Therapeutic options for the 2019 novel coronavirus (2019-nCoV)

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Therapeutic options in response to the 2019-nCoV outbreak are urgently needed. Here, we discuss the potential for repurposing existing antiviral agents to treat 2019-nCoV infection (now known as COVID-19), some of which are already moving into clinical trials.

The 2019 novel coronavirus (2019-nCoV; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) has spread rapidly since its recent identification in patients with severe pneumonia in Wuhan, China. As of 10 February 2020, 2019-nCoV has been reported in 25 countries across 4 continents and >40,000 cases have been confirmed, with an estimated mortality risk of ~2%.

Unfortunately, no drug or vaccine has yet been approved to treat human coronaviruses. Several options can be envisaged to control or prevent emerging infections of 2019-nCoV, including vaccines, monoclonal antibodies, oligonucleotide-based therapies, peptides, interferon therapies and small-molecule drugs. However, new interventions are likely to require months to years to develop. Given the urgency of the 2019-nCoV outbreak, we focus here on the potential to repurpose existing antiviral agents approved or in development for treating infections caused by HIV, hepatitis B virus (HBV), hepatitis C virus (HCV) and influenza[1], based on therapeutic experience with two other infections caused by human coronaviruses: severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).

Characteristics of 2019-nCoV

2019-nCoV is an enveloped, positive-sense, single-stranded RNA beta-coronavirus. Similar to SARS and MERS, the 2019-nCoV genome encodes non-structural proteins (such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase), structural proteins (such as spike glycoprotein) and accessory proteins (Online Fig. 1). The four non-structural proteins mentioned above are key enzymes in the viral life cycle, and the spike glycoprotein is indispensable for virus–cell receptor interactions during viral entry[2]. These five proteins were therefore recognized as attractive targets to develop antiviral agents against SARS and MERS[2].

Initial analyses of genomic sequences from 2019-nCoV indicate that the catalytic sites of the four 2019-nCoV enzymes that could represent antiviral targets are highly conserved, and share a high level of sequence similarity with the corresponding SARS and MERS enzymes[3]. Furthermore, protein structural analyses suggest that key drug-binding pockets in viral enzymes are probably conserved across 2019-nCoV, SARS and MERS[3]. It is, therefore, reasonable to consider repurposing existing MERS and SARS inhibitors for 2019-nCoV. Below, we discuss selected candidates with a focus on approved drugs or experimental agents that have been already tested in clinical trials for other diseases[4]. Supplementary Table 1 provides a longer list of anti-coronavirus agents, including preclinical compounds that could be considered for screening or starting points for optimizing antiviral agents against 2019-nCoV.

Potential repurposing candidates for 2019-nCoV

Virally targeted agents. Approved nucleoside analogues (favipiravir and ribavirin) and experimental nucleoside analogues (remdesivir and galidesivir) may have potential against 2019-nCoV. Nucleoside analogues in the form of adenine or guanine derivatives target the RNA-dependent RNA polymerase and block viral RNA synthesis in a broad spectrum of RNA viruses, including human coronaviruses[4]. Favipiravir (T-705), a guanine analogue approved for influenza treatment, can effectively inhibit the RNA-dependent RNA polymerase of RNA viruses such as influenza, Ebola, yellow fever, chikungunya, norovirus and enterovirus[4], and a recent study reported its activity against 2019-nCoV (EC_{50} = 61.88 μM in Vero E6 cells)[5]. Patients with 2019-nCoV are being recruited in randomized trials to evaluate the efficacy of favipiravir plus interferon-α (ChiCTR2000029600) and favipiravir plus baloxavir marboxil (an approved influenza inhibitor targeting the cap-dependent endonuclease) (ChiCTR2000029544). Ribavirin is a guanine derivative approved for treating HCV and respiratory syncytial virus (RSV) that has been evaluated in patients with SARS and MERS, but its side effects such as anaemia may be severe at high doses[2] and whether it offers sufficient potency against 2019-nCoV is uncertain. Remdesivir (GS-5734) is a phosphoramidate prodrug of an adenine derivative with a chemical structure similar to that of tenofovir alafenamide, an approved HIV reverse transcriptase inhibitor. Remdesivir has broad-spectrum activities against RNA viruses such as MERS and SARS in cell cultures and animal models, and has been tested in a clinical

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trial for Ebola. A recent study reported that remdesivir inhibited 2019-nCoV (EC_{50} = 0.77 μM in Vero E6 cells)[5], and a US patient with 2019-nCoV recovered after receiving intravenous remdesivir in January[6]. Two phase III trials were initiated in early February to evaluate intravenous remdesivir (200 mg on day 1 and 100 mg once daily for 9 days) in patients with 2019-nCoV (NCT04252664 and NCT04257656), with estimated completion dates in April 2020. Galidesivir (BCX4430), an adenosine analogue that was originally developed for HCV, is currently in early-stage clinical studies evaluating its safety in healthy subjects and its efficacy against yellow fever, and has shown antiviral activities in preclinical studies against many RNA viruses, including SARS and MERS[2].

Approved protease inhibitors including disulfiram, lopinavir and ritonavir have been reported to be active against SARS and MERS. Disulfiram, an approved drug to treat alcohol dependence, has been reported to inhibit the papain-like protease of MERS and SARS in cell cultures (Supplementary Table 1), but clinical evidence is lacking. Clinical trials (for example, ChiCTR2000029539) have been initiated to test HIV protease inhibitors such as lopinavir and ritonavir in patients infected with 2019-nCoV. Lopinavir and ritonavir were initially hypothesized to inhibit the 3-chymotrypsin-like protease of SARS and MERS, and appeared to be associated with improved clinical outcomes of patients with SARS in a non-randomized open-label trial[2]. However, it is debatable whether HIV protease inhibitors could effectively inhibit the 3-chymotrypsin-like and papain-like proteases of 2019-nCoV. HIV protease belongs to the aspartic protease family, whereas the two coronavirus proteases are from the cysteine protease family. Furthermore, HIV protease inhibitors were specifically optimized to fit the C2 symmetry in the catalytic site of the HIV protease dimer, but this C2-symmetric pocket is absent in coronavirus proteases. If HIV protease inhibitors alter host pathways to indirectly interfere with coronavirus infections, their potency remains a concern.

The spike glycoprotein is also a promising target. Griffithsin, a red-alga-derived lectin, binds to oligosaccharides on the surface of various viral glycoproteins, including HIV glycoprotein 120 and SARS-CoV spike glycoprotein[2]. Griffithsin has been tested in phase I studies as a gel or an enema for HIV prevention, but the potency and delivery systems of spike inhibitors should be re-evaluated for the treatment or prevention of 2019-nCoV.

Host-targeted agents. Pegylated interferon alfa-2a and -2b, approved for the treatment of HBV and HCV, could be used to stimulate innate antiviral responses in patients infected with 2019-nCoV, and trials involving interferons have been initiated, such as a trial testing the approved anti-HCV combination of a pegylated interferon plus ribavirin (ChiCTR2000029387). However, it is unclear whether a pegylated interferon and a nucleoside compound could act synergistically against 2019-nCoV. Owing to multiple adverse effects associated with subcutaneous interferon therapies, their evaluation should be closely monitored and dose reduction or discontinuation of therapy may be required.

Small-molecule agents approved for other human diseases may modulate the virus–host interactions of 2019-nCoV. An approved immune modulator, chloroquine, shows inhibitory effects against 2019-nCoV (EC_{50} = 1.13 μM in Vero E6 cells)[5] and is being evaluated in an open-label trial (ChiCTR2000029609). Nitazoxanide, approved for diarrhea treatment, could also inhibit 2019-nCoV (EC_{50} = 2.12 μM in Vero E6 cells)[5]. The antiviral efficacy of such agents needs to be assessed in clinical studies. It is also worth mentioning that although many attempts have been made to develop host-targeted small molecules against viral infections in the past 50 years, only maraviroc has gained approval by the FDA, for HIV treatment[1].

Outlook

The rapid identification of effective interventions against 2019-nCoV is a major challenge. Given the available knowledge on their safety profiles, and in some cases efficacy against closely related coronaviruses, repurposing existing antiviral agents is a potentially important near-term strategy to tackle 2019-nCoV. Phase III trials of remdesivir have been initiated, and many other trials are being established in China to test various treatment options such as umifenovir, oseltamivir and ASC09F (Supplementary Table 1). In addition, more than 50 existing MERS and/or SARS inhibitors, such as galidesivir, the protease inhibitors GC813 and compound 3k, the helicase inhibitor SSYA10-001 and the nucleoside analogue pyrazofurin (Supplementary Table 1) could be screened against 2019-nCoV by facilities that have appropriate biocontainment capability. However, the reported EC_{50} and IC_{50} values of existing MERS and/or SARS inhibitors are mostly in the micromolar range, and further optimization of their activities against 2019-nCoV is probably needed before agents would be ready for clinical evaluation.

With the ongoing efforts to prevent the spread of 2019-nCoV worldwide, we hope that the outbreak may subside in a few months, as with SARS and MERS. Nevertheless, the outbreak has emphasized the urgent need for renewed efforts to develop broad-spectrum antiviral agents to combat coronaviruses.

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Competing interests
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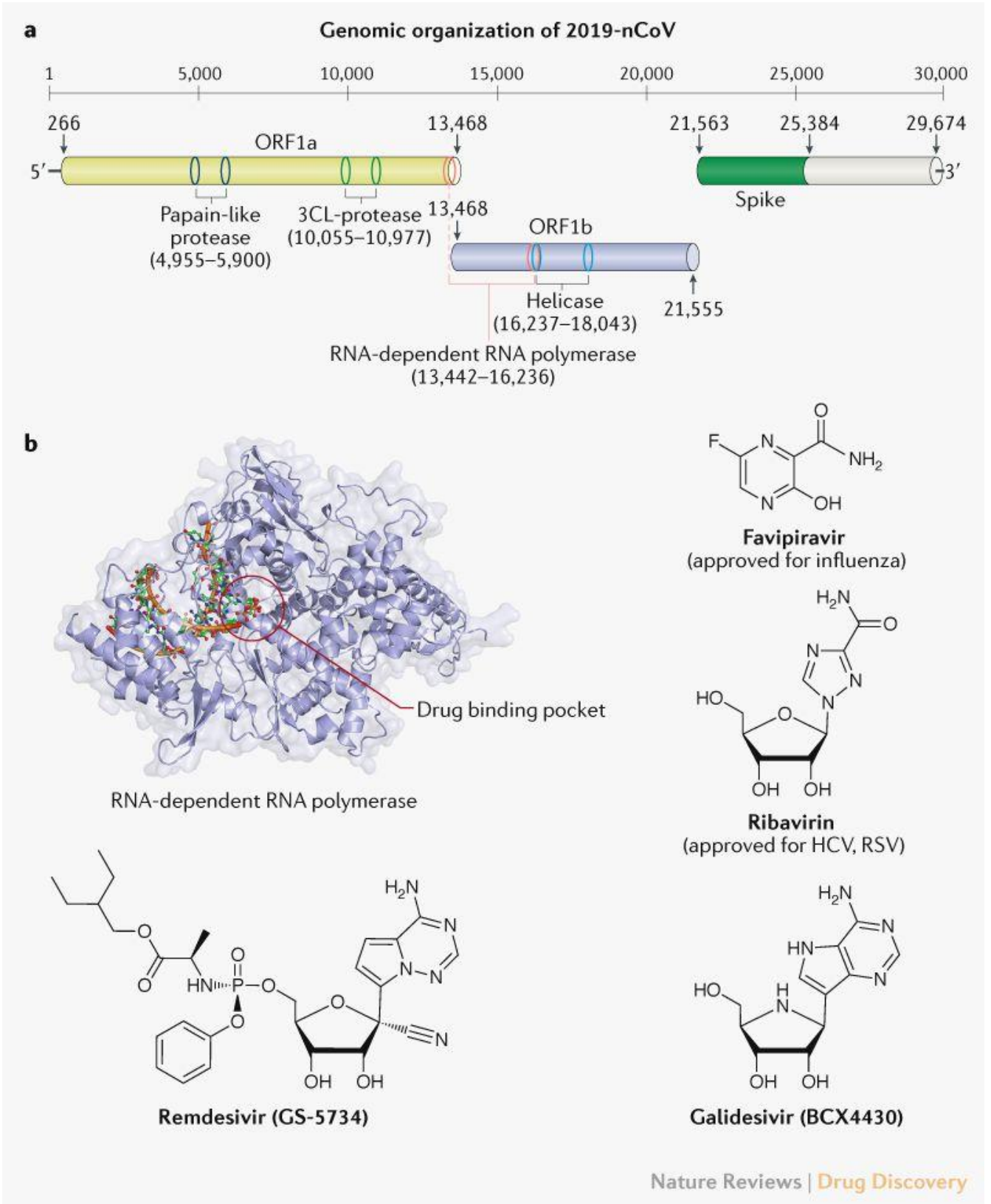

Fig. 1 | **Potential drug targets for beta-coronaviruses**. **a** | Genomic organization of 2019-nCoV (GenBank reference ID: MN908947.3), indicating the coding regions for proteins that are potential drug targets. **b** | A drug binding pocket is highlighted in the RNA-dependent RNA polymerase of SARS (PDB: 6NUR, 3H5Y), visualized using PyMOL V1.7 (https://pymol.org). Chemical structures of four potential inhibitors interfering with the RNA-dependent RNA polymerase of 2019-nCoV are also shown. 3CL, 3-chymotrypsin-like; HCV, hepatitis C virus; ORF, open reading frame; RSV, respiratory syncytial virus. Protein movies are available at www.virusface.com.

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SUPPLEMENTARY INFORMATION

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Supplementary Table 1 | Summary of antiviral compounds against human coronaviruses

Infectious diseases	Drug targets	Antiviral agents	Reported mechanism of action	Status	Ref.
Virus-based treatment strategies					
2019-nCoV; Influenza	RdRp	Favipiravir	Inhibits RdRp	• Approved for influenza in Japan • Randomized trial for 2019-nCoV (ChiCTR2000029544, ChiCTR2000029600)	[1,2]
2019-nCoV, MERS-CoV, SARS-CoV, RSV, HCV	RdRp	Ribavirin	Inhibits viral RNA synthesis and mRNA capping	• Approved for HCV and RSV • Randomized trial for 2019-nCoV in combination a pegylated interferon (ChiCTR2000029387). • Randomized trial for SARS (NCT00578825)	[2-8]
2019-nCoV	RdRp	Penciclovir	Inhibits RdRp	Approved for HSV	[2]
2019-nCoV, MERS-CoV, SARS-CoV	RdRp	Remdesivir (GS-5734)	Terminates the non-obligate chain	• Phase 3 for 2019-nCoV (NCT04252664, NCT04257656) • Phase 1 for Ebola (NCT03719586)	[1,2, 9-11]
Broad-spectrum (e.g. SARS-CoV, MERS-CoV, IAV)	RdRp	Galidesivir (BCX4430)	Inhibits viral RNA polymerase function by terminating non-obligate RNA chain	• Phase 1 for yellow fever (NCT03891420) • Phase 1 for Marburg virus (NCT03800173)	[12]
Broad-spectrum (e.g. CoV, ZIKV, CHIKV)	RdRp	6'-Fluorinated-aristeromycin analogues (Compound 2c)	Inhibits the activity of RdRp and host cell *S*-adenosyl-L-homocysteine hydrolase	Preclinical	[13]
HCoV-NL63, MERS-CoV	RdRp	Acyclovir fleximer analogues (Compound 2)	Doubly flexible nucleoside analogues inhibit RdRp	Preclinical	[14]
MERS-CoV, SARS-CoV	PLpro	Disulfiram	Inhibits PLpro	Approved for chronic alcohol dependence	[15]
MERS-CoV, SARS-CoV	PLpro	Thiopurine analogues (6-mercaptopurine and 6-thioguanine)	Inhibits PLpro	Preclinical	[16]
MERS-CoV	PLpro	Compound 6	Inhibits PLpro	Preclinical	[17]
2019-nCoV; MERS-CoV, SARS-CoV; HCoV-229E; HIV, HPV	3CLpro	Lopinavir	Inhibits 3CLpro	• Approved for HIV • Phase 3 for 2019-nCoV (NCT04252274, NCT04251871, NCT04255017, ChiCTR2000029539) • Phase 2/3 for MERS (NCT02845843)	[11, 18-21]
2019-nCoV, MERS-CoV	3CLpro	Ritonavir	Inhibits 3CLpro	• Approved for HIV • Phase 3 for 2019-nCoV (NCT04251871, NCT04255017, NCT04261270) • Phase 2/3 for MERS (NCT02845843)	[11,18, 20,21]
2019-nCoV	3CLpro	Darunavir and cobicistat	Inhibits 3CLpro	• Approved for HIV • Phase 3 for 2019-nCoV (NCT04252274)	-
2019-nCoV	3CLpro	ASC09F (HIV protease inhibitor)	Inhibits 3CLpro	Phase 3 for 2019-nCoV in combination with oseltamivir (NCT04261270)	-
MERS-CoV, SARS-CoV	3CLpro	GC376	Inhibits 3CLpro	Preclinical	[22]
MERS-CoV	3CLpro	GC813	Inhibits 3CLpro	Preclinical	[23]
SARS-CoV	3CLpro	Phenylisoserine derivatives (SK80)	Inhibits 3CLpro	Preclinical	[24]
MERS-CoV, SARS-CoV	3CLpro	Peptidomimetic inhibitors (Compound 6)	Inhibits 3CLpro	Preclinical	[25]
HCoV-229E	3CLpro	1,2,3-triazoles (Compound 14d)	Inhibits 3CLpro	Preclinical	[26]
SARS-CoV, MERS-CoV	3CLpro	Neuraminidase inhibitor analogues (compound 3k)	Inhibits 3CLpro	Preclinical	[27]
SARS-CoV	3CLpro	Unsymmetrical aromatic disulfides	-	Preclinical	[28]

SARS-CoV	3CLpro	Pyrithiobac derivatives (6-5)	Inhibits SARS-CoV 3CLpro	Preclinical	[29]
SARS-Cov, HCV	Helicase	Bananins and 5-hydroxychromone derivatives	Inhibits ATPase and helicase activities	Preclinical	[30]
SARS-CoV, MERS-CoV, MHV	Helicase	SSYA10-001 and ADKs	Inhibits helicase without affecting ATPase activity	Preclinical	[31,32]
MERS-CoV	Helicase	Triazole derivatives (Compound 16)	Inhibits ATPase and helicase activities	Preclinical	[33]
2019-nCoV, MERS-CoV	Spike glycoprotein	Nafamostat	Inhibits spike-mediated membrane fusion	Approved for anticoagulant therapy in Asian countries	[2,34]
SARS-CoV	Spike glycoprotein	Griffithsin	Griffithsin binds to the SARS-CoV spike glycoprotein, thus inhibiting viral entry	Phase 1 for the prevention of HIV transmission (NCT02875119 and NCT04032717)	[35,36]
Broad-spectrum (SARS-CoV, MERS-CoV, influenza)	Spike glycoprotein	Peptide (P9)	Inhibits spike protein-mediated cell-cell entry or fusion	Preclinical	[37]
MERS-CoV, IAV	Spike glycoprotein	α-Helical lipopeptides (e.g. LLS, FFS, IIS, IIK)	Inhibit spike protein-mediated cell-cell entry or fusion	Preclinical	[38]
MERS-CoV	S2 subunit of the spike glycoprotein	HR1P, HR1M, HR1L, HR2L, HR2P, HR2L	Inhibits MERS-CoV replication and spike protein-mediated cell-cell fusion	Preclinical	[39-41]
MERS-CoV	S2 subunit of the spike glycoprotein	HR2P-M1 HR2P-M2	Inhibits MERS-CoV spike protein-mediated cell-cell fusion and infection	Preclinical	[39,42, 43]
MERS-CoV	Spike glycoprotein	P21S10	Inhibits spike protein-mediated cell−cell fusion	Preclinical	[44]
MERS-CoV	Spike glycoprotein	Dihydrotanshinone E-64-C, and E-64-D	Blocks the endosomal entry pathway	Preclinical	[45,46]
HCoV (e.g. MERS, SARS)	Spike glycoprotein	OC43-HR2P (most promising EK1)	Inhibits pan-CoV fusion	Preclinical	[47]
MERS-CoV	Spike glycoprotein	MERS-5HB	Inhibits pseudo typed MERS-CoV entry and S protein-mediated syncytial formation	Preclinical	[48]
HCoV-229E	Spike glycoprotein	229E-HR1P 229E-HR2P	Inhibits spike protein-mediated cell-cell fusion	Preclinical	[49]
MERS-CoV	Nucleocapsid protein (possible)	Resveratrol	-	Clinical stages for several diseases (e.g. heart disease)	[50]
HCoV, influenza virus	Fusion inhibitors	1-thia-4-azaspiro [4.5] decan-3-one derivatives (Compound 8n)	-	Preclinical	[51]
MERS-CoV, SARS-CoV	DNA metabolism inhibitor	Gemcitabine hydrochloride	-	Approved as chemotherapy	[46]
MERS-CoV, SARS-CoV	-	Amodiaquine	-	Approved for malaria	[46]
MERS-CoV, SARS-CoV	-	Mefloquine	-	Approved for malaria	[46]
MERS-CoV, SARS-CoV HCoV-229E	-	Loperamide	-	Approved as an antidiarrheal agent	[19]
2019-nCoV; Influenza virus;	?	Arbidol (Umifenovir)	?	• Approved for influenza in Russia and China • Phase 4 for 2019-nCoV (NCT04260594, NCT04254874, NCT04255017)	-
2019-nCoV; Influenza virus;	?	Oseltamivir	Oseltamivir is an influenza neuraminidase inhibitor.	• Approved for influenza • Phase 4 for 2019-nCoV (NCT04255017), Phase 3 for 2019-nCoV (NCT04261270)	-
Host-based treatment strategies					
2019-nCoV; SARS-CoV; MERS-CoV	Interferon response	Recombinant interferons (interferon-✔, interferon-ঔ	Exogenous interferons	• Approved for metastatic renal cell carcinoma (IFN-α2a), melanoma (IFN-α2b), multiple sclerosis (IFN-β1a, 1b), chronic granulomatous disease (IFN-γ)	[3-8, 21]

		interferon-■		• Randomized trial for 2019-nCoV (NCT04251871, ChiCTR2000029638)	
2019-nCoV SARS-CoV MERS-CoV	Endosomal acidification	Chloroquine	A lysosomatropic base that appears to disrupt intracellular trafficking and viral fusion events	• Approved for malaria and certain amoeba infections • Open-label trial for 2019-nCoV (ChiCTR2000029609)	[2,19, 52,53]
Broad-spectrum (e.g. coronaviruses, 2019-nCoV)	Interferon response	Nitazoxanide	Induces the host innate immune response to produce interferons (✔ and ✔) by the host's fibroblasts and protein kinase R (PKR) activation	Approved for diarrhea treatment	[2,54]
SARS-CoV, MERS-CoV, HIV, HCV	Cyclophilins	Cyclosporine A	Cyclophilin inhibitor that could modulate the interaction of cyclophilins with SARS-CoV nsp1 and the calcineurin–NFAT pathway	Approved for immunosuppression during organ transplantation	[55-58]
SARS-CoV, MERS-CoV, HIV, HCV	Cyclophilins	Alisporivir	Modulates the interaction of cyclophilins with SARS-CoV nsp1 and the calcineurin–NFAT pathway	Phase 3 for HCV (e.g. NCT01860326)	[55-57,59]
MERS-CoV SARS-CoV	Abelson kinase	Imatinib mesylate	Blocks events of early viral entry and/or post-entry	Approved for treating cancers	[46,60]
MERS-CoV, SARS-CoV	Abelson kinase	Dasatinib	-	Approved for treating cancers	[46]
MERS-CoV SARS-CoV	Abelson kinase	Selumetinib	Inhibits the ERK/MAPK and PI3K/AKT/mTOR signaling pathways	Clinical trials for cancers (e.g. non-small cell lung cancer, thyroid cancer)	[61]
MERS-CoV, SARS-CoV	Abelson kinase	Trametinib	Inhibits the ERK/MAPK and PI3K/AKT/mTOR signaling pathways	Approved for treating cancers	[61]
MERS-CoV	Kinase signaling pathways	Rapamycin	Inhibits the ERK/MAPK and PI3K/AKT/mTOR pathways significantly inhibited MERS-CoV replication	Approved originally as an antifungal agent	[61]
MERS-CoV	Tyrosine kinases	Saracatinib	-	Approved for treating cancers	[62]
SARS-CoV MERS-CoV	Clathrin-mediated endocytosis	Chlorpromazine, Triflupromazine, Fluphenazine, Thiethylperazine, Promethazine	Antipsychotic that affects the assembly of clathrin-coated pits at the plasma membrane	The former three were approved as antipsychotic agents	[19,46]
Broad-spectrum (HCoV-229E)	Interferon response	Cyclophilin inhibitors (Compound 30)	Inhibiting the activity of PPIase	Preclinical	[63]
SARS-CoV MERS-CoV HCoV-229E	Endosomal protease	K11777, Camostat	Blocks endosomal protease-mediated cleavage and the endosomal entry pathway	Preclinical	[64]
SARS-CoV, MERS-CoV, HCoV-229E	Host cell membrane-bound viral replication complex	K22	Inhibits membrane-bound RNA synthesis and double membrane vesicle formation	Preclinical	[65,66]
Broad-spectrum (influenza virus, HCoV, Ebola, HIV, HCV)	Antibiotics	Teicoplanin derivatives	-	Widely used for treating gram-positive infections in Europe	[67]
Broad-spectrum (e.g. CoV, influenza virus, RSV)	-	Benzo-heterocyclic amine derivative (N30)	Depression of IMPDH activity	Preclinical	[68]
MERS-CoV, HBV, HCV	-	Mycophenolic acid	Inhibits IMPDH and guanine monophosphate synthesis	Approved immunosuppressant during organ transplantation	[16,69]
MERS-CoV, HCoV-229E, EBOV, Picornaviridae	eIF4A	Silvestrol	Inhibits the DEAD-box RNA helicase eIF4A to affect virus translation	Potential anticancer rocaglate derivative	[70]
Broad-spectrum (influenza A and B, RSV, HCoV)	DHODH	Pyrimidine (FA-613)	Inhibits DHODH	Preclinical	[71]
SARS-CoV, MERS-CoV, influenza	-	Convalescent plasma	Inhibits virus entry to the target cells	Phase 2 (NCT02190799 withdrawn)	[72-74]

Abbreviations

3CLpro: 3C-like protease, CHIKV: Chikungunya virus, DHODH: dihydroorotate dehydrogenase, HBV: hepatitis B virus, HCoV: human coronavirus, HCV: hepatitis C virus, IAV: influenza A virus, IMPDH: inosine-monophosphate dehydrogenase, IMPTH: inosine-5'-monophosphate dehydrogenase, JEV: Japanese encephalitis virus, MERS: Middle East respiratory syndrome, MERS-CoV: Middle East respiratory syndrome coronavirus, PEDV: porcine epidemic diarrhea virus, PLpro: papain-like protease, PPIase: peptidyl-prolyl isomerase, RBD: receptor-binding domain, RdRp: RNA-dependent RNA polymerase, RSV: respiratory syncytial virus, SARS-CoV: severe acute respiratory syndrome coronavirus, ZIKV: Zika virus.

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