
Wu et al.	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, RdRp, TMPRSSS2	**ribavirin**, valganciclovir, β-Thymidine, aspartame, oxprenolol, lymecycline, chlorhexidine, alfuzosin, cilastatin, famotidine, valganciclovir, ceftibuten, fenoterol, fludarabine, etc. (only listed part of the results)
AI-Khafaji et al.	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	saquinavir, **ritonavir**, **remdesivir**, delavirdine, cefuroxime axetil, **oseltamivir**, prevacid
Shah et al.	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	**lopinavir**, asunaprevir, **remdesivir**, CGP42112A, indinavir, **ritonavir**, ABT450, marboran (methisazone), galidesivir
Kandeel and Al-Nazawi	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	chromocarb, **ribavirin**, telbivudine, vitamin B12, aminophylline, nicotinamide, triflusal etc. (only listed part of the results)
Mahanta et al.	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	viomycin
Pant et al.	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	cobicistat, **ritonavir**, **lopinavir**, **darunavir**
Junmei Wang	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	carfilzomib, eravacycline, valrubicin, **lopinavir**, elbasvir
Odhar et al.	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	conivaptan, olaparib, loxapine, sonidegib, azelastine, idelalisib, tolvaptan, perampanel, suvorexant, ponatinib
Mittal et al.	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	leupeptin, hemisulphate, pepstatin A, nelfinavir, birinapant, lypression, octreotide
Das et al.	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	**ritonavir**, emetine, **lopinavir**, indinavir (only listed part of the results)
Farag et al.	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	**darunavir**, mitoxantrone, nelfinavir, moexpril, daunorubicin, rosuvastatin, saquinavir, metamizole, bepotastine, benzonatate, atovaqoune
Gimeno et al.	SARS-CoV-2 main protease (M^{pro} or $3CL^{pro}$)	perampanel, carprofen, celecoxib, alprazolam, trovafloxacin, sarafloxacin, ethyl biscoumacetate
Elfiky	RNA-dependent RNA polymerase (RdRp)	**ribavirin**, **remdesivir**, sofosbuvir, galidesivir, tenofovir, **hydroxychloroquine**, cefuroxime, **f**avipiravir, setrobuvir, YAK, IDX-184

Author	**Protein in focus**	**Proposed drugs/molecules (bold words indicate drugs in clinical trials reviewed above)**
Gupta et al.	SARS-CoV-2 envelope (E) protein	belachinal, macaflavanone E, vibsanol B
Beck et al.	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**, etc. (only listed part of the results)
Elmezayen et al.	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	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.	Spike (S) protein or Spike (S) protein-ACE2 interface complex	pemirolast, sulfamethoxazole, valaciclovir, sulfamerazine, tazobactam, nitrofurantoin
Oliveira et al.	Spike (S) protein	suramin sodium, 5-hydroxytrytophan, dihydroergocristine mesylate, quinupristin, nilotinib, dexamethasone-21-sulfobenzoate, tirilazad, selamectin, acetyldigitoxin, doramectin
Park et al.	Spike (S) protein	CR3022 human antibody, F26G19 mouse antibody, D12 mouse antibody

Table 3.

Drugs proposed by in vitro protein binding assays
(bold words indicate drugs in clinical trials reviewed above)

Author	**Main Method**	**Proposed Drugs/Molecules (bold words indicate drugs in clinical trials reviewed above)**
Gordon et al.	AP-MS	silmitasertib, valproic acid, haloperidol, entacapone, indomethacin, metformin, ponatinib, **ribavirin**, migalastat, etc. (only listed part of the results)
Li et al.	Y2H and co-IP, AP-LC-MS	Does not contain screening for drugs, only identified protein-protein interaction network
Jin et al.	FRET	ebselen, shikonin, tideglusib, PX-12, disulfiram, carmofur