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COVID-19 drug repurposing: Summary statistics on current clinical trials and promising untested candidates

Running Title: *COVID-19 drug repurposing: Trials and prospects*

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Summary

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Repurposing of existing antiviral drugs, immunological modulators, and supportive therapies represents a promising path toward rapidly developing new control strategies to mitigate the devastating public health consequences of the COVID-19 pandemic. A comprehensive text-mining and manual curation approach was used to comb and summarize the most pertinent information from existing clinical trials and previous efforts to develop therapies against related betacoronaviruses, particularly SARS and MERS. In contrast to drugs in current trials, which have been derived overwhelmingly from studies on taxonomically unrelated RNA viruses, a number of untested small molecule antivirals had previously demonstrated remarkable in vitro specificity for SARS-CoV or MERS-CoV, with high selectivity indices, EC_{50}, and/or IC_{50}. Due to the rapid containment of the prior epidemics, however, these were generally not followed up with in vivo animal studies or clinical investigations, and thus largely overlooked as treatment prospects in the current COVID-19 trials. This brief review summarizes and tabulates core information on recent or ongoing drug repurposing-focused clinical trials, while detailing the most promising untested candidates with prior documented success against the etiologic agents of SARS and/or MERS.

Keywords: COVID-19, drug repositioning, pandemics, antiviral agents, data mining, SARS

Main Text

The unprecedented public health, economic, and social challenges engendered by the current COVID-19 pandemic necessitate an urgent search for effective clinical interventions to help reduce viral load and epidemiological spread, improve prevention and control, and stem the tide of rising morbidity and mortality (Spinelli & Pellino, 2020). Due to the time lag of vaccine trials and *de novo* drug development based on standard drug-target modeling, compound screens, and multi-phase clinic testing, the most rapid and practical approach toward new clinical options lies in drug repositioning of proven or promising infectious control modalities (Li & De Clercq, 2020). For SARS-CoV-2, the etiologic agent of COVID-19, this effort may be significantly assisted by previous endeavors to develop therapeutics for two prior smaller epidemics, both caused by closely related coronavirus types. Severe acute respiratory syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS) each

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originated from outbreaks of betacoronaviruses with significant sequence and structural similarity to the SARS-CoV-2 betacoronavirus (Zhu et al., 2020).

Thousands of COVID-19-related clinical trials have been proposed or launched since January 2020, at multiple global sites, with many seeking to assay for efficacy of various repurposed drugs against SARS-CoV-2—most available on the National Library of Medicine's registry of clinical studies, others scraped from text-mining of the available literature. Figure 1 summarizes an early snapshot of such clinical investigations, focusing on 53 repurposing-based trials noted to be in planning or progress as of April 17, 2020, on the basis of the tested drugs, targets or mechanisms, preliminary efficacy studies, current and prior literature on the drug's efficacy for betacoronavirus-related disease, and the specific designating information for the relevant trials themselves including their phase, scale, expected completion date, and other key descriptors. The tested modalities attempt a variety of approaches to improve patient outcomes, some targeting the virus directly, others seeking to counter its deleterious physiological sequelae through immunomodulation or respiratory and circulatory support to reduce mortality and morbidity.

Summary statistics for these seminal trials are provided in Figure 2. As can be seen, drugs and targets linked to unique viral components and processes—such as the viral protease and RNA-dependent-RNA-polymerase—have predominated in early investigations. Several compounds had demonstrated promise in at least some preliminary studies including lopinavir/ritonavir, remdesivir, and chloroquine or hydroxychloroquine, and more than a third (for which comprehensive descriptions were provided) were already at or beyond Phase 3. Nevertheless, the scale of most trials remains small, the vast majority are not multi-centered, and evaluation of efficacy will take months or years to carry out. Only a few clinical trials are enrolling greater than 1,000 participants, including the global WHO DISCOVERY trial, the European-based INSERM trial, and the Adaptive COVID-19 Treatment Trial. Moreover, the most commonly tested drugs have been drawn from antiviral studies outside the prior body of research focusing on SARS and MERS.

Since the SARS and MERS outbreaks dissipated without approaching the global impact of COVID-19, fledgling therapeutic studies for these epidemics were generally not followed up. As a result, in vivo animal and human data for promising drug prospects, including blood concentrations

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and dose-response curves in animal studies, are largely unavailable. This has likely contributed to the pronounced preference, in existing COVID-19 clinical investigations, to repurpose therapeutic candidates like favipiravir, remdesivir, and lopinavir/ritonavir, all designed for taxonomically distinct viruses and viral classes (particularly HIV, Ebola, and influenza) relative to SARS-CoV-2. These therapeutic agents nonetheless benefit from prior in vivo data which the compounds effective against SARS-CoV and MERS-CoV lack, making them more readily adaptable to urgent COVID-19 clinical trials than drug candidates for fellow betacoronaviruses with higher likelihood of specific interactions with SARS-CoV-2 essential components.

Such factors, largely a product of practical urgencies amid a pressing pandemic and the contingent history of the SARS and MERS epidemics, further suggest that there may be substantial overlooked potential for new COVID-19 drugs showing prior promise in vitro against other betacoronaviruses. This suggestion is reinforced by a recent study which noted significant in vitro and in vivo activity of a known nucleoside analog with previous efficacy against SARS and MERS, β-D-N4-hydroxycytidine (NHC), in reducing viral load in cell culture and tissue damage in mice secondary to SARS-CoV-2 infection (Sheahan et al., 2020). NHC was one of nearly a dozen drugs to have demonstrated potential in reducing the disease burden from SARS, MERS, or both (De Clercq, 2006; Kumar, Jung, & Liang, 2013; Savarino, 2005), and the recent results support the notion that such repurposing may be fruitful for COVID-19.

We have therefore systematically combed available literature, reports, and commentaries to ascertain untested drugs with previous promise for SARS and MERS that merit consideration for additional COVID-19 trials, alongside the comprehensive clinical trial data elaborated previously. We utilized an approach combining careful manual curation and algorithmic scraping using a flexible Python language-based text-mining tool, previously developed for research into prospective repurposable drugs for Duchenne muscular dystrophy. Concomitantly, we systematically examined the drugs with previous reported efficacy in the context of SARS and MERS, then curated them on the basis of several factors most indicative of potential in clinical trials to repurpose them for SARS-CoV-2.

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In assessing criteria to identify highly promising candidates for COVID-19 drug repurposing, it has been noted that perhaps the primary predictor of eventual failure in clinical trials is non-selectivity for the target, contributing to unacceptable toxicity (Gayvert, Madhukar, & Elemento, 2016). Therefore, in examining the as yet untested or seldom-tested SARS and MERS drugs with potential for COVID-19 repositioning, particular weighting was given to those exhibiting a low reported EC_{50} (or IC_{50}) and high Selectivity Index (SI) from cell culture studies. Attention was likewise given to drugs which are not only selective for a viral target, especially a component indispensable for viral replication, but also substantially reduce viral load in vitro. Further consideration was given for modalities demonstrating confirmation of potential efficacy from multiple centers. With these factors as primary criteria for identifying COVID-19 drug repurposing candidates, several especially promising potential therapeutics were identified, summarized in Figure 3.

Of particular promise are a docking octapeptide, AVLQSGFR (Chou, Wei, & Zhong, 2003; Gan et al., 2006), and a Phe-Phe dipeptide inhibitor, 18c (Shie et al., 2005), with marked selectivity (> 1,000-fold) for the betacoronaviral protease of SARS-CoV (3C-like protease, also known as 3CL protease, 3CLpro, or Mpro) and demonstrated capacity to reduce viral load in cell culture. Both agents exhibit not only remarkable Selectivity Index (SI) values, but also low IC_{50} and/or EC_{50} measurements that suggest viability as practical drugs in vivo. As noted previously, the viral protease is also the most frequent target of COVID-19 clinical trials currently in progress or planning, but these candidates stand out for their proven ability to selectively target 3CLpro and to bring about a tangible reduction in viral infection capacity.

Encouraging results have also been observed for bananin (Huang, Zheng, & Sun, 2008; Tanner et al., 2005; Wang et al., 2011), a viral helicase inhibitor with > 30-fold selectivity in cell culture studies; for calpain inhibitor VI (Barnard et al., 2004), with > 100-fold selectivity; and for the herbal extract hesperetin (Lin et al., 2005), with an SI > 300 and a direct inhibitory effect on the 3CL protease. Bananin (Tanner et al., 2005) and calpain inhibitor VI (Barnard et al., 2004) have likewise been found to inhibit viral load and infection in vitro. Promising seminal studies for inhibition of SARS or MERS infection have also emerged for another protease inhibitor, cinanserin (Chen et al.,

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2005), and for nafamostat (Yamamoto et al., 2016), a cellular serine protease inhibitor that reduces viral spike protein priming.

As indicated above, a limitation in evaluating these compounds' potential as COVID-19 treatments is that all reported studies thus far are in vitro, without data on therapeutic or toxic blood concentrations, ED50, or dose-response behavior in animals—a result of the abrupt subsiding of the SARS and MERS epidemics. Yet this very fact, in conjunction with their striking findings in cell culture studies, helps to underscore their untapped potential for the current pandemic caused by a much more persistent betacoronavirus, and the value of testing them in an in vivo context. Alongside the recent findings by Sheahan and coworkers with NHC, such results suggest that animal studies and preliminary clinical trials with these agents, or closely related chemical derivatives, may prove fruitful in expanding the arsenal of drugs to combat the relentless spread, morbidity, and mortality of COVID-19.

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Conflict of Interest Statement

The authors certify that they have no affiliations with, or involvement in, any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other form of equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Ethics Statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

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Figure legends

Figure 1. Comprehensive summary data on drug repurposing-focused COVID-19 clinical trials completed, in progress, or in advanced planning stages as of April 17, 2020. Trial data were organized according to drug and target or pharmacologic mechanism, along with results and pertinent literature from any preliminary COVID-19 studies (or prior SARS and MERS studies), trial ID and phase, and data on investigational scale and structure including number of participants, blinding, single vs. multi-center status, and estimated completion date.

Figure 2. Cumulative statistics from drug repurposing-focused COVID-19 clinical trials, based on the aggregate number of trials (out of a total of 53 publicly reported by April 17, 2020) involving (A) a specific drug, (B) a classifying target or mechanism, (C) clinical research phase, (D) single center vs. multi-center, and (E) a given expected timeframe for reporting results.

Figure 3. Summary data on promising untested candidates for COVID-19 drug repurposing based on proven success in SARS and/or MERS in vitro studies, with focus on target selectivity, viral load reduction, and number of positive reports with independent confirmation.

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Drug	Target or mechanism (if known)	Prelim results for SARS-CoV-2 trials or case reports (if applicable)	DOI of pertinent prior studies: SARS, MERS, or related RNA viruses	DOI of prelim clinical trials, case reports, or in vitro studies: SARS-CoV-2/COVID-19	clinicaltrials.gov ID(s) or other study identifier and phase (if available)	Study 1 size, structure, est. completion date	Study 2 size, structure, est. completion date	Study 3 size, structure, est. completion date	Study 4 size, structure, est. completion date	Study 5 size, structure, est. completion date	Study 6 size, structure, est. completion date	Study 7 size, structure, est. completion date	Study 8 size, structure, est. completion date
favipiravir	RNA-dependent RNA polymerase		10.1016/j.pharmthera.2020.107512, 10.1177/2040206618764483, doi.org/10.2183/pjab.93.027		NCT04273763, NCT04310228	NCT04273763: 60 participants, randomized open-label sequential assignment, single center -- April 30, 2020	NCT04310228: 150 participants, randomized open-label parallel assignment, single center -- May 2020						
remdesivir	RNA-dependent RNA polymerase	effective in NEJM case report (Holshue et al.) and in cell culture (Wang et al.)	10.1126/scitranslmed.aal3653, 10.1038/s41467-019-13940-6	10.1056/NEJMoa2001191, 10.1038/s41422-020-0282-0	WHO SOLIDARITY, INSERM Discovery (NCT04315948), NCT04302766 (expanded access), NCT04280705 (phase 2), NCT04292899 (phase 3)	WHO SOLIDARITY: large-scale, multi-center, randomized open-label, otherwise TBA	INSERM Discovery (NCT04315948): 3100 participants, randomized open-label parallel assignment, multi-center -- March 2023	NCT04302766: TBA	NCT04280705 (Adaptive COVID-19 Treatment Trial): 440 participants, randomized double-blind parallel assignment, multi-center -- April 1, 2023	NCT04292899: 400 participants, randomized open-label parallel assignment, single center - May 2020			
β-D-N4-hydroxycytidine	RNA-dependent RNA polymerase	effective at reducing viral load in vitro (lung cell culture) and reducing clinical sequelae in vivo (mice) (Sheahan et al.)	10.1177/0956332020401500102, 10.1101/2020.03.19.997890v1.full	10.1101/2020.03.19.997890v1.full	(trial in planning)								
lopinavir/ritonavir	viral protease inhibitor	mixed efficacy in 2 small Chinese trials (Cao et al., Deng et al.)	10.1038/s41467-019-13940-6, 10.1093/infdis/jiz392, 10.1016/j.jhin.2018.09.005, (PMID: 14660806), 10.1136/thorax.2003.012658, 10.1016/j.jcv.2004.03.003	10.1056/NEJMoa2001282, 10.1016/j.jinf.2020.03.002	WHO SOLIDARITY, INSERM Discovery (NCT04315948), NCT04286503, NCT04307693 (phase 2), NCT04291729 (phase 4), NCT04261907, NCT04295551, NCT04251871	WHO SOLIDARITY: large-scale, multicenter, randomized open-label, otherwise TBA	INSERM Discovery (NCT04315948): 3100 participants, randomized open-label parallel assignment, multi-center -- March 2023	NCT04286503: 520 participants, randomized open-label parallel assignment, single center -- February 28, 2021	NCT04307693: 150 participants, randomized open-label parallel assignment, multi-center - May 2020	NCT04291729: 11 participants, non-randomized open-label single group assignment, single center -- March 19, 2020	NCT04261907: 160 participants, randomized open-label parallel assignment, multi-center -- June 30, 2020	NCT04295551: 80 participants, randomized open-label parallel assignment, multi-center -- April 14, 2021	NCT04251871: 150 participants, randomized open-label parallel assignment, single center -- January 22, 2021
ASC09/ritonavir	viral protease inhibitor				NCT04261907	NCT04261907: 160 participants, randomized open-label parallel assignment, multi-center -- June 30, 2020							
darunavir/cobicistat	viral protease inhibitor				NCT04252274 (phase 3)	NCT04252274: 30 participants, randomized open-label parallel assignment, single center -- December 31, 2020							
umifenovir (arbidol)	membrane fusion				NCT04273763, NCT04286503, NCT04260594 (phase 4)	NCT04273763: 60 participants, randomized open-label sequential assignment, single center -- April 30, 2020	NCT04286503: 520 participants, randomized open-label parallel assignment, single center -- February 28, 2021	NCT04260594: 380 participants, randomized open-label parallel assignment, single center -- December 30, 2020					
losartan	angiotensin II receptor type 1 (AT1)		10.1038/nm1267		NCT04312009 (phase 2)	NCT04312009: 200 participants, randomized double-blind parallel assignment, multi-center -- April 1, 2021							
chloroquine	viral uncoating (endosome acidification), ACE2 receptor	effective in cell culture (Wang et al.), lower therapeutic index than hydroxychloroquine (Yao et al.)		10.1038/s41422-020-0282-0, 10.1093/cid/ciaa237	WHO SOLIDARITY, NCT04303507, NCT04286503	WHO SOLIDARITY: large-scale, multi-center, randomized open-label, otherwise TBA	NCT04303507: 40,000 participants, randomized double-blind parallel assignment, multi-center -- April 2021	NCT04286503: 520 participants, randomized open-label parallel assignment, single center -- February 28, 2021					
hydroxychloroquine	viral uncoating (endosome acidification), ACE2 receptor	effective in cell culture, less toxic than chloroquine (Yao et al.), improved time to clinical recovery (TTCR) (Chen et al.)		10.1093/cid/ciaa237, 10.1101/2020.03.22.20040758	NCT04308668 (phase 2,3), NCT04307693 (phase 2), NCT04261517 (phase 3), HYDRA trial (NCT04315896, phase 3)	NCT04308668: 3000 participants, randomized quadruple-blind parallel assignment, single center -- May 12, 2020	NCT04307693: 150 participants, randomized open-label parallel assignment, multi-center -- May 2020	NCT04261517: 30 participants, randomized open-label parallel assignment, single center -- February 25, 2020	HYDRA trial (NCT04315896: 500 participants, randomized quadruple-blind parallel assignment, single center) -- March 22, 2022				
bromhexine HCl	mucolytic				NCT04273763	NCT04273763: 60 participants, randomized open-label sequential assignment, single center -- April 30, 2020							
interferon-beta (1b)	cellular antiviral induction		10.1093/infdis/jiz392		(part of combination therapy trials)								
interferon-alpha (2b)	cellular antiviral induction				NCT04273763, NCT04293887 (phase 1), NCT04251871	NCT04273763: 60 participants, randomized open-label sequential assignment, single center -- April 30, 2020	NCT04293887: 328 participants, randomized open-label parallel assignment, multi-center -- June 30, 2020	NCT04251871: 150 participants, randomized open-label parallel assignment, single center -- January 22, 2021					
interferon-alpha-2a, pegylated (Pegasys)	cellular antiviral induction				NCT04291729 (phase 4)	NCT04291729: 11 participants, non-randomized open-label single group assignment, single center -- March 19, 2020							
novaferon (recombinant IFNalpha-like)	cellular antiviral induction		10.1186/1475-2867-14-8		NCT04291729 (phase 4)	NCT04291729: 11 participants, non-randomized open-label single group assignment, single center -- March 19, 2020							
bevacizumab	VEGF (vascular permeability)				NCT04275414 (phase 2,3)	NCT04275414: 20 participants, non-randomized open-label single group assignment, single center -- May 2020							
camostat	TMPRSS2 (cellular serine protease), S protein priming	effective in cell culture reducing viral entry (Hoffmann et al.)	10.1128/JVI.00094-12, 10.1128/JVI.01890-13	10.1016/j.cell.2020.02.052	(trial in planning)								
azithromycin	synergistic with hydroxychloroquine				(part of combination therapy trials)								
pirfenidone	anti-fibrotic (procollagens I and II, growth factors)				NCT04282902 (phase 3)	NCT04282902: 294 participants, randomized open-label parallel assignment, single center -- June 1, 2020							
tetrandrine	anti-fibrotic				NCT04308317 (phase 4)	NCT04308317: 60 participants, randomized open-label parallel assignment, single center -- May 1, 2021							
thalidomide	anti-fibrotic, cytokine storm (immunomodulation, anti-inflammatory)				NCT04273529 (phase 2), NCT04273581 (phase 2)	NCT04273529: 100 participants, randomized double-blind parallel assignment, multi-center -- June 30, 2020	NCT04273581: 40 participants, randomized quadruple-blind parallel assignment, multi-center -- May 30, 2020						

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Drug	Target or mechanism (if known)	Prelim results for SARS-CoV-2 trials or case reports (if applicable)	DOI of pertinent prior studies: SARS, MERS, or related RNA viruses	DOI of prelim clinical trials, case reports, or in vitro studies: SARS-CoV-2/COVID-19	clinicaltrials.gov ID(s) of other study identifier and phase (if available)	Study 1 size, structure, est. completion date	Study 2 size, structure, est. completion date	Study 3 size, structure, est. completion date	Study 4 size, structure, est. completion date	Study 5 size, structure, est. completion date	Study 6 size, structure, est. completion date	Study 7 size, structure, est. completion date	Study 8 size, structure, est. completion date
carrimycin	macrolide antibiotic (immunomodulation, anti-inflammatory)				NCT04286503 (phase 4)	NCT04286503: 520 participants, randomized open-label parallel assignment, single center -- February 28, 2021							
sarilumab	IL-6 receptor (immunomodulation, anti-inflammatory)				NCT04315298 (phase 2)	NCT04315298: 400 participants, randomized quadruple-blind parallel assignment, single center -- March 16, 2021							
tocilizumab	IL-6 receptor (immunomodulation, anti-inflammatory)	effective in reducing morbidity in small Chinese trial (Xu et al.)		10.12074/202003.00026	NCT04310228	NCT04310228: 150 participants, randomized open-label parallel assignment, single center -- May 2020							
fingolimod	sphingosine-1-phosphate receptor (immunomodulation, anti-inflammatory)				NCT04280588 (phase 2)	NCT04280588: 30 participants, non-randomized open-label parallel assignment, single center -- July 1, 2020							
eculizumab (Soliris)	complement cascade (immunomodulation, anti-inflammatory)				NCT04288713	NCT04288713: expanded access							
methylprednisolone	corticosteroids (immunomodulation, anti-inflammatory)				NCT04273321, NCT04244591 (phase 2)	NCT04273321: 400 participants, randomized open-label single group assignment, single center -- May 30, 2020	NCT04244591: 80 participants, randomized open-label parallel assignment, multi-center -- December 25, 2020						
CD24Fc	cytokine inhibition (immunomodulation, anti-inflammatory)				NCT04317040	NCT04317040: 230 participants, randomized quadruple-blind parallel assignment, multi-center -- May 2022							
camrelizumab	PD-1 blocking antibody: anti-sepsis (immunomodulation, anti-inflammatory)				NCT04268537 (phase 2)	NCT04268537: 120 participants, randomized single-blind parallel assignment, single center -- October 31, 2020							
thymosin	anti-sepsis (immunomodulation, anti-inflammatory)				NCT04268537 (phase 2)	NCT04268537: 120 participants, randomized single-blind parallel assignment, single center -- October 31, 2020							
ascorbic acid	anti-sepsis (immunomodulation, anti-inflammatory)				NCT03680274 (phase 3), NCT04264533 (phase 2)	NCT03680274: 800 participants, randomized quadruple-blind parallel assignment, multi-center -- December 31, 2022	NCT04264533: 140 participants, randomized triple-blind parallel assignment, single center -- September 30, 2020						
mesenchymal stem cells (MSCs) and MSC-derived exosomes	immunomodulation, anti-inflammatory, anti-bacterial activity (secondary infections)				NCT04276987 (phase 1), NCT04252118 (phase 1), NCT04288102 (phase 1, 2), NCT04273646, NCT04302519 (phase 1), NCT04269525 (phase 2)	NCT04276987: 30 participants, non-randomized open-label single group assignment, single center -- July 31, 2020	NCT04252118: 20 participants, non-randomized open-label parallel assignment, single center -- December 2021	NCT04288102: 90 participants, randomized quadruple-blind parallel assignment, multi-center -- December 31, 2021	NCT04273646: 48 participants, randomized open-label parallel assignment, single center -- February 15, 2022	NCT04302519: 24 participants, non-randomized open-label single group assignment, single center -- July 30, 2021	NCT04269525: 10 participants, non-randomized open-label single group assignment, single center -- September 30, 2020		
APN01	supportive (rhACE2 for ARDS)				In progress (collaboration of APEIRON and Angalpharma)								
TB9 (dantonic)	supportive (systemic oxygen delivery)				NCT04285190	NCT04285190: 120 participants, randomized open-label parallel assignment, single center -- September 15, 2020							
nitric oxide	supportive (systemic oxygen delivery, vasodilation)				NCT04306393 (phase 2), NCT04312243 (phase 2)	NCT04306393: 200 participants, randomized single-blind parallel assignment, multi-center -- March 21, 2022	NCT04312243: 460 participants, non-randomized open-label parallel assignment, single center -- March 20, 2022						
aviptadil (synthetic VIP)	supportive (vasodilation, bronchodilation)				NCT04311697 (phase 2)	NCT04311697: 120 participants, randomized quadruple-blind parallel assignment, multi-center -- September 2020							
hydroxychloroquine + azithromycin	viral uncoating (endosome acidification), ACE2 receptor	effective in reducing viral load in preliminary clinical trial (Gautret et al.)		10.1016/j.ijantimicag.2020.105949	2020-000890-25 (EU Clinical Trials No.)	2020-000890-25 (EU Clinical Trials No.): 42 participants, non-randomized open-label parallel assignment, single center -- completed							
danoprevir (Ganovo) + ritonavir +/- interferon	protease inhibitor for HCV (danoprevir), combination therapy		10.1021/jm400164c (for danoprevir)		NCT04291729 (phase 4)	NCT04291729: 11 participants, non-randomized open-label single group assignment, single center -- March 19, 2020							
lopinavir/ ritonavir + interferon beta-1b (+/- ribavirin)	combination therapy		10.1186/s13063-017-2427-0 (MIRACLE trial for MERS)		NCT04276688 (phase 2)	NCT04276688: 70 participants, randomized open-label parallel assignment, single center -- July 31, 2022							
lopinavir/ritonavir + ribavirin + interferon-alpha (interferon alfa)	combination therapy		10.3851/IMP3002, 10.1016/j.ijantimicag.2014.07.026 (pegylated interferon for MERS)	10.1097/CM9.0000000000000790	listing in progress (ref: Zeng et al., 2020)								
favipiravir + tocilizumab	combination therapy				NCT04310228	NCT04310228: 150 participants, randomized open-label parallel assignment, single center -- May 2020							
lopinavir/ritonavir + umifenovir	combination therapy	ineffective in small trial in China (Deng et al.)		10.1016/j.jinf.2020.03.002	NCT04252885	NCT04252885: 125 participants, randomized open-label parallel assignment, single center -- July 31, 2020							
varied multidrug combinations	combination therapy				NCT04303299 (phase 3)	NCT04303299: 80 participants, randomized open-label parallel assignment, multi-center -- November 30, 2020							
traditional chinese medicine (TCM), herbal extracts	combination therapy				NCT04291729 (phase 4), NCT04251871	NCT04291729: 11 participants, non-randomized open-label single group assignment, single center -- March 19, 2020	NCT04251871: 150 participants, randomized open-label parallel assignment, single center -- January 22, 2021						
TCM (Xiyanping) + lopinavir/ritonavir	combination therapy				NCT04295551	NCT04295551: 80 participants, randomized open-label parallel assignment, multi-center -- April 14, 2021							

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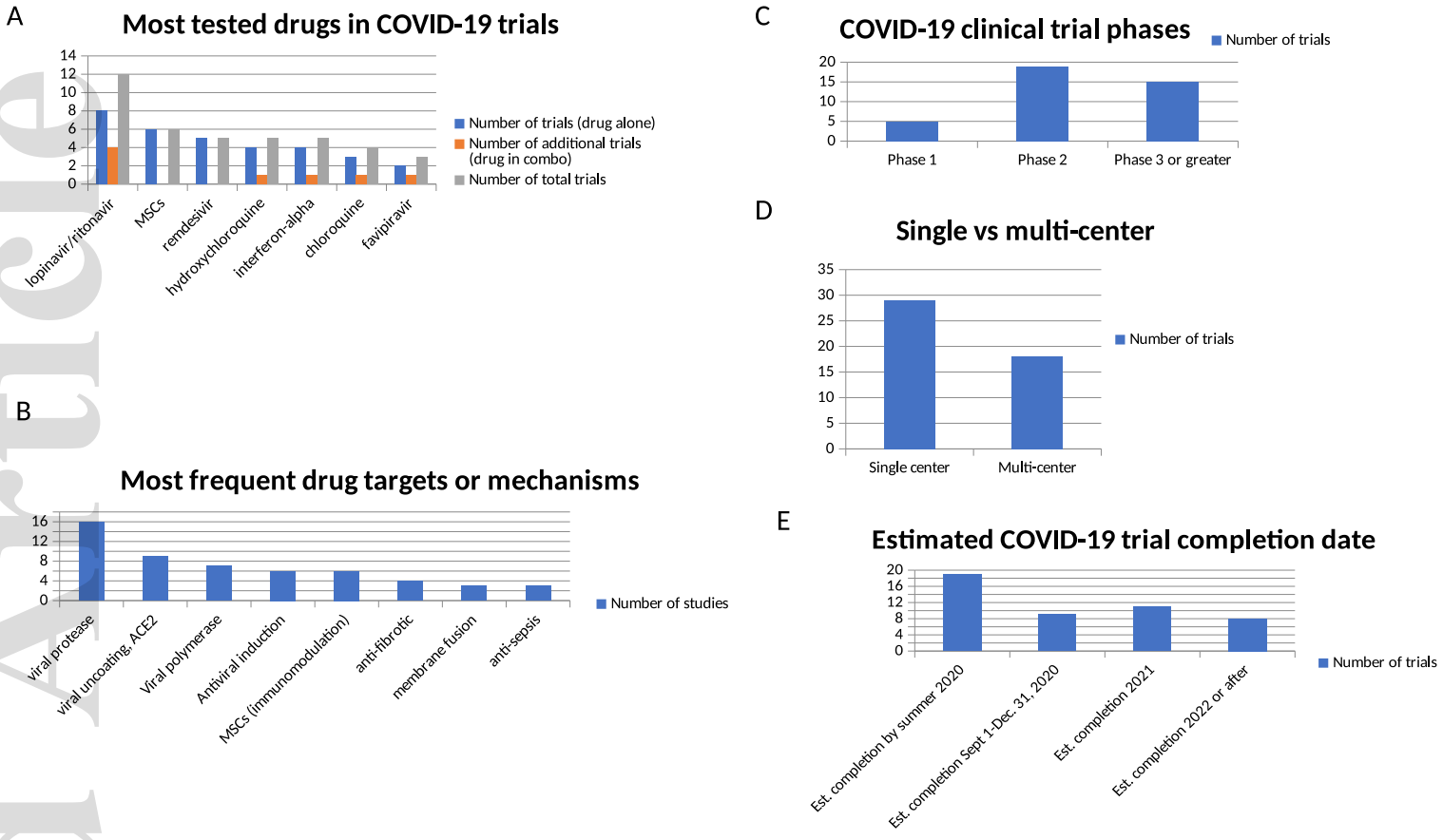

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Drug	Target in SARS-CoV or MERS-CoV (if known)	Reported EC50 (EC90) or IC50 vs. viral replication or target activity in vitro	Selectivity Index (SI, if known)	Testing for viral load reduction in cells?	# positive reports	# independent groups reporting positive	DOIs and primary authors of principal references
AVLQSGFR (docking octapeptide)	3CL protease (Mpro)	EC50: 0.027 µg/ml	>3700	Y	2	2	doi.org/10.1016/S0006-291X(03)01342-1 (Chou et al., 2003), doi.org/10.1016/j.peptides.2005.09.006 (Gan et al., 2006)
18c (Phe-Phe dipeptide inhibitor)	3CL protease (Mpro)	EC50: 0.18 µM	>1000	Y	1	1	10.1016/j.bmc.2005.05.065 (Shie et al., 2003)
hesperetin	3CL protease (Mpro)	IC50: 8.3 µM	>300	N	1	1	10.1016/j.antiviral.2005.07.002 (Lin et al.)
cinanserin	3CL protease (Mpro)	IC50: 5 µM, EC50: 19-34 µM		Y	1	1	10.1128/JVI.79.11.7095-7103.2005 (Chen et al., 2005)
bananin	helicase	EC50: <10 µM	>30	Y	3	3	10.1016/j.chembiol.2005.01.006 (Tanner et al., 2005), (PMID: 18708673, Huang et al., 2008), 10.1111/j.1742-4658.2010.07961.x (Wang et al., 2010)
calpain inhibitor VI (4-fluorophenylsulfonyl Val-Leu(CHO))	endosomal cathepsin-L-proteolysis	EC90: 3 µM	>100	Y	1	1	10.1177/095632020401500102 (Barnard et al., 2004)
nafamostat	TMPRSS2 (cellular serine protease), S protein priming	IC50: 0.1 µM		Y	1	1	10.1128/AAC.01043-16 (Yamamoto et al.)

Figure 3. Summary data on promising untested candidates for COVID-19 drug repurposing based on proven success in SARS and/or MERS in vitro studies, with focus on target selectivity, viral load reduction, and number of positive reports with independent confirmation.