Repurposing of therapeutics for SARS-CoV-2 an overview of current evidence.

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Contents

Abstract

Background

More than 131 million SARS-CoV-2 cases had been confirmed globally as of April 2021. There is a need for effective and accessible treatments for SARS-CoV-2. Repurposing drugs already approved for other indications may provide a rapid alternative to de-novo drug development.

Methods

We conducted searches for preclinical studies (in vivo, in vitro and in silico) and other publication types (e.g. systematic reviews, editorials, and opinion pieces) assessing drugs that could potentially be repurposed for SARS-CoV-2. Studies of drugs already in human trials or approved for use for SARS-CoV-2 were excluded. We produced an evidence map and narrative synthesis surrounding the most promising candidates for specific mechanisms of action, based on the best level of evidence.

Results

We identified 530 eligible studies, the majority of which were in silico studies (N = 242). Based on the best level of evidence and reporting by study authors: eight drugs were identified as having potential to inhibit SARS-CoV-2 entry into host cells; 11 were identified as potential inhibitors of spike protein attaching to host cells; one as possibly preventing viral entry into host cells via the ACE2 receptor; eight as potential inhibitors of viral replication; four as potentially being able to target SARS-CoV-2 RdRp; three as possible inhibitors of SARS-CoV-2 Mpro; and two as potential inhibitors of the SARS-CoV-2 cytopathic response and immune system effects.

Conclusions

Thirty-seven therapeutic agents with potentially promising effects on SARS-CoV-2 were identified. However, further well-designed preclinical and clinical research is needed to establish their efficacy.

Background

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) threatens public health at a global level, with more than 131 million confirmed cases globally (as of 06 April 2021[1]). Given the high infectivity of this virus, and the fact that one in five people infected are hospitalised with serious health consequences, it is vitally important to address how to improve treatment practices.[2] There are currently few approved medications for treating SARS-CoV-2,[3,4] however, a range of drug therapies are being trialled to test their efficacy and safety.[5] The treatments currently being evaluated range from those that target virus entry, replication or shedding (the life cycle of SARS-CoV-2), to those which reduce pulmonary effects, inflammation or cardiovascular effects.[5-10]

At least seven vaccines are now in use for immunisation against SARS-CoV-2 infection. Mass vaccination started in December 2020 and, as of 15 February 2021, 175.3 million vaccine doses had been administered globally. Nevertheless, the impact of COVID-19 vaccines on the pandemic is dependent upon the effectiveness of the vaccines; how quickly they are approved, manufactured, and delivered; the possible development of other variants; and how many people get vaccinated.[11] Furthermore, there is still a pressing need for more effective treatments for the long-term health impacts of SARS-CoV-2.

Due to the need for effective and accessible treatments for SARS-CoV-2, there have been specific efforts to repurpose or reposition approved and established drugs. This approach to identifying medications leads to a shorter drug development cycle than experimental drug development and only requires upscaling of established production processes rather than generation of de novo systems.[12] As generics of repurposed or repositioned drugs are often instantly available, the cost of drugs developed in this way tends to be lower.[12]

There is a burgeoning and disparate literature on repurposed or repositioned drug candidates for treating SARS-CoV-2 (from reduction in virus levels to recovery and rehabilitation). In October 2020, a mapping review was completed which provided an overview of evidence from hypothesis driving and preclinical studies that identified possible SARS-CoV-2 treatment candidates for clinical trial testing. In this review update, we incorporate additional findings from new studies published up until February 2020, that were not included in the earlier review.

Aim and objectives

Our aim is to give an up-to-date evidence overview of the drug repurposing research landscape in relation to SARS-CoV-2, and to identify the most plausible treatment candidates for trial as of February 2021.

To achieve this aim, our objectives are as follows.

1. To identify any hypothesis driving studies for SARS-CoV-2 (e.g. use of computational drug discovery for repositioning) that summarise potential repurposed drug candidates
2. To identify any drug library screening studies (including high throughput screening studies or virtual, in silico drug screens) that summarise potential repurposed drug candidates

3. To identify any in vitro and in vivo studies that summarise potential repurposed drug candidates for clinical trials
4. To produce a narrative synthesis and map of potential repurposed drug candidates for clinical trial, critically appraising the level of evidence indicating each as a potential candidate

Methods

Inclusion and Exclusion Criteria

Study design

We included the following studies: in vitro studies; in vivo in animal models including non-human primates; and drug library screens identifying repurposed therapeutic agents targeting SARS-CoV-2 (including high throughput screening studies or virtual, in silico drug screens), in addition to systematic and scoping reviews of these studies. We also included studies describing potential adverse effects of the identified candidate drugs, in addition to those describing potential therapeutic effects. Reviews, letters, editorials, and commentaries were included if they fulfilled the other inclusion criteria. At citation screening stage, we included studies where the title or abstract did not mention specific candidate drugs but instead only a candidate drug category or repurposing/repositioning for SARS-CoV-2. If the full text studies did not identify a specific drug, these studies were excluded.

We coded for but excluded any preclinical, in vitro, in silico and high-throughput studies where the candidate drug (or drugs) of interest are now being evaluated in humans (i.e. within randomised controlled trials, controlled clinical trials, cohort studies, case studies, cross-sectional studies and case-control studies), or which are now in human use for SARS-CoV-2. In addition, we coded for, but did not include non-English language studies. Coding for but not including these studies allows us to estimate the number of potentially relevant studies excluded from the review and allows for full assessment later if indicated.

Any studies on human participants were excluded. Otherwise, we did not restrict by animal models, cell line, cell culture or by the type of high-throughput screen or in silico/computational approaches in the studies reviewed. To be included a study must have focused on candidates for treating SARS-CoV-2 or its resultant physical morbidities.

Interventions

We included off-label drugs, vitamins and dietary supplements that have been approved by established regulatory authorities recognised by the International Coalition of Medicines Regulatory Authorities and could potentially be used in treating the SARS-CoV-2 infection or its resultant physical morbidities. Approval for indications other than SARS-CoV-2 was identified using the British National Formulary (BNF), US Food and Drug Administration (FDA), European Medicines Agency (EMA), Electronic Medicines Compendium (EMC) and GlobalData, using their respective websites. Both individual and combination therapies were included.

The following were excluded from the review:

- Studies identifying biological targets for treatment (e.g. a disease pathway that could be modulated) but no candidate drug
- Pre- and post-exposure prophylactic (preventative) interventions (e.g. SARS-CoV-2 vaccines and face masks)
- Complementary or alternative medicines
- Diagnostic tools (e.g. chest x-rays)
- Non-drug treatments (e.g. equipment and SOPs such as ventilator protocols, patient management techniques)
- Treatments involving gases (e.g. oxygen, hydrogen, nitrogen, mixed gas treatments)
- Any treatments already being used for treating SARS-CoV-2 patients in clinical trials or in practice (e.g. convalescent plasma therapy)

Main Outcome(s)

To be eligible for inclusion, the record had to identify at least one drug candidate as a potential treatment for SARS-CoV-2 infection or resultant physical morbidities. We excluded papers identifying candidate drug(s) for treating the mental health impacts of SARS-CoV-2.

Mechanisms of Action

Where reported within included records, we extracted data on the mechanism of action (MoA) or the World Health Organization (WHO) Anatomic Therapeutic Chemical classification (ATC) for each identified drug candidate. Extracted data was coded to our pre-defined categories (including 'miscellaneous' MoAs) with expert input if required (from either SA, FZ, AW or DO). Where the MoA was reported too vaguely for identification or not described at all candidate drugs were coded as 'not reported'.

We also consulted experts to validate the plausibility of each identified candidate drug for treating SARS-CoV-2 or SARS-CoV-2-induced physical morbidities.

Search Strategy

We performed the updated search on 12 February 2021 using three databases: the SARS-CoV-2-specific COAP Living Evidence on COVID-19 (includes pre-prints); Embase (1996 to 2021 week 05); and Scopus (2019 to February 2021). Full details of the search terms used for each database can be found in Appendix A. We present the flow of literature throughout the process and the results of the search using a PRISMA diagram.[13] Retrieved studies were downloaded into an Endnote X9 library and de-duplicated.

Data extraction (selection and coding)

De-duplicated titles and abstracts were uploaded to a Rayyan[14] screening library and screened independently by two reviewers (LT and EJ) in relation to the inclusion and exclusion criteria, with advice from a third reviewer where required (FP or AW).

Due to time constraints in the earlier review, only records that reported candidate drugs not in clinical development or in use for the treatment of SARS-CoV-2 in the title or abstract were included in the full

text screen. Any studies not reporting a relevant drug in the title or abstract were filed separately awaiting classification. A scoping exercise indicated that 60% of these filed records reported eligible drugs in their full text. Consequently, in the review update reported here, we included records regardless of whether they explicitly reported relevant drugs in their title or abstract, if they otherwise fit eligibility criteria. This included incorporating the studies that were previously filed as not reporting drug names in their title or abstract as relevant. Discrepancies in screening decisions were resolved through discussion between reviewers (LT and EJ) and adjudication if needed by a further reviewer (FP).

The full texts of potentially relevant records were screened using the same method (in duplicate by EJ and either LT, SA or FZ) and with adjudication if needed by a further reviewer (either FP or LT as appropriate). For the initial review, records were screened by reviewers with a background in evidence synthesis (LT and EJ) and an expert in drug development (AW) independently screened 10% of titles and abstracts to allow us to estimate the accuracy of screening decisions made by the review team. For the 2021 update, reviewers with a background in evidence synthesis (LT and EJ) and reviewers with a background in pharmacy (SA and FZ) undertook the full-text screening.

The full texts of included studies were uploaded to EPPI-Reviewer web software tool,[15] which was used for data extraction. We iteratively created a data extraction form within this software package, piloting it on a sample of included studies and refining as needed. For the original review, items on the data extraction form included the following: study citation; study design; candidate drug(s); in vitro or animal model (in vivo) tested; MoA or ATC classification; primary outcomes reported; descriptive list of known adverse events or toxicity; and conclusions (e.g. subset of drugs identified as being most promising amongst those listed). For the updated review, we did not extract information on outcomes reported other than candidate drugs, descriptive list of known adverse events or toxicity, pharmacodynamics or pharmacokinetics of the drugs. Data were extracted by one reviewer (out of LT, EJ, SA, FZ and RPWK) with 10% of studies extracted checked for accuracy and completeness by a second reviewer (out of SA and FZ). The opinion of a third reviewer (LT or EJ as appropriate) was sought to resolve discrepancies in relation to the extracted data.

Quality Appraisal

For the original review, we had initially planned to use the Office of Health Assessment and Translation (OHAT) Risk of Bias Tool for Human and Animal Studies [16] and a quality assessment checklist developed for computational studies by Silva et al [17] to evaluate the level of internal validity of included studies. These tools were piloted on a small sample (5%) of studies identified by the original search strategy (October 2020). A high level of items assessed by the tools were not reported in sufficient detail in each study assessed to make an informed judgement on whether they would introduce bias or not. The tools were thus unable to discriminate between high- and low-quality studies amongst those included in this review. Given this, planned quality assessment was not undertaken. However, we synthesised results preferentially from studies rated higher in the drug repositioning evidence level (DREL) with amendment (Table 1),[18] which grades each drug repositioning candidate according to the level of scientific evidence available.

Strategy for data synthesis

We present a narrative synthesis of results indicating the amount and quality of evidence available. We used a 'best available evidence' approach to synthesise the data from the available studies.[19] Using this method, for each MoA the highest level of available evidence is reported and, when data from the highest level of evidence were unavailable, the next level of evidence was referred to. The levels of evidence applied to this synthesis were an adapted version of the DREL criteria,[18] which grades drug repositioning candidates according to the level of scientific evidence available (Table 1). Non-experimental studies are lowest in the hierarchy, with increased position in the hierarchy for studies using models that are more applicable to humans. We also considered the reliability of the study design, with systematic reviews considered superior to individual studies. Scoping reviews which included some documentation of their methods, such as the search strategy used to locate primary evidence, were considered at the same level as full systematic reviews.

Table 1: Hierarchy of evidence used in this review (based on DREL criteria)[18]

Level of evidence	Type of study
1a	Systematic reviews of in vivo studies
1b	Primary in vivo studies
2a	Systematic reviews of in vitro studies
2b	Primary in vitro studies
3a	Systematic reviews of in silico studies
3b	Primary in silico studies
4	Non-research studies, including commentaries, opinion pieces, editorials and non-systematic reviews

No statistical analysis was planned. Rather, we produced a visual map indicating the volume and type of research indicating each drug as a most likely trial candidate and highlighting the MoA listed by study authors for each indicated candidate drug or, where no MoA was reported, as identified by an expert in drug development (AW or DO).

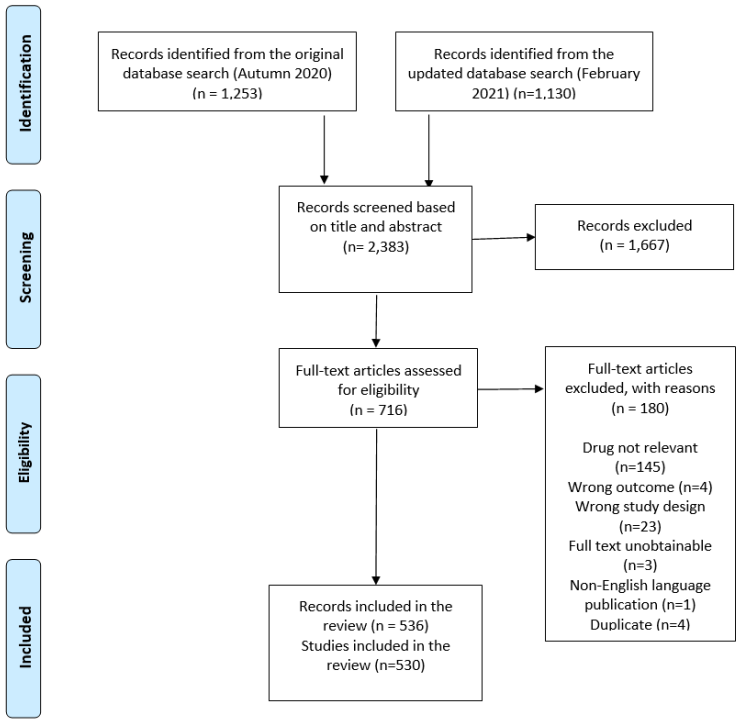
Results

After deduplication, 2383 records were identified from the searches. Following title and abstract screening, 716 records were judged to be relevant and were screened based on full text, where available. Of these, we excluded 180 records. Most records were excluded for breaching multiple inclusion criteria. The first noted exclusion reason for each record was as follows: 145 did not report a relevant drug; four investigated the wrong outcome; 23 did not use an eligible study design; full texts

were unobtainable for three records; one article was not published in English and four additional duplicates were identified.

The flow of literature is detailed in the PRISMA[13] diagram (Figure 1).

Figure 1: PRISMA[13] flow diagram depicting the flow of included and excluded studies through the systematic review process.



Description of included studies

The designs of the 530 included studies were varied and are summarised in Table 2. In brief, one study (0.19%) was purely in vivo, 52 were purely in vitro (10%) and 244 were purely in silico (46%). One hundred and eighty-nine papers (35.6%) were classified as being another design; details of these are documented in Table 2. Forty-four papers (8.1%) incorporated more than one design; details of design combinations are also presented in Table 2.

Table 2: Designs of papers included in this review	
Design	**Number**
Preclinical designs	
In vivo	1
In vitro	54
In silico	242
Other designs	
Research stakeholder insights	83
Non-systematic secondary research	96
Systematic secondary research	10
Combinations	
In vivo and in vitro	4
In vivo, in vitro and in silico	1
In vitro and in silico	26
In vitro and other	4
In silico and other	9

The primary cells, cell lines, tissues and virus strains used in the in vitro studies varied greatly and are summarised in Table 3. The most used cell-line across all studies was Vero E6. Nine studies used in vitro methods which either did not report or utilise primary cells, cell lines, cell culture, tissues or virus strains.[20-28] One study used A549 cells supplemented with a vector expressing ACE2, Calu-3 cells, and NHBE cells as well as two lung samples derived from COVID-19 patients compared against two healthy lung tissue biopsies.[29] Another study performed GRP78 gene expression studies in the blood of SARS-CoV-2 (+) versus SARS-CoV-2 (−) pneumonia patients.[30]

Table 3: Primary cells, cell lines, tissues and virus strains used in in vitro studies			
Originating organism	**Originating tissue**	**Primary cells, Cell lines, Virus strains**	**Study ID**
Human	Lung	A549	Abdulla 2020;[54] He 2020a;[37] Kim 2021;[38] Li 2020a;[61] Mousavi 2020;[57] Pickard 2021;[36] Scroggs 2020[62]
		A549-Ace2 cells	Meyer 2020;[85] Puhl 2020;[99] Rajasekharan 2020[86]
		Calu-1	Ramirez 2020[50]
		Calu-2	Ko 2020[43]
		Calu-3	Biering 2020;[88] Busnadiego 2020;[41] Cagno 2020;[89] Chen 2020b;[96] Choi 2021;[63] Holwerda 2020;[90] Stone 2021;[91] Swaim 2020;[92] Le 2020;[42] Pickard 2021;[36] Puhl 2020;[99] Wong 2021;[40]
		HCC515;	He 2020a[37]
		HLF(CCD-19Lu);	Pickard 2021[36]
		MRC5	Raymonda 2020;[55] Rietdijk 2021[56]
		HPAEpiC	Lin 2020[51]

	Bronchus	HBEC;	Hsu 2020[49]
		16HBE 140	Pickard 2021[36]
		NHBE	Mousavi 2020[57]
	Colon Epithelium	Caco-2	Choi 2021;[63] Pickard 2021;[36] Puhl 2020[99]; Schultz 2020;[39] Touret 2020[98]
		HCT-8	Yang 2020[46]
	Cervix	HeLa expressing human SARS-CoV-2 receptor	Bakowski 2020[47]
		HeLa-ACE2	Gawriljuk 2020[48]
	Liver	Huh7	Chen 2020b;[96] Pickard 2021;[36] Puhl 2020;[99] Ramirez 2020;[50] Rajasekharan 2020;[86]
		Huh7-hACE-2	Milani 2020[87]
		Huh7.5	Ramirez 2020[50]
		HepG2	Choi 2021[63]
	Kidney	Ab Podocytes; Hk-2; PODO/TERT256;	Pickard 2021[36]
	Embryonic Kidney	HEK-293	Al-Motawa 2020;[32] Mahdi 2020[31 32]
		HEK-293-T	Pickard 2021;[36] Rajasekharan 2020;[86] Zhang 2020c[33]
		ACE2 high expressing HEK-293-T	Le 2020;[42] Lu 2021;[34] Reznikov 2020[35]
	Spleen	CRL-8155;	Choi 2021[63]
	Bone	HTB-96;	Rajasekharan 2020[86]
	Skin	Hacat; HFF-1	Pickard 2021[36]
	Umbilical Vein	HUVECs	Ferraro 2020[52]
	Blood	THP-1	Wang 2020a[58]
		THP1	Pickard 2021[36]
		SW1353; TC28a;	Pickard 2021[36]
Primate	Kidney	Vero E6	Busnadiego 2020;[41] Ko 2020;[43] Pickard 2021;[36] Xiao 2020[53]
			Alnajjar 2020;[64] Biering 2020;[88] Bobrowski 2021;[65] Cagno 2020;[89] Chen 2020b;[96] Cho 2020;[66] Choi 2021;[63] Clarke 2020;[67] Fan 2020;[68] Ginez 2020;[69] Gorshkov 2020;[93] Guimond 2020;[70] Gupta 2021;[71] Holwerda 2020;[90] Huang 2020;[72] Hung 2020;[73] Konrat 2020;[94] Kuzikov 2020;[74] Li 2020a;[61] Meyer 2020;[85] Milani 2020;[87] Mostafa 2020;[75] Olaleye 2020;[76] Pathak 2020;[77] Puhl 2020;[99] Rajasekharan 2020;[86] Ramirez 2020;[50] Scroggs 2020;[62] Stone 2021;[91] Straus 2020;[78] Swaim 2020;[92] Touret 2020;[98] Verma 2020;[79] Vuong 2020;[80] Wan 2020;[97] Xing 2020;[81] Yuan 2020;[82] Zhang 2020b;[83] Zhou 2020a[84]

		Vero E6 selected for high ACE2 expression	Chen 2020a[95]
		Vero 76	Puhl 2020[99]
		LLC-MK2	Gorshkov 2020[93]
Mouse	Blood	RAW264.7	Wang 2020a[58]
	Brain	SIM-A9	Wang 2020a[58]
Hamster	Kidney	BHK-21; BSR-T7	Wan 2020[97]
E.coli	N/A	TOP10cells	Vatansever 2020[44]
		Lemo21 (DE3) cells	Eberle 2020[45]
SARS-CoV-2	Papain-like protease	PLpro mutant C111S	Gao 2021[59]
Feline	Type II coronaviruses	NTU156	Ke 2020[60]

Only one study was a purely in vivo design[100], which used male C57BL/6 J mice (1822 g) as its model organism.

The studies that combined an in vivo and in vitro approach similarly utilised different cell lines and animal models; these are summarised in Table 4.

Table 4: Primary cells, Cell lines, Virus strains and Animal models used within combined in vitro and in vivo studies

Study ID	Primary cells, Cell lines, Virus strains	Animal model
Cicka 2021[101]	Vero E6-TMPRSS2	SARS-CoV-2 mouse model and SARS-CoV-2 rhesus macaque model
Han 2020c[102]	Infected lung organoids	Humanized mice carrying hPSC-derived lung xenografts after four months maturation in vivo
Ho 2020[103]	A549-hACE2	Syrian Golden hamster model and 5-10 week old female B6.Cg-Tg(K18-ACE2)2Prlmn/J (K18-hACE2) mice
Weston 2020[104]	Vero E6; A549-hACE2	Mouse model (BALB/c mice)
Zhou 2020a[84] (also includes in silico design)	Mouse cells	Mouse model

A narrative synthesis was undertaken. The results are presented below grouped by the MoA, as reported by study authors or pharmacy experts, through which drugs are indicated as exerting their potential therapeutic effect. The following MoA groups were used: inhibition of viral entry; inhibition of viral entry via ACE2 receptors; inhibition of viral cell attachment to SARS-CoV-2 spike protein; inhibition of viral replication; inhibition of main viral protease (Mpro); inhibition of viral RNA-dependent RNA polymerase (RdRp); and inhibition of cytopathic and immune effects.

There were 29 papers where the MoA identified did not fall into any of the predefined categories.[23,32,40,82,105-129] In addition, 20 papers did not clearly report the MoA.[57,66,101,113,124,127,128,130-142] These studies are included in the evidence map as having 'Miscellaneous' or 'Not reported' MoAs, respectively. Of these papers, 25 partially reported on MoAs giving information for some drugs they listed as most effective and not for other listed drugs or, reporting MoAs that did not fall into predefined category.[23,32,57,108-111,113-116,118-123,125,127-130,138,140,142] For these 25 papers, we have only included the reported MoA or MoA that fell into one of the pre-defined categories and their drugs in the narrative synthesis.

Box 1. Candidate drugs identified by study authors in the top DREL, in relation to each MoA

Preventing SARS-CoV-2 viral entry into host cells
Pixatimod (PG545), haloperidol, panobinostat, miglustat, hydroxyzine dihydrochloride, azelastine hydrochloride, pimozide, apatinib

Inhibition of SARS-CoV-2 spike (S) protein from attaching to host cells
Nilotinib, ingenol, NKH477 (colforsin), osimertinib, trimipramine, nifedipine, ceftazidime, ambroxol hydrochloride (AMB), cathepsin L inhibitor, monensin, promethazine

Preventing viral entry into cells via the ACE2 receptor
Topotecan

Preventing viral replication
Clomipramine hydrochloride, fluspirilene, gemcitabine hydrochloride, promethazine hydrochloride, terconazole, thiethylperazine maleate, toremifene citrate, benzotropine mesylate

Targeting RNA-dependent RNA polymerase (RdRp), which regulates viral replication
Homoharringtonine, pralatrexate, rituximab, tilorone

Inhibition of SARS-CoV-2 main protease (Mpro)
Pentobarbital, vorinostat (WT-171), phenazopyridine

Inhibition of SARS-CoV-2 cytopathic response and immune system effects
Imipenem, lapatinib

Main Results

Figure 2 maps the amount of evidence for each study design related to each mechanism of action. The number of squares shown indicate the number of included studies.

Figure 2. An abbreviated map indicating volume (one square indicating one study) and types of study identifying repositioning drug candidates within each indicated mechanism of action

Inhibition of viral entry

The SARS-CoV-2 surface spike protein binds to the host cell angiotensin-converting enzyme 2 (hACE2) receptor once proteolytically activated, mediating a further chain of cellular events that mediate SARS-CoV-2 entry into the cell.[143] Different proteases are also important for cell entry, including cleavage of the SARS-CoV-2 spike protein to 'activate' cell-cell fusion and/or virus entry. Examples include: Cathepsin L; Elastase; Plasmin; TMPRSS2; and Trypsin. Fusion peptides (smaller than proteins) can also interact and facilitate viral fusion with the host cell membrane.[143]

Thirty papers assessed drugs for inhibition of viral entry.[35,42,44,61,70,86,97,138,144-163] Four studies had an in vitro design, [35,36,70,86] while three other studies had both an in vitro and in silico design.[42,44,97] Eleven studies had an in silico design.[61,146-148,150,155,157,159-161,164] Twelve had another design.[138,144,145,149,151-154,156,158,162,163]

The six studies with either an in vitro or combination of in vitro and in silico designs provided the best level of evidence for this MoA.[35,36,42,44,70,86,97] Guimond 2020 identified pixatimod (PG545),[70] Le 2020 identified haloperidol,[42] Pickard 2021 highlighted panobinostat,[36] Rajasekharan 2020 identified miglustat,[86] while Reznikov 2021 noted hydroxyzine dihydrochloride and azelastine hydrochloride to be effective.[35] Pimozide was the drug identified by Vatansever 2020 and, finally, Wan 2020 identified apatinib.[44,97]

Inhibition of surface spike protein

The SARS-CoV-2 surface spike (S) protein has two subunits: S2, which mediates the membrane fusion process; and S1, which utilises hACE2 as the receptor to infect human cells. Spike proteins assemble into trimers on the virion surface to form the distinctive "corona", or crown-like appearance. Spike proteins are an integral part of the virus "infection" protein, fusing with the human host cell through the S1 subunit or S2 subunit via the hACE 2 receptor.[143]

Forty-six studies identified possibly effective drugs that may inhibit the surface spike protein.[23,51,56,76,79,89,96,110,114,125,130,131,138,142,150,152,155,165-193] No in vivo studies were identified. Two studies employed purely in vitro methods,[56,76] while one used in vitro methods combined with another design.[89] In addition, four in vitro studies also employed in silico methods.[23,51,79,96] Twenty-nine studies used in silico methods.[110,114,131,150,155,165-175,177-179,181-184,186,187,189-193] Two studies used both in silico methods and another design.[130,142] Seven studies used another design.[125,138,152,176,180,185,188]

As no in vivo studies were identified for this MoA, the in vitro studies provided the best level of evidence.[23,51,56,76,79,89,96] In terms of the purely in vitro studies, Olaleye 2020 identified ambroxol hydrochloride (AMB),[76] Rietdijk 2021 identified cathepsin L inhibitor.[56] With regards to the studies that combined in vitro with in silico methods, Chen 2020b identified ingenol, NKH477 (colforsin), osimertinib and trimipramine.[96] Verma 2020 identified both monensin and promethazine as potential inhibitors of surface spike protein.[79] Hsieh 2020 identified nifedipine and Lin 2020 noted ceftazidime to be potentially most effective.[23,51] Cagno 2020, which combined in vitro and other methods, identified nilotinib as a potential inhibitor of surface spike protein.[89]

Angiotensin-converting enzyme (ACE) interaction

The main method of virus entry to the host cell, as has already been outlined, is by spike protein penetration, cell membrane fusion and injection of viral genetic material via the ACE2 receptor.[143]

Thirty-three studies investigated drugs targeting this mechanism of action.[20,103,119] Three of these studies used mixed designs: one used in vitro and in vivo methods;[103] another study employed in vitro and in silico methods;[20] and the third study involved combination of in silico and meta-analysis.[119] A further seven studies used a purely in vitro design[21,33,34,36,37,49,68] and eight studies used an in silico design only.[111,155,167,171,172,190,194,195] The remaining eleven studies used other methods comprising two computational analyses of transcriptomic datasets,[196,197] 5 opinion pieces[125,140,198-200] and eight narrative reviews.[109,128,138,201-205]

The in vitro and in vivo study by Ho (2020) represented the top level of evidence for identifying drugs targeting the interaction between SARS-CoV-2 and the ACE2 receptor.[103] This study reported that two doses of Topotecan, an FDA-approved Top1 inhibitor, suppressed infection-induced inflammation and reduced morbidity and mortality in mouse and hamster models.[103]

Inhibition of RdRp

RNA-dependent RNA polymerase (RdRp), which regulates viral replication, is proposed as a potential therapeutic target. This enzyme is involved in the replication and transcription of viral RNA, which becomes encased in viral proteins (as a capsule). Its inhibition arrests viral replication.[143]

Thirty-one studies assessed drugs targeting the RdRp enzyme. Three studies used in vitro methods only[27,53,83] and one study employed a mixed design, involving in vitro and in silico methods.[72] One study was a scoping review of in silico studies,[176] one study comprised molecular docking and a literature review[152] and seventeen used an in silico design only.[116,121,169,181,195,206-218] The remaining eight studies were non-systematic reviews.[188,205,219-224]

The top level of evidence for this mechanism of action was provided by the three studies that used in vitro methods only[27,53,83] and the study which used a mixed methods (in vitro and in silico) design.[72] The drugs identified by the authors of these studies as being most effective, ordered here alphabetically, were: homoharringtonine (investigated by Huang 2020);[72] pralatrexate (identified by Zhang 2020b);[83] rituximab (reported by Li 2021)[27] and tilorone (highlighted by Xiao 2021).[53]

Inhibition of SARS-CoV-2 main protease (Mpro)

The SARS-CoV-2 main protease (Mpro), also known as 3CLpro, is an enzyme belonging to a group of proteases that are involved in the formation of viral proteins. It is one of the coronavirus non-structural proteins (Nsp5) designated as a potential target for drug development.[143] Mpro cleaves the viral polyproteins, generating 12 non-structural proteins (Nsp4-Nsp16), including the RNA-dependent RNA polymerase (RdRp, Nsp12) and the helicase (Nsp13). Inhibition of Mpro would prevent the virus from replication and, therefore, constitute one of the potential anticoronavirus strategies.[143]

One hundred and twenty studies identified drugs in relation to this mechanism of action. Eight of these studies used in vitro methods only.[26,30,31,57,64,77,81,225] Five studies used a combination of in vitro and in silico methods[22,60,72,73,79] and one study used in vitro methods and presented a hypothesis.[80] Eighty-eight studies used in silico methods only;[97,114,116,129,131,133,168,174,177,178,181,186,194,197,214,215,226-296] three studies used in silico in addition to other methods, which included testing a hypothesis regarding the molecular structure of Sars-CoV-2,[297] meta-analysis of gene expression profile datasets in relation to different cell types,[119] and a Bayesian approach to a systematic review.[298] The remaining studies used other methods comprising a systematic review of in silico methods,[134] non-systematic reviews[44,120,152,162,188,205,299,300] and opinion pieces.[125,199,200,222,301]

The top level of evidence was from the studies that used meta-analyses of gene expression profile datasets in relation to different cell types.[119] The authors identified pentobarbital, vorinostat (WT-171) and phenazopyridine as potential inhibitors of SARS-CoV-2 Mpro.[119]

Inhibition of viral replication

There are six stages involved in viral replication, which include attachment, penetration, uncoating, replication, assembly and release. Specifically, the replication and assembly stages differ depending upon the type of viral genome (i.e. RNA or DNA). SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus. This RNA is used as a core template to produce both viral genomic RNA and mRNA. The latter of these instructs and directs the invaded host cell to produce and synthesise viral proteins and then to assemble the new virions. Firstly, once it has entered the host cell the viral capsid coat is removed by a series of enzymes, exposing the viral genomic material. Once exposed, the viral genomic material (RNA) enters various areas of the host cells (organelles, ribosomes, endoplasmic reticulum, etc.) and, via a process of protein synthesis (translation), produces amino acid sequences. Then, peptides and proteins are assembled to deliver both structural and non-structural proteins (enzymes) etc. New viral genomes are also produced by polymerase enzymes, which are then encased in newly produced viral capsid proteins and other protein components to form a new integral virus. This newly formed virus, with many more, is released from the host cell either by sudden rupture or extrusion over time.[143]

Forty-five studies identified drugs that may be effective in inhibiting viral replication.[23,32,35,42,47,67,78,86,104,113,115,122,123,128,138,157,162,171,197,200,204,207,220-222,224,247,283,293,302-316] One study employed both in vivo and in vitro methods.[104] Seven studies were in vitro,[32,35,36,47,67,78,86,115] while two were both in vitro and in silico.[23,42] Seventeen used in silico methods, [113,123,157,171,207,247,283,293,303-305,307-311,314] while another 17 had another design.[122,128,138,162,197,200,220-222,224,302,306,312,313,315-317]

As both an in vivo and in vitro study, Weston 2020 provided the best level of evidence for this mechanism of action.[104] The study authors identified clomipramine hydrochloride, fluspirilene, gemcitabine hydrochloride, promethazine hydrochloride, terconazole, thiethylperazine maleate, toremifene citrate and benzotropine mesylate as potentially having being the most efficacious in terms of inhibiting SARS-CoV-2 viral replication.[104]

Inhibiting cytopathic response and immune system effects

SARS-CoV-2 creates plaque-like cytopathic effects in human airway epithelial (HAE) cells. These effects include cell fusion, cell death, destruction of epithelium integrity and cilium (hair) shrinking. Infection with SARS-CoV-2 virus (and many other viruses) has been shown to initiate a cytokine storm in some individuals. A cytokine storm is a recognised physiological and immunological reaction in which the individual's innate immune system produces an exaggerated and uncontrolled release of pro-inflammatory molecules termed cytokines, which, in the case of SARS-CoV-2, has led to organ damage. The major cytokines included in the release during a storm are interleukins 1 and 6 (IL-1, IL-6), tumour necrosis factor alpha (TNF-α) and interferon. These cytokines serve to signal the influx of certain immune cells, (namely macrophages, neutrophils and T cells) which, in turn, lead to inflammation and cell damage.

Forty studies identified drugs targeting this mechanism of action. One study used in vivo methods only.[100] Four studies used a purely in vitro design[28,32,38,46] and in silico methods only were used by ten studies.[123,163,171,172,285,318-322] Mixed designs were used in in the following studies: Zhou 2020a, who used a combination of in vivo, in vitro and in silico methods;[84] Chen 2020a and Jia 2020, who both used in vitro and in silico methods.[25,95] The remaining studies were of the following designs: opinion piece,[118,144,158,199,200,323-331] non-systematic review,[108,128,162,219,332,333] letter to the editor,[334] and Commentary.[335]

The top level of evidence was from the two studies that incorporated an in vivo design. The most effective drugs identified by the authors of these studies were imipenem (reported by Su 2020) and lapatinib (reported by Zhou 2020a).[84,100]

Discussion

Summary of results

This review synthesised pre-clinical evidence identifying potential drug candidates for treating SARS-CoV-2. The results could be useful in highlighting therapeutic candidates to be evaluated in human clinical trials. Study author conclusions from the top level of evidence, assessed using DREL criteria, in relation to each MoA, suggests that the following drug candidates may be considered as potential treatment candidates:

- **Prevention of viral entry into host cells:** pixatimod (PG545), haloperidol, panobinostat, miglustat, hydroxyzine dihydrochloride, azelastine hydrochloride, pimozide, apatinib
- **Inhibition of the SARS-CoV-2 spike (S) protein from attaching to host cells:** nilotinib, ingenol, NKH477 (colforsin), osimertinib, trimipramine, nifedipine, ceftazidime, ambroxol hydrochloride (AMB), cathepsin L inhibitor, monensin, promethazine
- **Inhibition of SARS-Co-V-2 main protease (Mpro):** Pentobarbital, vorinostat (WT-171), phenazopyridine
- **Prevention of viral entry into cells via the ACE2 receptor:** topetecan
- **Inhibition of viral replication:** clomipramine hydrochloride, fluspirilene, gemcitabine hydrochloride, promethazine hydrochloride, terconazole, thiethylperazine maleate, toremifene citrate and benzotropine mesylate
- **Inhibition of RdRp:** homoharringtonine, pralatrexate, rituximab, tilorone
- **Inhibition of the cytopathic effects of SARS-CoV-2:** imipenem, lapatinib

Much of the evidence for the above summary was generated from in silico studies. Two hundred and forty-two of the studies included in this review were solely in silico studies. As such, these candidate drugs likely need further pre-clinical assessment before assessment of their therapeutic activity within clinical trial. However, it is important to note that the effectiveness of many candidate drugs already assessed within clinical trials has not reflected the promise of the collated pre-clinical data. Within this review there were a greater proportion of studies identifying drugs that may inhibit SARS-CoV-2 main protease (Mpro). However, the best available evidence from in-vivo studies, identified drugs for preventing viral entry into cells via the ACE2 receptor; inhibition of viral replication, and inhibition of the cytopathic effects of SARS-CoV-2. To be effective anti-viral medications identified in this report would need administration days after infection before the inflammatory immune response causes tissue damage. For many anti-viral drugs this is impractical especially where medication cannot be administered orally.

The following identified points could also plausibly hinder the therapeutic value of candidate drugs identified: Poor bioavailability (the rate and extent to which a drug becomes available at its target site); Toxicity to humans at the dosages required for effective treatment of SARS-CoV-2; A wide therapeutic index (the extent to which the drug has greater therapeutic than toxic effects - potentially making chemotherapy drugs unsuitable for treating SARS-CoV-2 patients); risk of resistance (where the body may stop responding to the treatment) and drug production costs.

Given the above points for consideration some of the drugs identified in the report may be problematic for treating newly infected individuals and those with mild disease. For patients admitted to hospital with severe SARS-CoV-2, the anti-inflammatory drugs identified in this report may be appropriate; these could be administered via IV preparations and narrower thearapeutic index may be acceptable.

Strengths and limitations of this review

As far as we are aware, this is the first overview of the development landscape of repurposed medications for SARS-CoV-2.

Where possible, we endeavoured to conduct this review following best-practice systematic review principles. For example, we double-screened in a blinded manner at both title and abstract stage and at full-text stage to minimise selection bias, a step which is not adopted by up to 40% of rapid reviews.[336] However, due to the review's rapid nature, elements of best practice as would be utilised in a systematic review were omitted. We have been transparent about these and tried to indicate, when plausible, the impact this may have had on the findings. For the original review, it took nine weeks from the initial team meeting to sharing of the final report. The updated review begun in February 2021 also took nine weeks to complete.

The bibliographic component of our search strategy was not abbreviated. However, due to time constraints, we chose not to search for grey literature beyond pre-print repositories and we did not perform reference or citation checking. Omitting these components of a non-abbreviated systematic searching strategy may have narrowed the scope of our identified records and resulted in some potentially relevant studies being missed. However, it has been suggested that abbreviated searches are a viable option for conducting rapid syntheses, with the caveat that reviews reliant on such searches may have less certainty in their overall results and face a small risk of making an incorrect conclusion.[337] They indicate that abbreviated searches are more robust in reviews, such as ours, of pharmacological interventions and which include 10 or more studies.

The trajectory of the research surrounding SARS-CoV-2 is currently steep; running the updated search in February 2021, five months after the original September 2020 search date, produced a further 1130 papers to screen and 267 included papers. Given the topical nature of this research area, it is likely that further research has been published since completing this review update. It is therefore, important to be aware that if new in vivo studies have been published the best candidates presented according to DREL may be outdated compared to those reported in this report.

As double-blind screening during the original review was completed by reviewers and not topic experts, there is some possibility that eligible studies could have been excluded at title and abstract stage erroneously. For the initial version of this review, a member of the team with expertise in pharmacy and drug development (AW) assessed 10% of the 1,243 records screened at title and abstract stage during the original review, given the identified agreement between reviewers less than 7% of the excluded studies were likely to have been erroneously excluded. A small proportion of potentially eligible candidate drugs could have been missing from our original analyses due to these records being erroneously excluded. However, for the updated review we assessed the full text of and subsequently

included 120 papers from the original search that did not appear to present any eligible drugs in the title and abstract. In addition, two reviewers with a background in pharmacy (SA and FZ) joined the full-text screening for the updated review. This has helped ensure that we have captured as much of the literature and as many of the candidate drugs as possible, when taken together with the original results and studies identified by the updated search.

Data extraction was undertaken by a single reviewer, with a second reviewer checking a small sample of extracted data items for consistency. While this is not best practice followed in a full systematic review, double blind data extraction is a process often omitted from rapid reviews.[336] The Cochrane Rapid Review Methods group recommend single data extraction with verification as a pragmatic approach when conducting a review of this nature.[338]

In the original review, we attempted to extract information regarding the adverse event profile, pharmacodynamics and pharmacokinetics of drugs identified by each paper. However, data on these were sparse. Given this and the large amount of literature added to the updated review, we took a pragmatic decision not to extract these data for every new paper. However, one reviewer (EJ) extracted information regarding toxicity in relation to drugs from studies classified as representing the top level of evidence for each mechanism of action, where this information was reported (please see Appendix B). It was not possible to provide more detailed information regarding the levels of toxicity or the likely side-effects of the drugs in this review, since this would depend on the dosage when used in humans and this information was not reported in the preclinical studies included in this review. Consequently, the toxicity and acceptability of the potential candidate drugs identified in this review would need to be considered seperately. In addition, we did not actively seek or extract information regarding the effects of the candidate drugs on specific variants of SARS-CoV-2 (e.g. the Kent or South African variants). Included studies from the top level of evidence were screened for information regarding the effects of identified drugs on SARS-CoV-2, however, no relevant information was identified (please see appendix B). It is possible that that future publications will assess the effects of drugs on covid variants.

In our original protocol we specified that we would assess risk of bias using the tool developed by the Office of Health Assessment and Translation (OHAT) and the internal validity of in silico studies using a checklist developed to assess their methodological quality. We deviated from protocol by not implementing the OHAT tool or the checklist because we found they were not discriminating between studies. However, for rapid reviews, if the purpose is to scope available literature (akin to mapping preclinical research on SARS-CoV-2) rather than evaluate specific intervention effects, it is generally accepted that risk of bias assessment is not required. Although we did not assess each study for risk of bias, we did employ a modification of the DREL criteria to our analyses,[18] grading drug repositioning candidates according to the level of scientific evidence available. This ensured that our main findings were focused on the best level of evidence available.

Crucially, the results of this rapid review rely on the judgements made within studies by individual study authors. We used the study authors' conclusions to base our assessments of which studied candidate drugs were the most effective without harmonising, for example, the thresholds for binding or other pertinent parameters that authors were using to identify the most effective candidate drugs. This was a

pragmatic approach but does mean that the results should be interpreted with some caution and with the other 'less' effective candidate drugs indicated by study authors in mind.

Conclusion

This rapid review gives an overview of the current drug repositioning studies and level of evidence supporting individual drug candidates for the treatment of SARS-CoV-2 from hypothesis driving studies through to in vivo studies. We identified 35 therapeutic agents with potentially promising therapeutic influence on SARS-CoV-2. These drug candidates were identified from four studies involving in vivo components to their design, 20 studies involving in vitro components to their design, and one meta-analysis of in vitro studies. None of these therapeutics can be recommended for treatment without further well-designed preclinical and clinical research to establish their efficacy. We found no evidence for repurposed candidates to treat: pulmonary complications (dyspnoea, acute respiratory distress, lung injury, scarring, fibrosis); cardiovascular complications (e.g. oedema, hypertension, thrombus); other complications; or rehabilitation (fatigue, continual dyspnoea, cardiovascular abnormalities).

Appendix A: Search Strategy

Database: SARS-CoV-2-specific COAP Living Evidence on COVID-19 https://ispmbern.github.io/covid-19/living-review/index.html

Searched 12 February 2021

#1 (investigational) or (repurpose) or (repurposing) or (re-purpose) or (re-purposing) or (reposition) or (repositioning) or (re-position) or (re-positioning) or (reprofile) or (reprofiling) or (re-profile) or (re-profiling) or (off licence) or (off-licence) or (off license) or (off-license) or (unlicenced) or (unlicensed) or (off label) or (off-label)

Database: Embase 1996 to 2021 week 05, searched 12 February 2021

Searches

1 sars coronavirus/ or sars-related coronavirus/

2 severe acute respiratory syndrome/

3 (coronavir* or corona virus* or HCoV* or ncov* or 2019nCoV or 2019 novel coronavirus or 2019 novel cov or cov 2 or cov2 or covid or covid19 or covid 19 or sars cov* or sarscov* or Sars coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp.

4 or/1-3

5 Middle East respiratory syndrome/

6 (middle east respiratory syndrome or mers or mers cov or mers coronavirus).mp.

7 or/5-6

8 (repurpos* or re purpos* or reposition* or re position* or reprofil* or re-profil* or off licenc* or off licens* or unlicen* or off label).mp.

9 (201911* or 201912* or 2020* or 2021*).dc.

10 4 and 8 and 9

11 7 and 8 and 9

12 10 or 11

13 limit 8 to covid-19

14 12 or 13

Database: Scopus 2019 to February 2021, searched 12 February 2021

((TITLE-ABS-KEY (coronavirus OR "corona virus" OR hcov* OR ncov* OR 2019ncov OR "2019-ncov" OR "2019 novel coronavirus" OR "2019 novel cov" OR "2019 novel-cov" OR "cov 2" OR "cov-2" OR cov2 OR covid OR covid19 OR "covid 19" OR "covid-19")) OR (TITLE-ABS-KEY ("sars cov*" OR "sars-cov*" OR sarscov* OR "Sars coronavirus" OR "Severe Acute Respiratory Syndrome Coronavirus")) OR (TITLE-ABS-KEY ("middle east respiratory syndrome" OR mers OR "mers cov" OR "mers-cov" OR "mers coronavirus" OR "mers-coronavirus")))

AND

(TITLE-ABS-KEY (repurpos* OR "re purpos*" OR "re-purpos*" OR reposition* OR "re position*" OR "re-position*" OR reprofil* OR "re profil*" OR "re-profil*" OR "off licenc*" OR "off-licenc*" OR "off licens*" OR "off-licens*" OR unlicen* OR "off label" OR "off-label"))

AND

(LIMIT-TO (PUBYEAR, 2021) OR LIMIT-TO (PUBYEAR, 2020) OR LIMIT-TO (PUBYEAR, 2019))

Appendix B: Drug toxicity and potential against SARS-CoV-2 variants for the studies with the best level of evidence

Paper	Drug	Toxicity info	Variant info
Viral entry			
Guimond 2020	Pixatimod	"tolerable safety profile" in patients with advanced solid tumors "Based on these data, pixatimod has potent antiviral activity against SARS-CoV-2 at therapeutically relevant concentrations"	NR
Le 2020	Haloperidol	"In particular, three of our four consensus drug hits demonstrated antiviral efficacy, with haloperidol showing reproducible inhibition in Calu-3 cells [...] without cytotoxicity"	NR
Pickard 2021	Panobinostat	NR	NR
Rajasekharan 2020	Miglustat	"The activity of Miglustat is here demonstrated for SARS-CoV-2 at concentrations achievable in the plasma by current clinical regimens without cytotoxicity"	NR
Reznikov 2021	Hydroxyzine dihydrochloride	"The EC50 values for in vitro antiviral activity are above concentrations expected in plasma following recommended dosing for hydroxyzine"	NR
	Azelastine hydrochloride	"The azelastine concentrations used in the study effectively inhibit SARS-CoV-2 below prescribed nasal spray doses"	NR
Vatansever 2020	Pimozide	NR	NR
Wan 2020	Apatinib	NR	NR
Surface spike protein			
Cagno 2020	Nilotinib	"expected concentrations in human lung epithelia should be much higher than measured EC50 in vitro. In addition, it is worth noting that nilotinib has an established safety profile for human use at therapeutic doses and is relatively well tolerated"	NR
Chen 2020b	Ingenol	NR	NR
	NKH477 (colforsin)	NR	NR
	Osimertinib	"We found it to rescue the SARS-CoV-2 CPE to 60% efficacy, albeit with a narrow therapeutic window due to cytotoxicity"	NR
	Trimipramine	NR	NR

Hsieh 2020	Nifedipine	NR	NR
Lin 2020	Ceftazidime	"The inhibitory concentration (IC50) was 113.2 μM, which is far below the blood concentration (over 300 μM) of ceftazidime in patients when clinically treated with recommended dose. Notably, ceftazidime is a drug clinically used for the treatment of pneumonia with minimal side effects compared with other antiviral drugs."	NR
Olaleye 2020	Ambroxol hydrochloride (AMB)	"inhibited SARS-CoV-2 infection-induced cytopathic effect at micromolar concentrations" "excellent safety and pharmacologic profile"	NR
Rietdijk 2021	Cathepsin L inhibitor	NR	NR
Verma 2020	Monensin	NR	NR
	Promethazine	NR	NR
ACE interaction			
Ho 2020	Topotecan (TPT)	"Therapeutic treatment with two doses of Topotecan (TPT), a FDA-approved Top1 inhibitor, suppresses infection-induced inflammation in hamsters." Nb: this was 10mg/kg per dose "In clinical practice, the Top1 inhibitors TPT and Irinotecan have well-characterized pharmacokinetics and toxicity profiles […], albeit in patients without SARS-CoV-2 infection. Doses that are 5-fold lower than those used in the treatment of small-cell lung cancer (TPT)[…] and colorectal cancer (irinotecan)[…] are expected to cause little to no toxicity, and importantly no risk of neutropenia. This significant dose reduction, together with the wealth of clinical experience in the use of TPT and irinotecan should reassure us about potential concerns over cytotoxicity."	NR
RdRp			
Huang 2020	Homoharringtonine	"We experimentally confirmed that the predicted compounds significantly inhibited SARS-CoV-2 replication in Vero E6 cells at nanomolar, relatively non-toxic concentrations" NB: the half-maximal concentration for homoharringtonine was 165.7 nM	NR

Li 2021	Rituximab	NR	NR
Xiao 2021	Tilorone	The paper lists drugs that have a safety index of >600 – tilorone is not one of these drugs	NR
Zhang 2020b	Pralatrexate	"EC50 values of 0.008Mm"	NR
MPRO			
Loganathan 2020	Pentobarbital	"reported to have various adverse effects hepatotoxicity, laryngospasam, amenia, bradycardia and respiratory depression"	NR
	Vorinostat	NR	NR
	Penazopyridine	NR	NR
Viral replication			
Weston 2020	Clomipramine hydrochloride	Figures and graphs showing the cytotoxicity of the drugs are presented in the paper, but the level of toxicity is unclear	NR
	Fluspirilene		NR
	Gemcitabine hydrochloride		NR
	Promethazine hydrochloride		NR
	Terconazole		NR
	Thiethylperazine maleate		NR
	Toremifene citrate		NR
	Benzotropine mesylate		NR
Cytopathic effects			
Su 2020	Imipenem	"dose-dependently inhibited TNF-α release with the half-maximal inhibitory concentration (IC50) as […] 11 μM"	NR
Zhou 2020a	Lapatinib	Table 2 suggests potential effects of lapatinib at different doses (ranging from 10 mg to 1500 mg) and predicts their Cmax on the brain, heart, lungs, kidneys, intestines and liver "Further clinical data mining revealed that lapatinib has a favorable pharmacokinetic profile to ensure that the lapatinib concentrations in various tissues can reach the levels that are significantly higher than the IC50 value after orally taking a lower dose of lapatinib"	NR

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