Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

European Journal of Medicinal Chemistry 209 (2021) 112862

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

Primed for global coronavirus pandemic: Emerging research and clinical outcome

Shakir Ahamad [a], Scotty Branch [b], Shea Harrelson [b], Mohd Kamil Hussain [c, **], Mohammad Saquib [d, ***], Saeed Khan [b, *]

[a] Department of Chemistry, Aligarh Muslim University, Aligarh, 202002, UP, India
[b] Vikor Scientific Biotechnology, Department of Drug Research and Development, 22 WestEdge, Suite 806, Charleston, SC, 29403, USA
[c] Department of Chemistry, Govt. Raza P.G. College, Rampur, 244901, UP, India
[d] Department of Chemistry, University of Allahabad, Allahabad, 211002, UP, India

ARTICLE INFO

Article history:
Received 8 July 2020
Accepted 17 September 2020
Available online 19 September 2020

Keywords:
COVID-19
SARS-CoV-2
Vaccines
Small molecule drugs
Drug repurposing
Antiviral drugs
Monoclonal antibodies
Clinical trials

ABSTRACT

The global effort to combat and contain the coronavirus disease 2019 (COVID-19) caused by the recently discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is now proceeding on a war footing. The world was slow to react to the developing crisis, but once the contours of the impending calamity became evident, the different state and non-state actors have raced to put their act together. The COVID-19 pandemic has blatantly exposed the shortcomings of our healthcare system and the limitations of medical science, despite considerable advances in recent years. To effectively tackle the current pandemic, almost unprecedented in the modern age, there is an urgent need for a concerted, sustained, and coordinated effort towards the development of new diagnostics, therapeutic and vaccines, and the ramping up of the healthcare infrastructure, especially in the poorer underprivileged nations. Towards this end, researchers around the world are working tirelessly to develop new diagnostics, vaccines, and therapeutics. Efforts to develop a vaccine against COVID-19 are presently underway in several countries around the world, but a new vaccine is expected only by the end of the year-at the earliest. New drug development against COVID-19 and its approval may take even longer. Under such circumstances, drug repurposing has emerged as a realistic and effective strategy to counter the current menace, and several antiviral and antimalarial medicines are currently in different stages of clinical trials. Researchers are also experimenting with nutrients, vitamins, monoclonal antibodies, and convalescent plasma as immunity boosters against the SARS-CoV-2. This report presents a critical analysis of the global clinical trial landscape for COVID-19 with an emphasis on the therapeutic agents and vaccines currently being tested at pandemic speed.

Contents

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CoV, coronaviruses; MERS-CoV, middle east respiratory syndrome virus; ACE2, angiotensin-converting enzyme-2; RdRP, RNA-dependent RNA polymerase.

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: mkhcdri@gmail.com (M.K. Hussain), saquibem@gmail.com (M. Saquib), skhan@vikorscientific.com (S. Khan).

https://doi.org/10.1016/j.ejmech.2020.112862
0223-5234/

1. Introduction

Coronavirus disease 2019 (COVID-19) is a highly contagious malady caused by recently discovered *severe acute respiratory syndrome coronavirus 2 (*SARS-CoV-2). COVID-19 has rapidly transformed into a deadly pandemic, almost unprecedented in the annals of the modern age [1,2]. The world faced a similar crisis in 1918 when the Spanish flu pandemic broke out [3]. Recent reports suggest that COVID-19 originated in the city of Wuhan, in the Hubei province of China, on December 12, 2019, from where it quickly spread around the globe [4]. World Health Organization (WHO) declared it a public health emergency of international concern (PHEIC) on January 30, 2020, and a pandemic on March 11, 2020. As of July 8, 2020, 11,863,477 cases and 544,949 deaths had been reported in 188 countries [5].

Coronaviruses (CoV) belong to the subfamily Orthocoronavirinae of the family Coronaviridae, order Nidovirales and realm Riboviria. These zoonotic viruses are composed of a positive-sense single-stranded RNA genome and a nucleocapsid of helical symmetry enclosed in a lipid envelope. Coronaviridae family can be further divided into four genera: α-coronavirus (α-CoV), β-coronavirus (β-CoV), γ-coronavirus (γ-CoV), and δ-coronavirus (δ-CoV), based on the variation in protein sequences. Amongst these, β-CoV is the most dangerous and poses a significant threat to human health. However, the β-Cov virus is non-pathogenic in animals, and reported from bats, mice and domesticated animals like camels. These animals serve as a reservoir but are generally immune to coronavirus-induced diseases [6].

Studies focused on the source of β-Cov revealed inter-species transmission of the virus from animals to humans in the recent past, as in the case of Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 and the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 [7]. Scientists believe that the SARS-CoV2 virus was probably transmitted to humans from bats through an intermediary animal, in the Wuhan seafood market, in the same way as the other coronaviruses [8,9]. The infected patient manifested flu-like symptoms (infection in the lower respiratory system, fever, dry cough, and sore throat), but SARS-CoV-2 appears much more transmissible and dangerous than flu [10]. This highly contagious and virulent virus forced approximately one-third of the world's population under a complete lockdown. However, the situation is slowly improving in many countries across the globe [11].

These crown-like viruses contain 27–34 kilobase (kb) single-stranded positive-sense RNA (ss-RNA) genome surrounded by a membrane studded with glycoprotein spikes. These spikes interact with the angiotensin-converting enzyme-2 (ACE2) receptors to gain entry into the host cell. The virus is internalized by endocytosis, and viral RNA is released from the endosome by acidification or action of intracellular protease (Fig. 1) [12].

Subsequently, viral RNA translation generates the RNA-dependent RNA polymerase, a critical step in the formation of the replication-transcription complex to generate genomic RNA by replication, and sub-genomic RNA (sgRNA) by transcription [13]. Sub-genomic RNA is translated to the structural viral proteins and subsequently transported to the endoplasmic reticulum, where these proteins move along the secretory pathway into the endoplasmic reticulum-Golgi intermediate compartment, and combine with the nucleocapsids. After the final step of the virus assembly within the Golgi vesicles the new virus particles are released out of the cell by exocytosis, and the host cell dies by necrosis (Fig. 1) [14].

Currently, no FDA approved vaccine to prevent, or drug to treat, COVID-19 or diseases caused by other coronaviruses are available [15]. Academic and research institutions, pharmaceutical firms, and government and non-government organizations around the world are currently working in tandem towards the the speedy development of vaccines, drugs and other therapies for prevention and treatment of COVID-19. Fortunately, the fact that SARS-CoV-2 shares 82% nucleotide identity with SARS-CoV-1 (GenBank ID: NC_004718.3), and more than 90% nucleotide identity with MERS-CoV, has greatly assisted scientists in their efforts at designing vaccines and therapies for COVID-19 (Fig. 2) [16].

Currently, numerous clinical trials are underway for the development of vaccines and repurposing of existing therapeutics. Besides, many monoclonal antibodies and several novel small molecule inhibitors are also being tested for the treatment of COVID-19 infection [17,18]. Although a few reports summarising the development of vaccines and therapeutics against COVID-19 have been published in the last 2–3 months, these articles generally focus on specific topics such as the development of vaccines or repurposing of existing drugs [19–25]. Consequently, a comprehensive review which captures a broader panorama of the current efforts directed towards the development of various prophylactic and therapeutic agents against COVID-19 is urgently needed. In this review article, we exhaustively discuss the current status of various

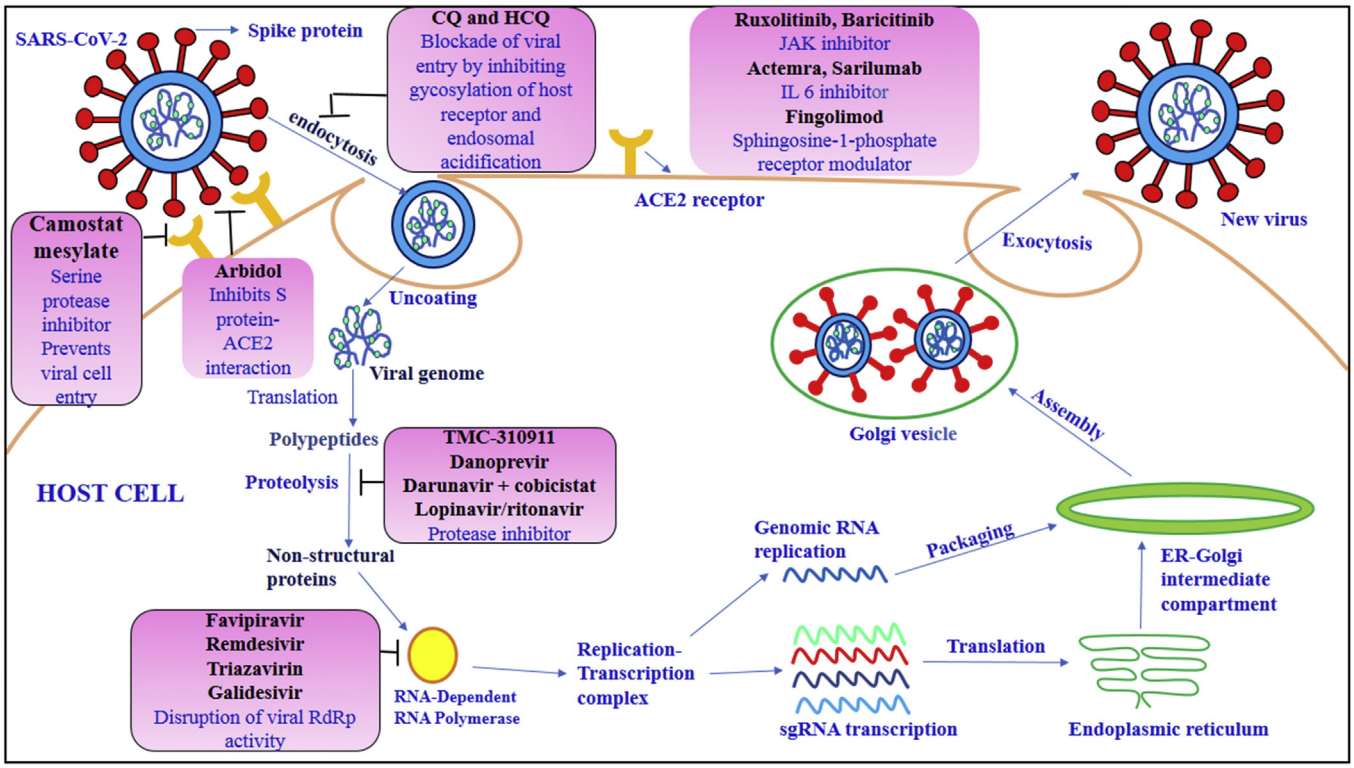

Fig. 1. Life cycle of SARS-CoV-2 and potential therapeutic targets for COVID-19.

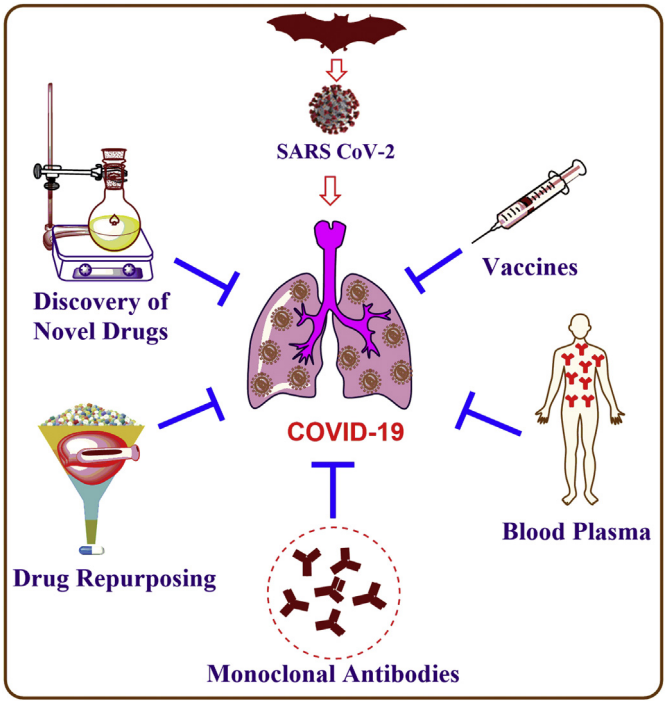

Fig. 2. Different preventive and curative strategies to combat COVID-19.

preventive and therapeutic agents in various stages of preclinical and clinical development against COVID-19, including vaccines, repurposed drugs, monoclonal antibodies, plasma therapy, and other miscellaneous therapies.

2. Clinical trials on vaccines

A vaccine is a preventive or preemptive approach against a disease that provides long-term protection. It is a biological preparation in which an attenuated form of the microbe, its toxins or one of its surface proteins provides active acquired immunity against specific infectious diseases. However, despite all-out global efforts, a vaccine against COVID-19 is not expected to be available before the end of 2020. Several clinical trials are currently ongoing in a number of countries around the world to develop a vaccine against SARS-CoV-2. Kaiser Permanente Washington Health Research Institute (KPWHRI) in Seattle, United States of America (USA), is presently carrying out a National Institute of Allergy and Infectious Diseases (NIAID, NIHH, supported Phase-1 clinical trial on an investigational vaccine, mRNA-1273, against SARS-CoV-2. NIAID scientists in collaboration with the biotechnology company, Moderna Inc. based in Cambridge, USA, designed and developed this vaccine to target the Spike protein of the SARS-CoV-2 [26]. Coalition for Epidemic Preparedness Innovations (CEPI) supported the manufacturing of this vaccine for clinical trial studies [27]. The interim data from the Phase-I trial of this vaccine has shown positive results for efficacy and safety. On May 06, 2020, the FDA, after reviewing the investigational new drug (IND) application permitted a Phase-II study. On May 12, 2020, Moderna Inc. received FDA fast track designation for this vaccine. Subsequently, on May 29, 2020, the dosing of the first set of participants in all age cohorts was initiated. Meanwhile, the Phase-III study protocol has also been approved, and the trial is expected to start in July 2020 (Table 1, Entry 1) [28–30].

A Hong Kong-based biotech firm, CanSino Biologics Inc., together with the Academy of Military Medical Sciences (AMMS), China, has developed a novel recombinant coronavirus vaccine (adenovirus type 5 vectors) which encodes for a full-length Spike

Table 1
Potentials vaccines undergoing clinical trials for prevention of COVID-19.

S.N.	Vaccine	Company/Developer	Current stage of clinical evaluation	Comment
1	mRNA-1273	Moderna Inc., USA	Phase-I, NCT04283461 (ClinicalTrials.gov)	Spike protein
2	Non-Replicating Viral Vector, Ad5-nCoV	CanSino Biologics Inc. and Beijing Institute of Biotechnology, China	Phase-I, NCT04313127 (ClinicalTrials.gov) ChiCTR2000030906 (ICTPR) PhaseII, NCT04341389 (ClinicalTrials.gov) ChiCTR2000031781(ICTPR)	Adenovirus type 5 vector (Ad5)
3	ChAdOx1	University of Oxford, UK	Phase-I, NCT04324606 Phase II, NCT04341389 (ClinicalTrials.gov)	Chimpanzee adenovirus vaccine vector
4	INO-4800	Inovio Pharmaceuticals, USA	Phase-I, NCT04336410 (ClinicalTrials.gov)	DNA plasmid vaccine electroporation device
5	BacilleCalmette-Guérin (BCG) vaccine	Murdoch Childrens Research Institute, Australia, Universidad de Antioquia, Colombia, and Texas A&M University, USA	Phase-III,NCT04328441 NCT04327206,NCT04362124 NCT04348370 (ClinicalTrials.gov)	Tuberculosis vaccine
6	Recombinant new coronavirus (2019-nCOV) vaccine (adenovirus vector)	Institute of Biotechnology, Academy of Military Medical Sciences, China	Phase-II, ChiCTR2000031781 (ICTPR)	Adenovirus vector
7	BNT162	BioNTech, Germany and Pfizer Inc., USA	Phase- I/II 2020-001038-36 (EU-CTR)	1) Nucleoside modified mRNA (modRNA) 2) Uridine containing mRNA (uRNA) 3) Self-amplifying mRNA (saRNA)
8	NVX-CoV2373	Novavax Inc., USA	Phase I/II NCT04368988	4) Engineered genetic sequence of SARS-CoV-2
9	CIGB 2020	Centre for Genetic Engineering and Biotechnology (CIGB), Havana, Cuba.	Phase- I/II RPCEC00000306	Activates the innate immune system
10	Recombinant chimeric COVID-19 epitope DC	Shenzhen Third People's Hospital, China	Phase- I/II ChiCTR2000030750 (ICTPR)	Epitope gene recombinant chimeric DC vaccine
11	BacTRL-Spike	Symvivo Corporation, Canada	Phase-I NCT04334980 (ClinicalTrials.gov)	Engineered *Bifidobacterium longum* which delivers plasmids containing synthetic DNA encoding spike protein from SARS-CoV-2
12	Inactivated novel coronavirus	Sinovac Biotech Ltd., China	Phase- I/II, ChiCTR2000031809 (ICTPR) NCT04352608 (ClinicalTrials.gov)	Inactivated virus

(S) protein of SARS-CoV-2. A Phase-I vaccine trial was conducted on the residents of Wuhan, the city where the virus originated to check whether this vaccine could stimulate antibody production and boost immunity against SARS-CoV-2. In preclinical studies, Ad5-nCoV showed an acceptable safety profile and generated a robust immune response in animal models. Currently, a randomized, double-blinded, and placebo-controlled Phase-II clinical study with Ad5-nCoV (registered on April 10, 2020) is ongoing. This trial will evaluate the immunogenicity and safety of Ad5-nCoV in 500 healthy adults over 18 years of age (Table 1, Entry 2) [31–33].

The University of Oxford's Jenner Institute, along with the Oxford vaccine group, has also developed a single-dose vaccine, ChAdOx1nCov-19, from a non-replicating adenovirus vaccine vector (ChAdOx1), that generates a robust immune response. Phase I-II clinical trial with this vaccine is ongoing while recruitment for the Phase II-III clinical trial is currently in progress (Table 1, Entry 3) [34].

On April 06, 2020, Inovio Pharmaceuticals, an American biotechnology company, announced an open-label Phase-I clinical trial with the INO-4800 vaccine in 40 healthy adults to evaluate its safety. INO-4800 is a DNA vaccine that translates into proteins within the cell and initiates an intense, targeted antibody and T-cell response by activating the immune system. The clinical trial are presently underway at the University of Pennsylvania, Philadelphia and the Centre for Pharmaceutical Research, Kansas City, and preliminary results are expected by the end of June 2020. The International Vaccine Institute (IVI), Seoul, South Korea, in collaboration with Seoul National University Hospital has also started a Phase I-II clinical trial on the INO-4800 vaccine in South Korea. The Phase–II–III efficacy trial for INO-4800 is slated to begin in the summer of 2020, upon regulatory approval (Table 1, Entry 4) [35,36]. In this endeavor, two Phase-III clinical trials with Bacillus Calmette-Guérin (BCG) vaccine to protect people against COVID-19 are also advancing in six countries (Table 1, Entry 5).

The Institute of Biotechnology, AMMS, China, registered a randomized, double-blind, placebo-controlled Phase-II clinical trial of recombinant novel coronavirus (2019-nCOV) vaccine (adenovirus vector) in healthy adults aged 18 and above on April 10, 2020, (Table 1, Entry 6). The same day BioNTech, a German biotechnology company, and the American pharmaceutical company Pfizer secured an approval from the German regulatory authority to conduct a Phase I-II clinical trial for BioNTech's BNT162 vaccine against COVID-19 infection. An initial vaccine trial would start in Germany and after regulatory approval clinical trials would also begin in USA and China. This project includes four COVID-19 vaccine candidates, two of which utilize a modified nucleoside mRNA (modRNA), one candidate utilizes self-amplifying mRNA (saRNA), and the fourth one is based on uridine containing mRNA (uRNA) (Table 1, Entry 7).

On May 25, 2020, Novavax Inc., Rockville, USA, enrolled the first participants in a Phase-I-II clinical trial for NVX-CoV2373, a COVID-19 vaccine candidate. NVX-CoV2373 is a stable, prefusion engineered protein made from the genomic sequence of SARS-CoV-2, and is anticipated to work by stimulating the production of neutralizing antibodies. Phase I-II clinical trial will be conducted in two parts. Phase-I trial would involve approximately 130 healthy participants at two sites in Australia in a randomized, observer-blinded, placebo-controlled study for the evaluation of the

vaccine immunogenicity and safety while the Phase-II trial would assess immunity, safety, and COVID-19 disease reduction at multiple locations across the globe (Table 1, Entry 8) [37]. Additional vaccine candidates currently undergoing clinical trials are CIGB 2020, recombinant chimeric COVID-19 epitope dendritic cell vaccine, and BacTRL-Spike (Table 1, Entries 9–11). On June 13, 2020, Sinovac Biotech Ltd. announced positive results from its ongoing Phase I-II clinical trial on the CoronaVac vaccine against COVID-19, conducted on 743 healthy participants (143 for Phase-I and 600 for Phase-II, aged 18 to 59) in China. No adverse effects were observed in these randomized, double-blind, placebo-controlled trials. Furthermore, the Phase-II study showed that CoronaVac prompted positive immune response indicated by the production of neutralizing antibodies after 14 days of vaccine administration, with a 90% seroconversion rate. Now, the company is planning to carry out its Phase III study in Brazil [38]. Preclinical studies carried out earlier showed that the inactivated vaccine candidate provides protection and is entirely safe for rhesus macaques [39].

3. Clinical trials on existing drugs (Drug repurposing)

Drug repurposing, also known as drug repositioning, drug retasking or drug reprofiling, is a developmental strategy for establishing new uses for existing drugs, including approved, investigational, or discontinued therapeutics. As compared to the new drug development process, drug repurposing is a highly efficient and relatively riskless process, as prior knowledge and literature regarding the existing drug such as pharmacokinetics, pharmacology, formulation, potential toxicity, and manufacturing data are already available. Reduced number of required steps for FDA approval further reduces the time and costs for the medicine to reach the market. Although this strategy has been known for quite some time now, its importance has only been recognized in the last decade or so. Currently, repurposing of drugs constitutes about one-third of the total drug approvals and around 25% of the annual revenue from the pharmaceutical industry [40]. Consequently, when the goal is the development of an effective drugagainst a disease in a limited time-frame, like in the case of COVID-19, drug repurposing stands out as a promising strategy. Notable efforts towards the repurposing of drugs for developing an effective therapeutic for COVID-19 are discussed below.

3.1. Small molecule drugs

The use of an effective vaccine to prevent COVID-19 infections could be a potentially fool-proof strategy for controlling this epidemic. However, vaccine development for clinical use is projected to take a minimum of 6–8 months, a significant drawback in this time of crisis. Similarly, the development of a new drug against COVID-19 would take even longer. Under such circumstances, drug repurposing has emerged as an attractive approach to combat COVID-19, primarily because of the relatively low investment costs, shorter development timelines, and faster approval rates [41–43]. Various existing drugs are now under investigation as potential treatment of COVID-19. Clinical trials on truvada [emtricitabine (**1**) and tenofovir (**2**)], azvudine, a reverse transcriptase inhibitor used for the treatment of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) (**3**), and ruxolitinib, a Janus kinase (JAK) inhibitor (**4**), are currently in progress (Table 2, Entries 1–3). Likewise the first affiliated hospital of Zhejiang University, China, is conducting a trial to evaluate and compare the safety and efficacy of a combination of TMC-310911(ASC09) (**5**) and ritonavir (**6**) against COVID-19 (Table 2, Entry 4) [44].

A combination of lopinavir (**7**) and ritonavir (**6**), developed by Abbott Laboratories, Chicago, USA, and sold under the brand name kaletra, was approved to treat HIV-AIDS. Kaletra inhibits chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro), viral protease enzymes responsible for the cleavage of viral protein into short peptides during the assembly of new virus particles within the host cells. A clinical study conducted with lopinavir-ritonavir on 199 hospitalized adults with severe COVID-19 (99 patients in the lopinavir-ritonavir group and 100 patient in the placebo group) in China-Japan Friendship Hospital, Beijing, China, showed no benefit with lopinavir-ritonavir treatment beyond standard care (ChiCTR2000029308) (Table 2, Entry 5) [45]. However, another open-label, randomized, multi-center, Phase-II trial, testing the efficacy and safety of a combination of lopinavir-ritonavir, ribavirin, and β-interferon in adult patients with mild to moderate COVID-19 symptoms revealed promising results. This University of Hong Kong sponsored triple combination therapy (lopinavir-ritonavir, ribavirin, and β-interferon) trial involved 127 COVID-19 patients (86 patients in the combination therapy group and 41 patients assigned to the control group). Study results showed that triple-drug combination was safe and more effective at reducing the duration of viral shedding as compared to lopinavir-ritonavir alone in patients with mild to moderate symptoms [46].

Umifenovir (arbidol®) (**8**), a broad-spectrum antiviral compound used to treat influenza infection in China and Russia, is currently under investigated for the treatment of COVID-19. Arbidol interferes with the binding of viral spike glycoprotein to the mammalian cell receptor ACE2, and thus prevents the virus entry into the host cells through endocytosis [47–49]. Guangzhou Eighth People's Hospital in Guangzhou, China, conducted a randomized controlled study on COVID-19 patients to evaluate the efficacy and safety of arbidol or lopinavir/ritonavir (LPV/r) in clinical settings. Of the 44 mild to moderately ill adult COVID-19 patients enrolled in the trial, 21 patients were randomly assigned to receive LPV/r, 16 to receive arbidol, and 7 to the control group with no antiviral medication. The results indicated little benefit for LPV/r or arbidol monotherapy. On the contrary, LPV/r treatment resulted in more adverse events. However, additional studies with larger sample size are required to reach more definitive conclusions (NCT04252885) (Table 2, Entry 6) [50].

Prezcobix is a two-drug combination of darunavir (**9**), an HIV-1 protease inhibitor, and cobicistat (**10**), a CYP3A inhibitor used for the treatment of HIV-1 infection. Prezcobix is currently in Phase-III clinical trial at the Shanghai Public Health Clinical Center in China, and in Spain (Table 2, Entry 7). However, *in vitro* testing of darunavir, a key component of prezcobix, against SARS-CoV-2, revealed no antiviral activity at clinically relevant concentrations [51]. Johnson & Johnson (J&J) in a statement have stated that they have no evidence to support the use of darunavir against SARS-CoV-2, and that the company is screening additional antiviral compounds, including darunavir, for potential activity against SARS-CoV-2 in collaboration with different organizations [52]. Clinical trials on the therapeutic agents, triazavirin (**11**), baricitinib (**12**), thialiomide (**13**), fingolimod (**14**), ganovo (danoprevir, **15**), galidesivir (BCX4430) (**16**), mefloquine (**17**), celecoxib (**18**), oseltamivir (**19**), pirfenidone (**20**), and camostat mesylate (foypan, **21**) are also underway, either as a single agent or as a combination of two or more drugs (Table 2, Entries 8–18). On April 16, 2020, Karyopharm Therapeutics Inc., Newton, USA, initiated a global, randomized clinical trial with selinexor (**22**) in severely ill COVID-19 patients. Selinexor, an FDA approved drug for relapsed refractory multiple myeloma, blocks the transport of several viral proteins from the nucleus to the cytoplasm of the host cells by inhibiting the cellular protein XPO1 (Table 2, Entry 19).

Another class of drugs, potentially effective against COVID-19, is glucocorticoid based medications. Glucocorticoids are known to decrease inflammation by suppressing the immune system, and

Table 2
Potential small molecule drugs undergoing clinical investigation for treatment of COVID-19.

S.N.	Drug	Institute/Country	Clinical Trials	Mechanism
1	Truvada (emtricitabine, **1** and tenofovir, **2**)	Plan Nacionalsobre el Sida (PNS) and Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, China	Phase-II NCT04334928 (ClinicalTrials.gov) ChiCTR2000029468 (ICTPR)	Reverse transcriptase inhibitor
2	Azvudine (**3**)	The First Affiliated Hospital of HeNan University of CM, China	Phase-0 ChiCTR2000030487 ChiCTR2000030424 ChiCTR2000030041 ChiCTR2000029853 (ICTPR)	Reverse transcriptase inhibitor
3	Ruxolitinib (**4**) (Jakafi, Jakavi)	Tongji Hospital, Hubei, China, University of Jena, Germany, Grupo Cooperativo de Hemopatías Malignas, Mexico, and Fundación de investigación HM, Spain	Phase-0, ChiCTR2000029580 (ICTPR) Phase II, NCT04338958 PhaseI/II, NCT04334044 PhaseII, NCT04348695 (In combination with Simvastatin) (ClinicalTrials.gov)	JAK inhibitor
4	TMC-310911 (ASC-09) (**5**)	Ascletis, First Affiliated Hospital of Zhejiang University, Tongji Hospital, China	Clinical Studies of Combinational Therapies NCT04261907, NCT04261270 (ClinicalTrials.gov)	Novel investigational protease inhibitor
5	Kaletra (lopinavir**6**/ ritonavir **7**) combinational therapy	AbbVie Inc., USA. Included in WHO SOLIDARITY Trial	>10 latest stages clinical studies and included in WHO NCT04252885, NCT04321174 NCT04255017, NCT04307693 (ClinicalTrials.gov) ChiCTR2000029308 (ICTPR)	3CL protease inhibitor
6	Umifenovir (Arbidol) (**8**)	Ruijin Hospital, China	Clinical studies in China ChiCTR2000029621 (ICTPR) NCT04260594 NCT04252885 (ClinicalTrials.gov)	ACE2 inhibitor
7	Prezista/Prezcobix (darunavir (**9**) + cobicistat (**10**))	Janssen Pharmaceuticals, Belgium, Fundacio Lluita Contra la SIDA, Spain, and Medical Institutions in China	Phase-3 Clinical Studies in Spain NCT04304053, 3 clinical Studies in China NCT04252274 (ClinicalTrials.gov) ChiCTR2000030259 ChiCTR2000029541 (ICTPR)	Protease inhibitor
8	Triazavirin (**11**)	Health commission of Heilongjiang province, China	Phase-3 Clinical Study in China ChiCTR2000030001 (ICTPR)	Inhibits RNA synthesis
9	Baricitinib (**12**)	Hospital of Prato And University of Colorado, Denver, USA	Phase-3 Clinical Study in Italy NCT04320277 NCT04340232 (ClinicalTrials.gov)	JAK/NAK inhibitor
10	Thaliomide (**13**)	First Affiliated Hospital of Wenzhou Medical University,China	Phase 2 Clinical Study in China NCT04273581, NCT04273529 (ClinicalTrials.gov)	Mechanism of action is not fully understood
11	Fingolimod (14)	First Affiliated Hospital of Fujian Medical University,China	Phase-II Clinical Study in China NCT04280588 (ClinicalTrials.gov)	Sphingosine 1-phosphate receptor modulator
12	Ganovo (Danoprevir) (**15**)	Ascletis Pharma Inc., and the Ninth Hospital of Nanchang, China	Phase-IV Clinical Study (In Combinational Therapies) NCT04291729 (ClinicalTrials.gov)	Protease inhibitor (Hepatitis C)
13	Galidesivir (BCX4430) (**16**)	BioCryst Pharmaceuticals, USA	Phase-I NCT03891420 (ClinicalTrials.gov)	Nucleoside RNA polymerase inhibitor
14	Mefloquine (**17**)	FISABIO, Spain	Phase-III 2020-001194-69 (EU-CTR)	Antimalarial drug
15	Celecoxib (**18**)	Guangzhou Eighth People's Hospital, China	Phase-0 ChiCTR2000031630	COX-2 inhibitors
16	Oseltamivir (Tamiflu) (**19**)	Tongji Hospital, China	Phase III. Alone and in combination withASC09F or Ritonavir NCT04261270 (ClinicalTrials.gov)	Neuraminidase inhibitor (influenza). Prevents new viral particles from being released form cell
17	Pirfenidone (**20**)	Huazhong University of Science and Technology and Guangzhou Medical University, China	Phase-III, NCT04282902 (ClinicalTrials.gov) ChiCTR2000030892 ChiCTR2000030333 (ICTPR)	Used for the treatment of idiopathic pulmonary fibrosis
18	Camostatmesylate (Foypan)^{TM} (**21**)	University of Aarhus , Denmark and Tabriz University of Medical Sciences, Iran	Phase 2 Clinical Study in Germany NCT04321096 (ClinicalTrials.gov) IRCT20200317046797N1 (ICTPR)	Spike protein
19	Selinexor (XPOVIO) (**22**)	Karyopharm Therapeutics Inc, USA	Phase-II, NCT04349098 (ClinicalTrials.gov)	XPO1 inhibitor
20	Ciclesonide (**23**)	Korea University Guro Hospital,Korea	Phase-II Alone and in combination with hydroxychloroquine NCT04330586 (ClinicalTrials.gov)	Glucocorticoid used to treat asthma and allergic rhinitis
21	Methylprednisolone (**24**)	Various Institutes in China	Phase-II/III NCT04273321, NCT04244591 (ClinicalTrials.gov) ChiCTR2000029656, ChiCTR2000029386 (ICTPR) In combination with Tacrolimus NCT04341038 (ClinicalTrials.gov)	Glucocorticoid used to treat asthma and allergic rhinitis
22	Favilavir (Favipiravir) (**25**)	Zhejiang Hisun Pharmaceutical Co., and various research institutes in China	Approved in China ChiCTR2000029996, ChiCTR2000030894, CHICTR2000029600, ChiCTR2000030254 (ICTPR)	RNA-dependent RNApolymerase (RdRP)
23	Sovodak (sofosbuvir (**26**)/daclatasvir **(27**))	Tehran University of Medical Sciences, Iran	Phase-III IRCT20200128046294N2 (ICTPR)	RNA polymerase inhibitor

Table 2 (*continued*)

S.N.	Drug	Institute/Country	Clinical Trials	Mechanism
24	Remdesivir (GS - 5734) (28)	Gilead Sciences,USA	>10 Clinical studies worldwide and included in WHO SOLIDARITY Trial NCT04323761, NCT04257656 NCT04315948 (ClinicalTrials.gov)	RNA polymerase
25	Chloroquine (**29**)	Research Institutes Worldwide	>10 Studies worldwide > 10 Clinical Studies in China andincluded in WHO SOLIDARITY Trial ChiCTR2000029609 (ICTPR) NCT04261517 (ClinicalTrials.gov)	Blocks viral entry by inhibiting glycosylation of host receptors, and endosomal acidification
26	Hydroxychloroquine (**30**)	Research Institutes Worldwide	>10 Clinical Studies worldwide and included in WHO SOLIDARITY Trial NCT04321278, NCT04261517 (ClinicalTrials.gov) ChiCTR2000029868 ChiCTR2000029559 (ICTPR) EUCTR2020-000890-25	Blocks viral entry by inhibiting glycosylation of host receptors, and endosomal acidification
27	Azithromycin (**31**)	Research Institutes Worldwide	>10 trials incombination n with other drugs, NCT04322396, NCT04321278 NCT04322123 (ClinicalTrials.gov)	Antibiotic
28	Harvoni (sofosbuvir (**26**)/ ledipasvir (**32**))	Tehran University of Medical Sciences, Iran	Phase-II/III IRCT20100228003449N29 (ICTPR)	RNA polymerase inhibitor
29	Umifenovir (Arbidol) (**8**)	Ruijin Hospital,China	Clinical studies in China ChiCTR2000029621 (ICTPR) NCT04260594 (ClinicalTrials.gov)	ACE2 inhibitor
30	Colchicine (**33**)	Montreal Heart Institute, Canada	Phase-III NCT04322682 (ClinicalTrials.gov)	Multiple proinflammatory mechanisms
31	Farxiga (dapagliflozin) (**34**)	AstraZeneca and Saint Luke's Mid America Heart Institute, USA	Phase-III, NCT04350593 (ClinicalTrials.gov)	Sodium-glucose transportpro-tein-(SGLT2) inhibitor
32	Tradipitant (ODYSSEY Trial) (35)	Vanda Pharmaceuticals, USA with the Feinstein Institutes for Medical Research, USA	Phase-III, NCT04326426 (ClinicalTrials.gov)	Neurokinin-1 receptor (NK-1R) antagonist
33	Calquence (acalabrutinib) (**36**)	AstraZeneca, UK	Phase-II, NCT04346199 (ClinicalTrials.gov)	Bruton's tyrosine kinase (BTK)
34	Tranilast (**37**)	The First Affiliated Hospital, USTC, China	Phase-IV ChiCTR2000030002 (ICTPR)	Suppression of the expression and/or action of the TGF-β pathway
35	Tetrandrine (**38**)	Henan Provincial People's Hospital, China	Phase-IV, NCT04308317 (ClinicalTrials.gov)	Calcium channel blocker
36	Suramin (**39**)	The First Affiliated Hospital of Zhejiang University, China	Phase-0, ChiCTR2000030029 (ICTPR)	Combines with trypanosomal glycolytic enzymes to inhibit energy metabolism
37	Sildenafil (**40**)	Tongji Hospital, China	Phase-III, NCT04304313 (ClinicalTrials.gov)	Phosphodiesterase-5 inhibitor, and vasodilator agent
38	polyinosinic-polycytidylicacid (41)	The First Affiliated of Wenzhou Medical University, China	Phase-IV ChiCTR2000029776	Toll-like receptor 3 (TLR3)
39	Nintedanib (**42**)	Tongji Hospital, China	Phase-II, NCT04338802 (ClinicalTrials.gov)	Used for the treatment of idiopathic pulmonary fibrosis
40	Linagliptin (**43**)	University of Miami, USA	Phase- IV, NCT04341935	DPP4 inhibitor
41	Leflunomide (**44**)	Renmin Hospital of Wuhan University, China	Phase-III, ChiCTR2000030058 (ICTPR)	Inhibits DHODH
42	Itraconazole (**45**)	Belgium - FPS Health-DGM	Phase-II 2020-001243-15 (EU-CTR)	P-glycoprotein inhibitor
43	Imatinib (Gleevec) (**46**)	Amsterdam UMC, Netherlands	Phase-II 2020-001236-10 (EU-CTR) NL8491 (NTR)	Tyrosine kinase inhibitor
44	Losartan (**47**)	Various Research Institutes in USA and Iran	NCT04340557, NCT04311177 NCT04335123, NCT04312009 (ClinicalTrials.gov) IRCT20180802040678N4 (ICTPR) In combination with Simvastatin and Aspirin NCT04343001 (ClinicalTrials.gov)	Angiotensin-II type 1 receptor blocker
45	Nitazoxanide (**48**)	Azidus Brazil, Romark Laboratories L.C., USA, and Tanta University, Egypt	Phase = NA, NCT04348409 Phase-IV, NCT04341493 Phase III, NCT04343248 Combination with IvermectinPhase-II NCT04360356 (ClinicalTrials.gov)	Used for the treatment of various helminthic, protozoal, and viral infections
46	TranexamicAcid (TXA) (**49**)	University of Alabama at Birmingham, USA	Phase II NCT04338126 NCT04338074 (ClinicalTrials.gov)	Reduces conversion of plasminogen to plasmin
47	Amiodarone (**50**)/ Verapamil (**51**)	Nicolaus Copernicus University, Poland	Phase-II/III NCT04351763 (ClinicalTrials.gov)	KCNH2 and CACNA2D2 inhibitor
48	CM4620-Injectable Emulsion (IE) (**52**)	CalciMedica, Inc., US	Phase-II, NCT04345614 (ClinicalTrials.gov)	CRAC channel inhibitor
49	Dalargin (**53**)	Burnasyan Federal Medical Biophysical Center, Russia	Phase-II, NCT04346693 (ClinicalTrials.gov)	Antioxidant
50	Deferoxamine (Desferal) (**54**)	Kermanshah University of Medical Sciences, Iran	Phase-I/II, NCT04333550 (ClinicalTrials.gov)	Chelating agent
51	Dexmedetomidine (**55**)	The Third Affiliated Hospital of Zunyi Medical University, China	Phase-0 ChiCTR2000030853 (ICTPR)	Selectively binds to presynaptic alpha-2 adrenoceptors
52		S.L.A· Pharma AG, Switzerland	Phase-III, NCT04335032 (ClinicalTrials.gov)	Omega-3 fatty acid

(*continued on next page*)

Table 2 (*continued*)

S.N.	Drug	Institute/Country	Clinical Trials	Mechanism
	Eicosapentaenoic Acid (**56**)			
53	Fluvoxamine (**57**)	Washington University School of Medicine, USA	Phase-II, NCT04342663 (ClinicalTrials.gov)	Selective serotonin reuptake inhibitor (SSRI)
54	Ibuprofen (58)	King's College London, UK	Phase-IV, NCT04334629 (ClinicalTrials.gov)	NSAID
55	Valsartan (**59**)	Radboud University, Netherlands	Phase-IV, NCT04335786 (ClinicalTrials.gov)	Angiotensin II inhibitor
56	Telmisartan (**60**)	Laboratorio Elea Phoenix S.A., Argentina	Phase-II, NCT04355936 (ClinicalTrials.gov)	Non-peptide angiotensin II receptor antagonist
57	Tofacitinib (**61**)	Università Politecnica Delle Marche (UNIVPM), Italy	Phase-II, NCT04332042 (ClinicalTrials.gov)	Janus kinase (JAK) inhibitor
58	Spironolactone (**62**)	Istanbul University-Cerrahpasa, Turkey	Phase-IV, NCT04345887 (ClinicalTrials.gov)	Aldosterone antagonist
59	Sirolimus (**63**)	University of Cincinnati, USA	Phase II, NCT04341675 (ClinicalTrials.gov)	Immuno- suppressive and antineoplastic agent
60	Methotrexate (**64**)	Azidus, Brazil	Phase-/II, NCT04352465 (ClinicalTrials.gov)	Inhibits the enzyme dihydrofolatereductase
61	Naproxen (**65**)	Assistance Publique - Hôpitaux de Paris (AP-HP), France	Phase-III, NCT04325633 (ClinicalTrials.gov)	NSAID
62	Piclidenoson (**66**)	Can-Fite Bio Pharma, Israel	Phase-II, NCT04333472 (ClinicalTrials.gov)	AntagonisT of adenoside A3 receptors
63	Pyridostigmine bromide (**67**)	Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico	Phase-II, NCT04343963 (ClinicalTrials.gov)	Acetylcholinesterase inhibitor
64	Captopril (ACEIs) (**68**)	Tanta University, Egypt	Phase-III, NCT04345406 (ClinicalTrials.gov)	Angiotensin-converting-enzyme inhibitors
65	BLD2660	Blade Therapeutics, USA	Phase-II, NCT04334460 (ClinicalTrials.gov)	Calpain inhibitor
66	Vazegepant (**69**)	Biohaven Pharmaceuticals, Inc. USA	Phase-II, NCT04346615 (ClinicalTrials.gov)	CGRP receptor antagonist
67	Vafidemstat (**70**)	Oryzon Genomics S. A. Spain	Phase-II 2020-001618-39(EU-CTR)	LSD1 inhibitor
68	Triiodothyronine (**71**)	Uni-pharma Kleon Tsetis Pharmaceutical Laboratories S.A., Greece	Phase-II, NCT04348513 (ClinicalTrials.gov)	Thyroid hormone
69	Sitagliptin (**72**)	Shahid Beheshti University of Medical Sciences, Iran	Phase-II/III IRCT20200420047147N1 (ICTPR)	Dipeptidyl peptidase-4 (DPP-4) inhibitor
70	Ribavirin (tribavirin or VIRAZOLE) (**73**)	Bausch Health Americas Inc., USA	Phase-I, NCT04356677 (ClinicalTrials.gov)	Inducies mutations in RNA-dependent replication in RNA viruses
71	Noscapine (**74**)	Qazvin University of Medical Sciences, Iran	Phase-II IRCT20160625028622N1 (ICTPR)	σ−receptor agonist
72	Nafamostat mesylate(**75**)	University Hospital Padova, Italy	Phase-II, NCT04352400 (ClinicalTrials.gov)	Serine protease inhibitor
73	Melatonin (**76**)	Instituto de Investigación Hospital Universitario La Paz (IdiPAZ), Bolivia, and Semnan University of Medical Sciences, Iran	Phase-II, NCT04353128 (ClinicalTrials.gov) In combination with Vitamin C and Zn IRCT20151228025732N52(ICTPR)	Hormone that regulates the sleep −wake cycle
74	Isotretinoin (77)	Kafrelsheikh University. Egypt	Phase-III, NCT04353180 (ClinicalTrials.gov)	Amplifies production of neutrophil gelatinase-associated lipocalin (NGAL) in the skin
75	Formoterol (**78**)	Masih Daneshvari Hospital, Iran	Phase-III NCT04326114 (ClinicalTrials.gov)	Long acting β_2 agonist used as a bronchodilator
76	Etoposide (**79**)	Boston Medical Center, USA	Phase-II NCT04356690 (ClinicalTrials.gov)	Prevents cytokine storm
77	Estradiol (**80**)	Stony Brook University, USA	Phase-II NCT04359329 (ClinicalTrials.gov)	Estrogen steroid hormone
78	Doxycycline (**81**)	Nantes University Hospital, France	Phase-III NCT04371952 (ClinicalTrials.gov)	Antibiotic
79	Crocetin (**82**)	Mashhad University of Medical Sciences, Iran	Phase-II IRCT20081019001369N3 (ICTPR)	NMDA receptor antagonist
80	Chlorpromazine (**83**) and Chlorpromazine injection	Centre Hospitalier St Anne and Cairo University, Egypt	Phase-III, NCT04366739 Phase-II, NCT04354805 (ClinicalTrials.gov)	D2 dopamine antagonist
81	Bromhexine (**84**)	Tabriz University of Medical Sciences, Iran	Phase-III IRCT20200317046797N4 (ICTPR)	Enhances mucus production in the respiratory tract
82	Bemcentinib (**85**)	University Hospital Southampton NHS Foundation Trust, UK	Phase-II 2020-001736-95 (EU-CTR)	Inhibitor of AXL kinase
83	Atorvastatin (**86**)	Mazandaran University of Medical Sceinces, Iran	Phase-II/III IRCT20190727044343N2 (ICTPR)	Used to prevent cardiovascular disease
84	Almitrine (**87**)	Assistance Publique− Hôpitaufx de Paris (AP-HP), France	Phase-III NCT04357457 (ClinicalTrials.gov)	Agonist of peripheral chemoreceptors present on the carotid bodies
85	Ramipril (**88**)	University of California, San Diego, USA	Phase-II, NCT04366050 (ClinicalTrials.gov)	Non-sulfhydryl ACE inhibitor
86	Progesterone (**89**)	Cedars-Sinai Medical Center, USA	Phase-I, NCT04365127 (ClinicalTrials.gov)	Progestogen sex hormone
87	Prazosin (**90**)	Johns Hopkins University, USA	Phase-II, NCT04365257 (ClinicalTrials.gov)	Competitive alpha-1 adrenergic receptor blocker
88	N-acetylcysteine (**91**)	Memorial Sloan Kettering Cancer Centre, USA	Phase-II, NCT04374461 (ClinicalTrials.gov)	Mucolytic
89	Levamisole (**92**) + Isoprinosine (**93**)	Ain Shams University,Egypt	Phase-III, NCT04360122 (ClinicalTrials.gov)	Modifies or stimulaties cell-mediated immune processes
90	Lenflunomide (**44**)	The Third Hospital of Wuhan City, China	Phase-III ChiCTR2000030058	Inhibits dihydroorotate dehydrogenase
91		Hospital Universitario de Getafe, Spain	Phase-IV, NCT04361643 (ClinicalTrials.gov)	

Table 2 (*continued*)

S.N.	Drug	Institute/Country	Clinical Trials	Mechanism
	Lenalidomide (Revlimid) (**94**)			Interacts with the ubiquitin E3 ligase cereblon
92	Ivermectin (**95**)	Qazvin University of Medical Sciences, Iran	Phase-III IRCT20200408046987N1(ICTPR)	Anti-parasitic
93	Ibrutinib (**96**)	AbbVie Inc., USA	Phase-II NCT04375397 (ClinicalTrials.gov)	Protein kinase inhibitor
94	Fluoxetine (**97**)	University of Toledo Health Science Campus, USA	Phase-IV, NCT04377308 (ClinicalTrials.gov)	Selective serotonin reuptake inhibitor
95	Duvelisib (**98**)	Washington University School of Medicine, USA	Phase-II, NCT04372602 (ClinicalTrials.gov)	Phosphoinositide 3-kinase inhibitor
96	Atazanavir (**99**)	Tehran University of Medical Sciences, Iran	Phase-II/III IRCT20171122037571N2(ICTPR)	Protease inhibitor
	IMU-838 (vidofludimus calcium) (**100**)	Immunic Therapeutics, USA	CALVID-1 trial, Phase-II, NCT04379271 . (ClinicalTrials.gov)	Inhibitor of dihydroorotate dehydrogenase (DHODH) enzyme
97	Fluvoxamine (**57**)	Washington University School of Medicine, USA	Phase-II, NCT04342663 (ClinicalTrials.gov)	Selective serotonin reuptake inhibitor (SSRI)
98	ABX464 (**101**)	Abivax SA, France	Phase-IIb/III	Upregulation of miR-124
99	Naltrexone (102) and Ketamine (103)	William Beaumont Hospitals, USA	Phase II NCT04365985 (ClinicalTrials.gov)	Anti-inflammatory, and blocks Toll-like receptor 4 (TLR4)
100	Indomethacin (104)/ Zithromax (Azithromycin)	Perseverance Research Center, LLC, Scottsdale, USA	Phase II NCT04344457 (ClinicalTrials.gov)	NSAID,i n combination with hydroxychloroquine
101	Clevudine (105)	Bukwang Pharmaceutical, South Korea	Phase II NCT04347915 (ClinicalTrials.gov)	Nucleoside
102	Atovaquone (106)	HonorHealth Research Institute, Scottsdale, USA	Phase II NCT04339426 (ClinicalTrials.gov)	Antipneumocystic lin combination with azithromycin
103	Amoxicillin (107)/ Clavulanate (108)	Nantes University Hospital, France	Phase III NCT04363060 (ClinicalTrials.gov)	Antibiotic, used in combination with azithromycin

therefore, can be good candidates for managing the symptoms of COVID-19 patients with severe pneumonia. A Phase-II trial, investigating whether the ciclesonide (**23**), a glucocorticoid, alone or in combination with hydroxychloroquine (HCQ) could eliminate SARS-CoV-2 from the respiratory tract of patients with mild COVID-19 symptoms (Table 2, Entry 20), is currently underway at Korea University Guro Hospital, Seoul, South Korea. Another glucocorticoid, methylprednisolone (**24**), is presently being investigated in ongoing clinical trials at various medical institutes in China (Table 2, Entry 21).

Zhejiang Hisun Pharmaceutical's favilavir (Favipiravir, **25**), an influenza medicine, is the first approved drug for SARS-CoV-2 treatment in China. It inhibits the RNA-dependent RNA polymerase (RdRP) of RNA viruses [53]. An open-label study at the Third Peoples Hospital of Shenzhen, China, compared the effect of favipiravir (FPV) plus interferon (IFN)-α aerosol inhalation (FPV arm, 35 patients) with that of lopinavir (LPV)/ritonavir (RTV) with interferon (IFN)-α aerosol inhalation (Control arm, 45 patients) on COVID-19 patients. Patients in the FPV arm reported shorter viral clearance time, notable improvement in chest imaging, and fewer adverse events as compared to the control arm. Furthermore, FPV was independently associated with faster viral clearance as confirmed by multivariable Cox regression. These preliminary clinical results indicate that FPV is a better therapeutic agent for COVID-19 treatment in terms of disease progression and viral clearance (ChiCTR2000029600) [54]. Another randomized clinical trial at Zhongnan Hospital of Wuhan University, China, compared the efficacy of favipiravir versus arbidol in 240 COVID-19 patients (120 patients each for favipiravir group and arbidol group). Study results showed that favipiravir is superior to arbidol as it reduced the incidence of fever and cough more effectively, and had a better 7-days clinical recovery rate (ChiCTR2000030254) (Table 2, Entry 22) [55]. On May 13, 2020, the Russian Direct Investment Fund (RDIF), Russia's sovereign wealth fund, and the ChemRar group reported positive results from an open-labeled, multi-center, randomized, comparative clinical trial of the drug favipiravir in COVID-19 patients. Sixty percent of the patients treated with favipiravir drug (n = 40) tested negative for coronavirus after five consecutive days of treatment [56]. The recovery rate with favipiravir was 2-times higher relative to those on standard therapy. Interestingly, these results concur with the findings from earlier studies on favipiravir, which reported a reduction in the disease duration from 11 days to 4–5 days and a faster recovery from COVID-19 disease [57].

Recently, another Phase-III clinical trial with sovodak (sofosbuvir 400 mg/daclatasvir 80 mg), and harvoni (sofosbuvir 400 mg/ledipasvir 90 mg) on COVID-19 patients began in different hospitals in Tehran, Iran (Registered on March 14, 2020). Sovodak and harvoni are Iranian antiviral drugs approved for the treatment of Hepatitis C. This study is not aimed as a cure for COVID-19 but rather testing the drugs as a supportive medicine to hasten the healing of COVID-19 patients (Table 2, Entry 23). There are several additional small molecules listed in Figs. 3–6, which are currently undergoing clinical validation (Table 2, Entries 24–103).

3.2. Important clinical trials

3.2.1. SOLIDARITY trial

To address the unprecedented medical emergency due to COVID-19, WHO recently announced the launch of an exclusive and expansive, 4-arm pragmatic clinical trial, called SOLIDARITY TRIAL. This promising multinational trial is currently investigating four promising therapeutics/therapeutic combinations: viz. remdesivir (Table 2 Entry 24), a combination of chloroquine/hydroxychloroquine (Table 2 Entries 25 and 26), lopinavir/ritonavir (Table 2 Entry 5), and lopinavir/ritonavir/interferon-beta (Fig. 7) [58]. Despite the failure of lopinavir/ritonavir in initial studies, WHO is very optimistic about the potential efficacy of this drug combination against COVID-19, and has included it in SOLIDARITY trials [59,60]. As of June 03, 2020, 83 clinical trials on this combination therapy are active across the world [61].

Reports suggest that antimalarial drugs, chloroquine (CQ) and hydroxychloroquine (HCQ) initially exhibited appreciable efficacy against COVID-19, possibly by interfering with ACE2 glycosylation

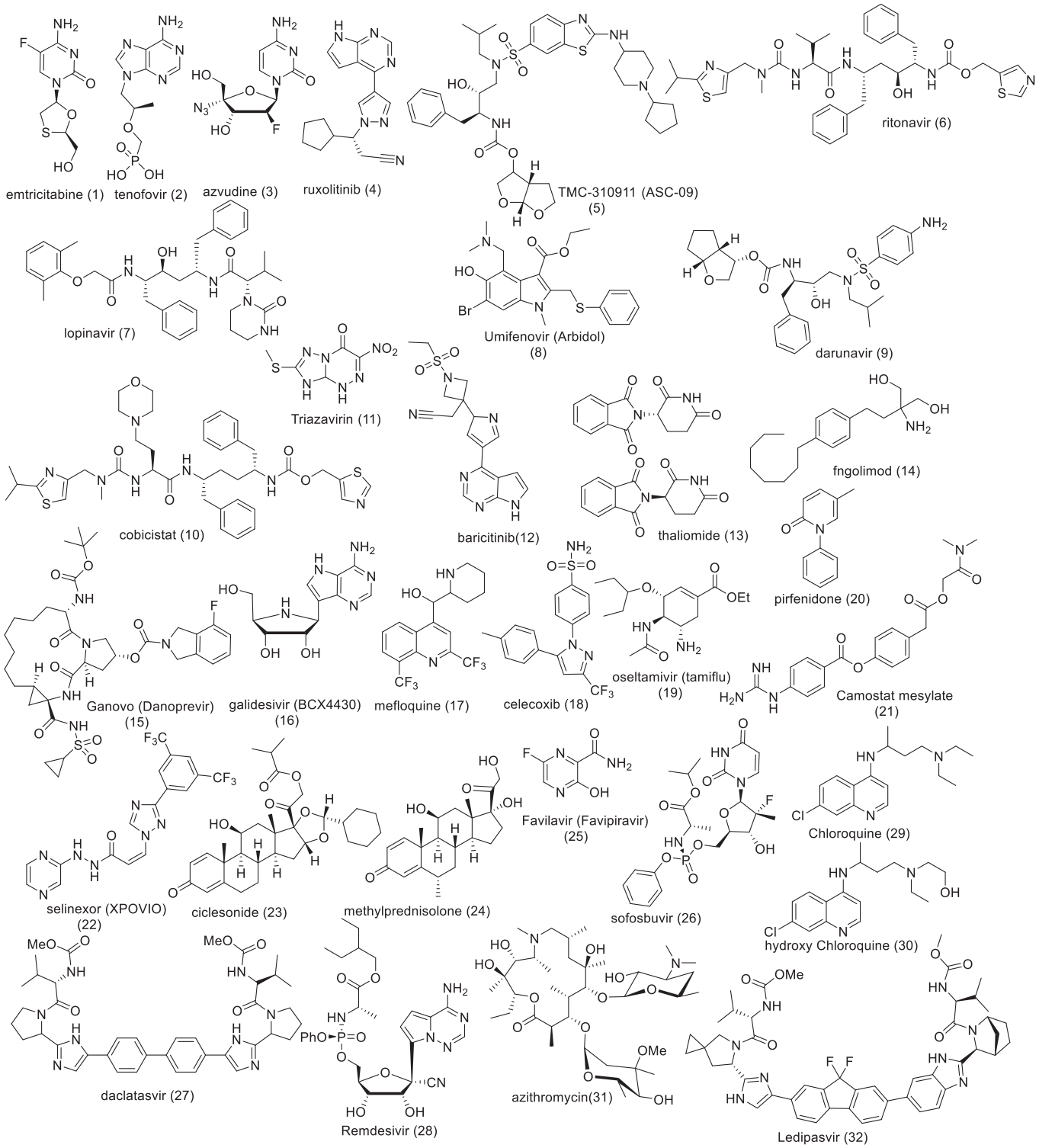

Fig. 3. Known drugs undergoing clinical trials for COVID-19 (Drug repurposing).

and blocking endosomes acidification [62–65]. An open-label, non-randomized clinical trial at Institut Hospitalo-Universitaire (IHU) of the Fondation Méditerranée Infection (FMI), Marseille, France, in early March 2020, with a combination of the HCQ and azithromycin in 20 COVID-19 patients demonstrated significant viral load reduction. Although the results of this small size study were promising, further validation using a large sample size is needed for definitive conclusions (EUCTR2020-000890-25) [64]. Another clinical study at Shanghai Public Health Clinical Centre (SPHCC), China, investigated the therapeutic efficacy of HCQ in 30 patients with COVID-19 disease (15 each for the HCQ and the control group), and reported a good prognosis in the HCQ group. The research team, however, expressed the need for a larger sample size to further validate the findings [66].

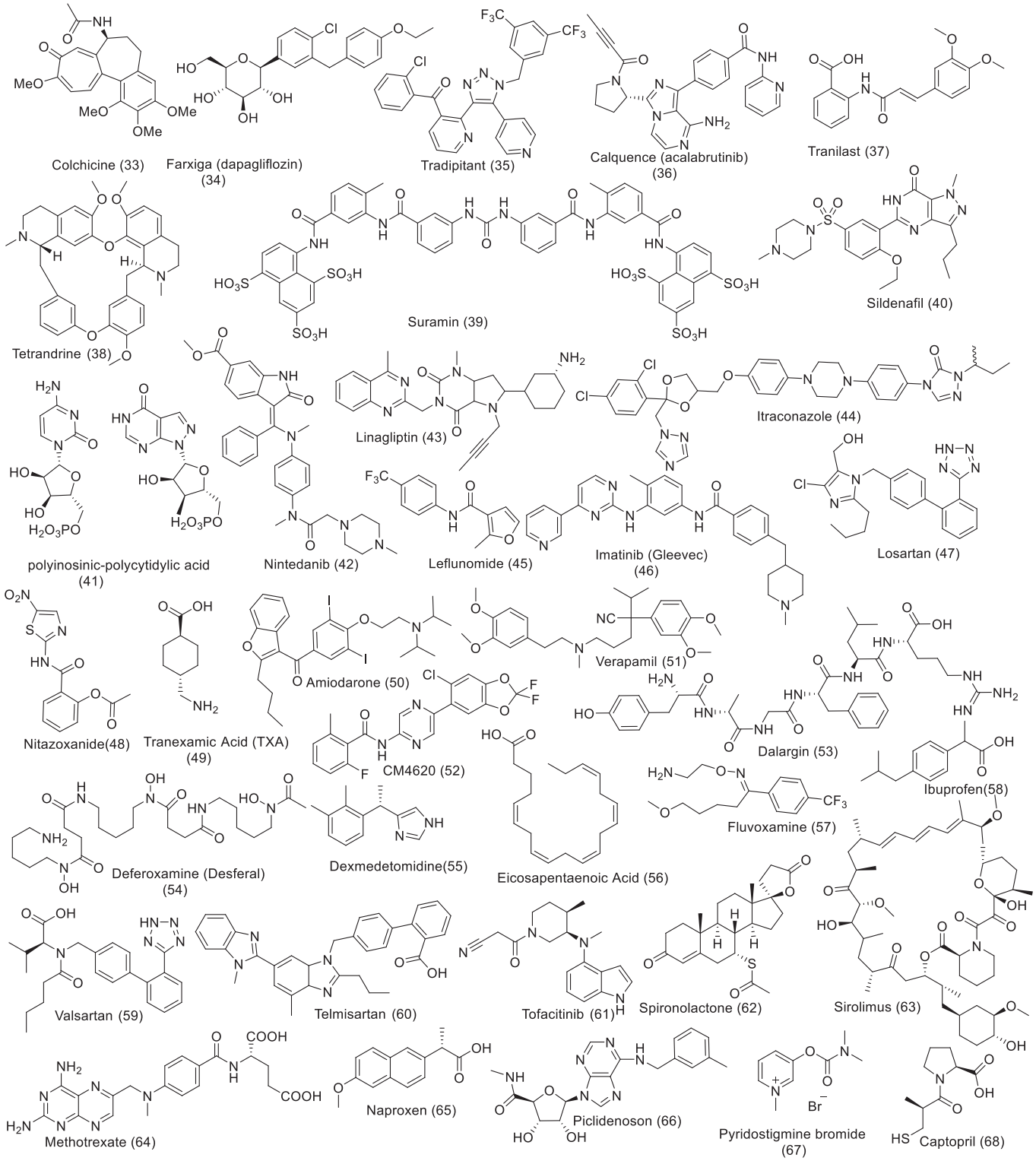

Fig. 4. Known drugs undergoing clinical trials for COVID-19 (Drug repurposing).

In February 2020, Renmin Hospital, Wuhan University, China, carried out another study on 62 patients to evaluate the efficacy of HCQ in the treatment of COVID-19 disease. This study partially confirmed the therapeutic potential of HCQ in the treatment of COVID-19 as the HCQ treatment significantly shortened the time to clinical recovery (TTCR) and promoted the resolution of pneumonia. Nevertheless, more expansive clinical studies are required to confirm the utility of HCQ in COVID-19 patients (ChiCTR2000029559) [67]. However, two HCQ clinical trials conducted by the US Department of Veterans Affairs, and Columbia University Irving Medical Centre (CUIMC), New York, NY, USA, respectively, showed early negative results for efficacy and safety

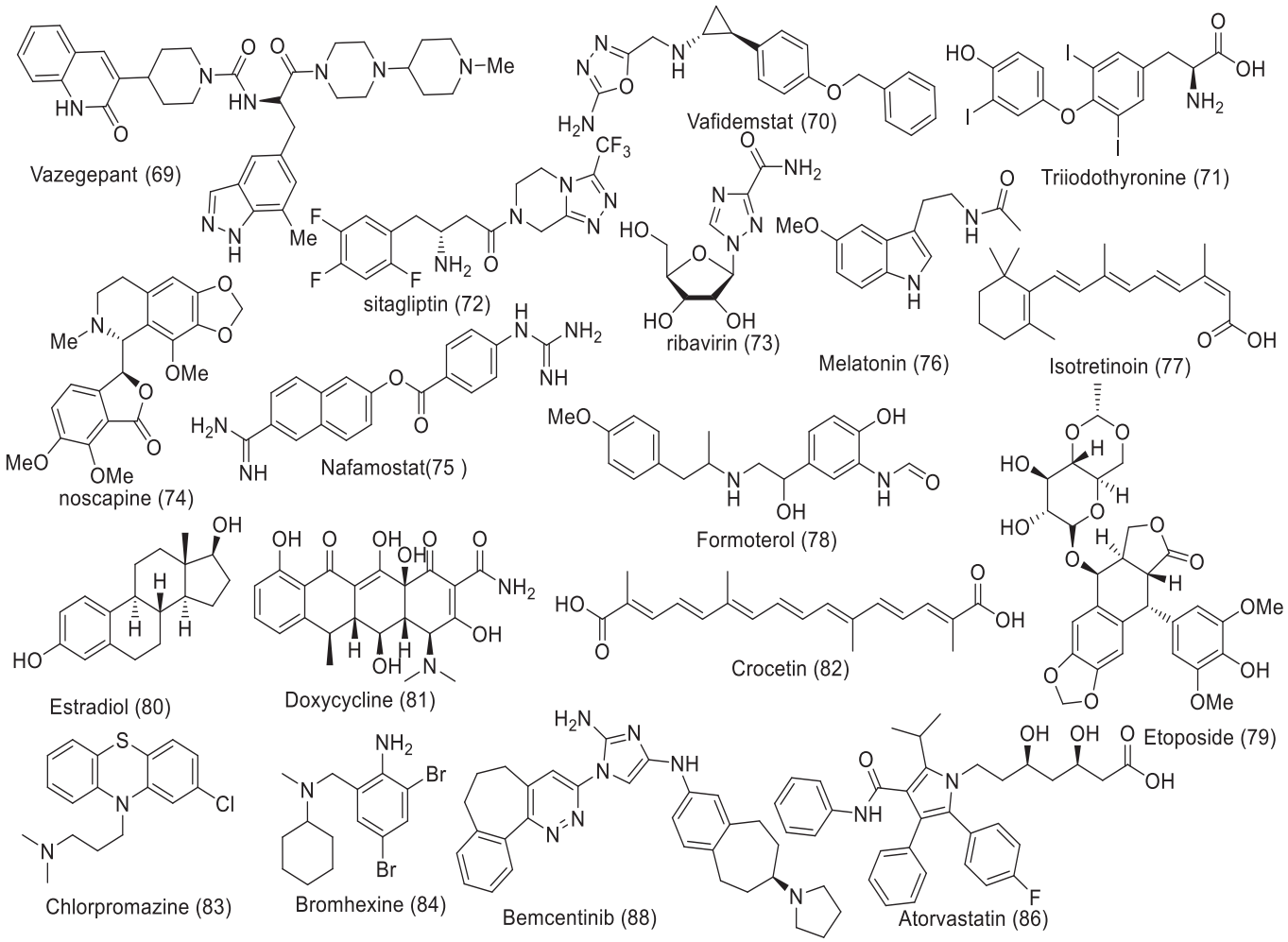

Fig. 5. Effective drugs undergoing clinical trials for COVID-19 (Drug repurposing).

[68,69]. The US Department of Veterans Affairs study conducted on 368 COVID-19 patients found no evidence to demonstrate that the use of HCQ, either with or without azithromycin, reduced the risk of death or mechanical ventilation over supportive care. Moreover, HCQ treatment alone increased the overall mortality [68].

CUIMC conducted another large-scale clinical study with HCQ on 1376 participants with moderate to severe COVID-19 disease. Eight hundred eleven patients received HCQ, while 565 patients did not receive any drug (placebo). Remarkably, HCQ treated COVID-19 patients reported a similar level of risk from intubation or death as the placebo group [69]. As of June 04, 2020, as many as 398 clinical trials using HCQ and/or CQ were active worldwide [61]. Nonetheless, on June 17, WHO announced the suspension of the HCQ arm of the SOLIDARITY trial [70]. Earlier on June 15, 2020, FDA revoked the emergency authorization for HCQ and CQ as a treatment for COVID-19 after determining that the efficacy of these drugs against COVID-19 is questionable. Moreover, the use of HCQ and CQ for COVID-19 treatment is associated with severe side-effects [71].

Many nucleoside and nucleotide analogs are well-known antiviral agents and useful for the treatment of HIV, hepatitis B, cytomegalovirus, and herpes simplex virus infections. The nucleoside and nucleotide analogs get incorporated into the DNA and RNA, as they resemble the naturally occurring nucleic acid monomers leading to faulty viral RNA or DNA synthesis. These agents inhibit various enzymes such as DNA-dependent DNA polymerases (DdDP), RNA-dependent DNA polymerases (RdDP), RNA-dependent RNA polymerases (RdRP), ribonucleotide reductase, kinases, and nucleoside phosphorylase [72]. Consequently, nucleoside and nucleotide analogs are the most preferred candidates for the design and development of new antiviral drugs. Remdesivir, an RNA-dependent RNA polymerase based inhibitor drug initially developed by Gilead Sciences to combat Hepatitis C (Patent US20170071964), has shown appreciable efficacy against SARS-CoV-2, and is presently undergoing Phase-III clinical trial in China since February 06, 2020. Recently, the University Hospitals, Cleveland, USA, disclosed that they would conduct a couple of clinical trials with remdesivir [65]. Currently, remdesivir is a part of the WHO's SOLIDARITY trial. Likewise, the University of Chicago, Chicago, USA, is presently evaluating the efficacy of remdesivir in a Phase-III clinical trial involving severally ill COVID-19 patients. On April 16, 2020, the medical news website, STAT, published a report on early results from a remdesivir clinical trial which revealed significant improvement in the fever and respiratory symptoms in COVID-19 patients receiving remdesivir, with nearly all remdesivir treated patients getting discharged from the hospital in less than a week [73].

On April 29, 2020, Gilead Inc. reported the results from another ongoing Phase-III trial (Adaptive COVID-19 Treatment Trial 1(ACTT1), NCT04280705) with remdesivir, in patients with severe COVID-19. The results revealed that patients receiving drug

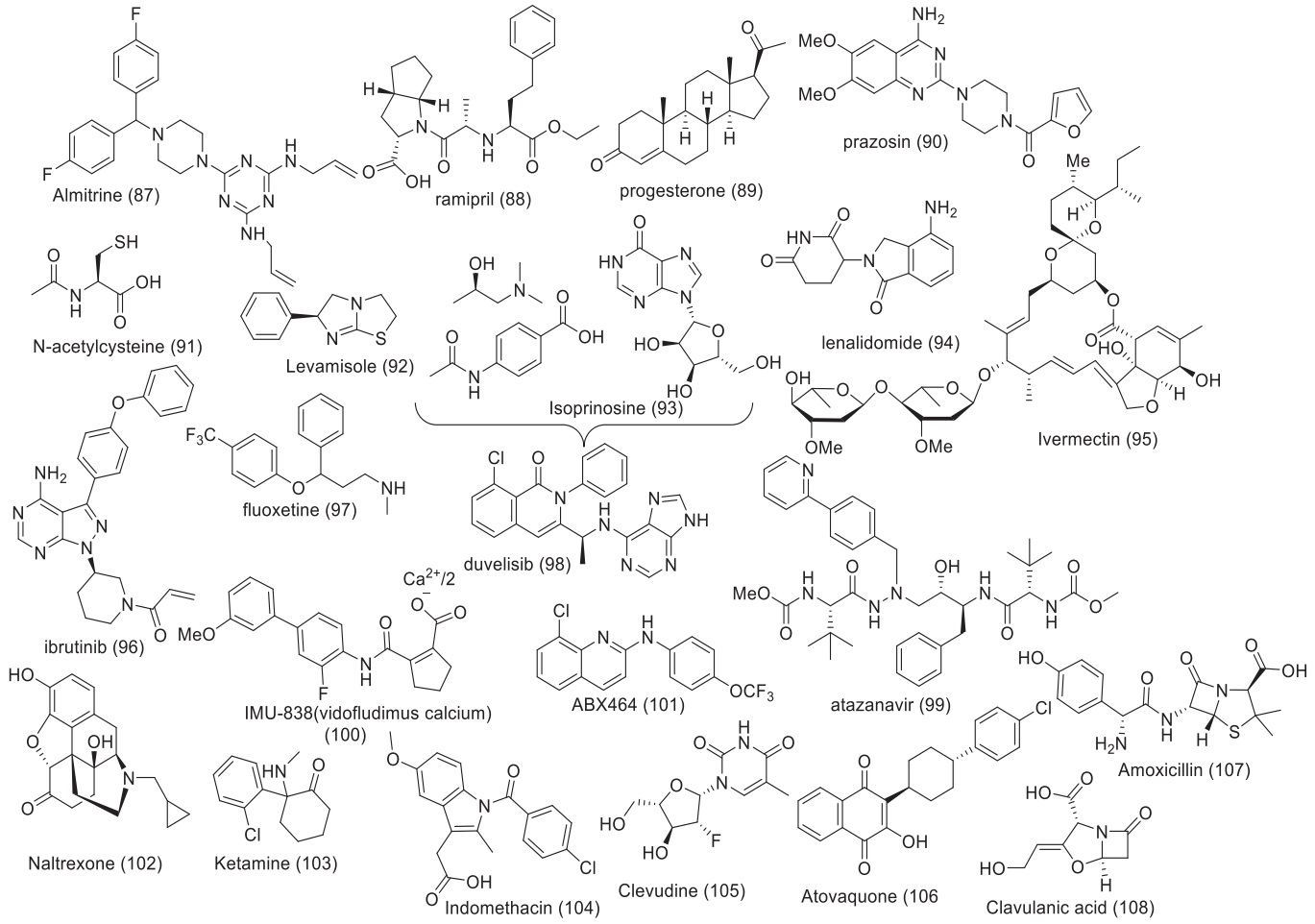

Fig. 6. Known drugs undergoing clinical trials for COVID-19 (Drug repurposing).

remdesivir recovered in 11 days as compared to the recovery time of 15 days for the placebo group. Furthermore, remdesivir showed the same clinical improvement in patients receiving a five-day treatment as those receiving a 10-day treatment. The drug candidate was well-tolerated and safe, and more than half of the patients were discharged by day 14 in both subject groups, with 31% faster recovery time as compared to placebo [74,75]. Additionally, Montefiore Health System, New York, USA, and Albert Einstein College of Medicine, New York, USA, have started the ACTT2 study (next stage of ACTT trial) with remdesivir plus baricitinib on severely ill COVID-19 patients in USA [76]. According to information listed on the ClinicalTrials.gov website, Gilead terminated its trials with remdesivir on moderate and severe COVID-19 patients in China, in April 2020. The primary reason for the abrupt termination of the remdesivir trial was the difficulty in recruiting enough infected patients for trials as the COVID-19 outbreak in China has mostly been contained [77]. As of June 29, 2020, about 19 clinical trials with remdesivir are registered and active [78]. Moreover, the results from remdesivir clinical trials have been extensively discussed and disseminated [79].

3.3. RECOVERY trail

Another notable large multi-arm RECOVERY trial began on March 19, 2020, in UK for developing potential coronavirus treatment (EudraCT 2020-001113-21, ISRCTN50189673 and NCT04381936). The primary objective of this Phase II-III clinical trial is the randomised evaluation of COVID-19 therapy (RECOVERY) by assessing the effects of different treatments. The RECOVERY trial continually reviews the latest reports on new drugs being repurposed as a potential treatment for COVID-19 and incorporates the most promising of these drugs in the clinical trials. Currently, drugs included in the RECOVERY trials are azithromycin, hydroxychloroquine, low-dose dexamethasone, lopinavir/ritonavir combination, and tocilizumab [80,81].

On June 16, 2020, a preliminary study on the Dexamethasone arm of the RECOVERY trial showed promising results in reducing mortality in critically ill COVID-19 patients. It was observed that mortality in patients on ventilators was reduced by one-third, and in patients who required oxygen support by one-fifth, compared to patients receiving standard care. However, no such reduction in mortality was observed in patients with milder illness not requiring respiratory support [82,83]. This report is the first proven instance of any drug improving survival in critically ill COVID-19 patients. However, Although the study was useful and based on high-quality evidence, some experts have called for further research to conclusively establish the reported benefits [84]. Consequent to these findings dexamethasone has already been approved for critically ill COVID-19 patients requiring oxygen support or on the ventilator, in the UK and India [85,86].

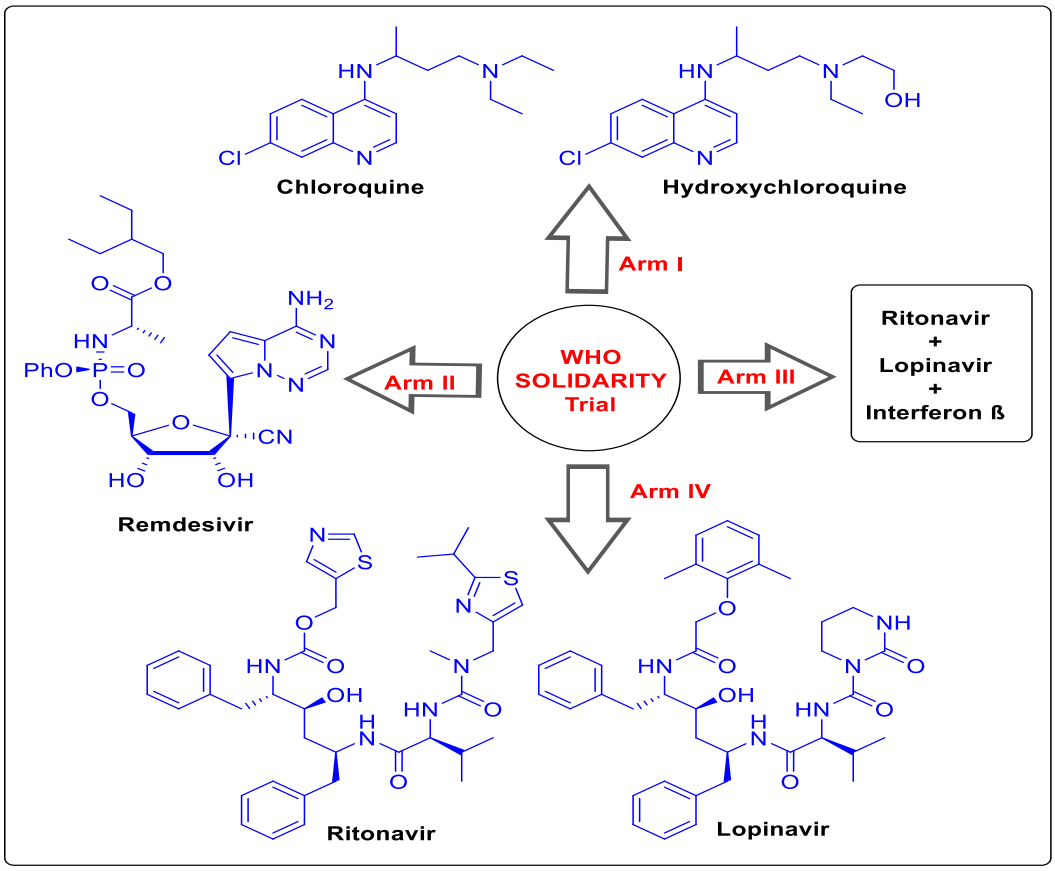

Fig. 7. Drugs included in WHO's four arm SOLIDARITY trial.

3.3.1. ACCORD (accelerating COVID-19 research & development) trial

ACCORD is a fast-track clinical trial program launched by the UK government, which involves the government, academia and industry, for the development of new drug candidates to treat COVID-19 patients. The current program includes six different drugs and drug combinations. Initially two drugs would be investigated in Phase-II trials in various hospitals across the UK to assess their safety and efficacy. Bemcentinib, an AXL kinase inhibitor manufactured by the Norwegian pharma company BerGenBio, is the first candidate to enter the ACCORD program and is presently undergoing a Phase II clinical study to evaluate its safety and efficacy on 120 participants (60 in the bemcentinib and 60 in the SoC group). Two molecules developed by the London based British-Swedish multinational pharmaceutical AstraZeneca, a Bruton's tyrosine kinase (BTK) inhibitor, and a Phase-II drug candidate targeting interleukin 33 (IL-33) are also part of this program. In addition to the six initial candidates, the ACCORD program would evaluate the effectiveness and safety of additional drugs and drug combinations. Successful candidates would then be moved ahead rapidly for further studies on large scale trial platforms such as the RECOVERY trial [87].

3.3.2. CATALYST trial

The University of Birmingham (UK) has launched the CATALYST trial to evaluate a series of drugs for the treatment of COVID-19 patients. The trial will test a series of drugs, including existing therapeutics for cancer and inflammatory diseases such as rheumatoid arthritis. Initially the trial will assess four drugs and cellular therapies under a new adaptive trial design intended for a rapid investigation of effectiveness [88]. The drugs, namilumab (IZN-101) and infliximab (CT-P13) would be initially evaluated in a study conducted by the University of Birmingham and University of Oxford in collaboration with Izana Bioscience, Oxford, UK, and Celltrion Healthcare, Incheon, South Korea [89].

3.3.3. CALVID-1 trial

Vidofludimus calcium (IMU-838) (**100**, Fig. 6) is an orally available, next-generation dihydroorotate dehydrogenase (DHODH) inhibitor currently under investigation for the treatment of several chronic inflammatory diseases. Immunic Inc., a biopharmaceutical company, based in San Diego, USA, has secured regulatory approval from the Federal Institute for Drugs and Medical Devices (BfArM), the medical regulatory body in Germany, on May 13, 2020, to conduct a Phase-II clinical trial named CALVID-1 with IMU-838 in COVID-19 patients. The company had earlier reported that IMU-838 prevents the replication of SARS-CoV-2 clinical isolates, the causative agent of COVID-19 [90–92]. On June 15, 2020, Immunic, Inc. announced the initiation of the phase-II trial with IMU-838 [93].

3.3.4. Austrian coronavirus adaptive clinical trial (ACOVACT)

To compare the various antiviral agents available for treatment of COVID-19, Medical University of Vienna, Austria, in collaboration with Kaiser Franz Josef Hospital, Vienna is conducting an open-label, randomized-controlled, multi-arm ACOVACT trial (NCT04351724). ACOVACT trial includes three primary study arms, and patients are randomly assigned to receive HCQ, lopinavir/ritonavir, or standard therapy. Interestingly, patients from these three arms may enroll in multiple sub-studies which includes sub-study A (randomized to rivaroxaban versus standard care), sub-

Table 3
Potential therapeutics other than small molecule drugs undergoing clinical trials for COVID-19.

S.N.	Drug Name	Company/Developer	Function	Comment
1	Actemra (tocilizumab)	Roche, Switzerland	Interleukin-6 inhibitor	Recombinant humanized monoclonal antibody Phase-III NCT04320615, NCT04317092 NCT04331795, (ClinicalTrials.gov)
2	Sarilumab (Kefzara)	Feinstein Institute, New York, USA, Gilead Sciences Inc., USA and Regeneron Pharmaceuticals, USA	Interleukin-6 inhibitor	Recombinant humanized monoclonal antibody NCT04315298, (ClinicalTrials.gov)
3	Leronlimab	CytoDyn, Canada	CCR5 antagonist	Humanized IgG4 monoclonal antibody Phase-II, NCT04343651 NCT04347239, (ClinicalTrials.gov)
4	Ultomiris (ravulizumab-cwvz)	Alexion Pharmaceuticals, USA	Inhibits C5	Recombinant humanized monoclonal antibody
5	Gimsilumab	Kinevant Sciences GmbH, Switzerland and Roivant Sciences, Switzerland	Acts on granulocyte-macrophage colony-stimulating factor (GM-CSF)	Fully humanized monoclonal antibody Phase-II, NCT04351243 (ClinicalTrials.gov)
6	Meplazumab	Tang-Du Hospital, China	Blocks interleukin 5	Humanized monoclonal antibody, Phase-I/II NCT04275245 (ClinicalTrials.gov)
7	Lenzilumab	Humanigen Inc., USA	CSF2/GM-CSF	Humanized monoclonal antibody, NCT04351152 (ClinicalTrials.gov)
8	Ixekizumab	Xiangya Hospital of Central South University, China	Interleukin 17A inhibitor	Humanized monoclonal antibody ChiCTR2000030703
9	Bevacizumab (Avastin)	Various institutes in Chiana, france and Italy	VEGF-A inhibitor	Recombinant humanized monoclonal antibody NCT04344782, NCT04275414 NCT04305106, (ClinicalTrials.gov)
10	Adalimumab (Humira)	Shanghai Changzheng Hospital, China	TNF inhibitor	Fully humanized monoclonal antibody Phase-IV, ChiCTR2000030089, (ICTPR)
11	Clazakizumab	NYU Langone Health and Cedars-Sinai Medical Center, USA	IL-6 inhibitor	An aglycosylated, humanized rabbit monoclonal antibody Phase-II, NCT04343989, NCT04348500 (ClinicalTrials.gov)
12	Siltuximab	Fundacion Clinic per a la Recerca Biomédica, Spain	IL-6 inhibitor	Phase-II, NCT04329650 (ClinicalTrials.gov)
13	Nivolumab	Assistance Publique - Hôpitaux de Paris, France	PD-1	human IgG4 monoclonal antibody, phase II NCT04343144 (ClinicalTrials.gov)
14	IFX-1	InflaRx GmbH, Germany	C5a	Monoclonal antibody phase II, NCT04333420 2020-001335-28 (EU-CTR)
15	TJ003234	I-Mab Biopharma Co. Ltd., China	Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Humanized immunoglobulin G1 (IgG1) monoclonal antibody, Phase-I, NCT04341116, (ClinicalTrials.gov)
16	LY3127804	Eli Lilly and Company, USA	Angiopoietin 2 (Ang2)	Humanized and engineered IgG4 isotype antibody Phase II, NCT04342897, (ClinicalTrials.gov)
17	sirukumab	Janssen Pharmaceutica N.V., Belgium	Interleukin 6	Human monoclonal antibody Phase-II, NCT04380961 (ClinicalTrials.gov)
18	Kineret (anakinra)	University Hospital Ghent, Belgium	Interleukin-1 receptor antagonist	Human interleukin-1 receptor antagonist (IL-1Ra), 2020-001500-41 (EU-CTR)
19	Novaferonc Nova	Hu'nan Haiyaohongxingtang Pharmceutical Co. Ltd., China	Boosts immune system	Cytokine gene-derived recombinant protein ChiCTR2000029496 (ICTPR)
20	ATYR1923	aTyr Pharma Inc., USA	Selective modulator of neuropilin-2	A fusion protein comprised of the immuno-modulatory domain of histidyltRNAsynthetase fused to the FC region of a human antibody
21	IFN-α2b	Tongji Hospital, China	Interferes with viral replication	Type I interferons NCT04293887, (ClinicalTrials.gov)
22	APN01	APEIRON Biologics, Austria	Blocks virus entry through ACE2	A recombinant human angiotensin-converting enzyme 2 (rhACE2) Phase-I, NCT00886353 Phase-II, NCT04335136 (ClinicalTrials.gov)
23	Sargramostim (Leukine)	University Hospital, Ghent, Belgium	Immunostimulator	RecombinantGM-CSF (Glycoprotein) Phase-IV, NCT04326920 (ClinicalTrials.gov) 2020-001254-22(EU-CTR)
24	CD24Fc	OncoImmune Inc., USA	Interleukin 1 beta inhibitor, interleukin 6 inhibitor, and tumour necrosis factor alpha inhibitor	Modulate host inflammatory response (Recombinant fusion proteins) Phase-III, NCT04317040 (ClinicalTrials.gov)
25	PD-1 mAB	Jianfeng Xie, Southeast University, China, and West China Hospital, Sichuan University, China	PD-1 blocking antibody	Antibody, Phase-II, NCT04268537 (ClinicalTrials.gov) ChiCTR2000030028, (ICTPR)
26	Intravenous immunoglobulin (IVIG)	Peking Union Medical College Hospital, China, and Centre Hospitalier St Anne, France	Enhance passive immunity, and anti-inflammatory and immunomodulatory effect	Immunoglobulin NCT04261426, NCT04350580 (ClinicalTrials.gov)
27	Angiotensin (1−7)	Hôpital Erasme, Belgium	Antioxidant and anti-inflammatory	Heptapeptide Phase-II, NCT04332666 (ClinicalTrials.gov)
28	Aviptadil (RLF-100)	Relief Therapeutics, Switzerland in collaboration with NeuroRx, USA	Used in the treatment of ARDS	Analog of vasoactive intestinal polypeptide Phase-IIb/III, NCT04311697 (ClinicalTrials.gov)
29	Ulinastatin	Shanghai Changzheng Hospital, China	Trypsin inhibitor	

(*continued on next page*)

Table 3 (*continued*)

S.N.	Drug Name	Company/Developer	Function	Comment
				Glycoprotein Phase-IV ChiCTR2000030779 (ICTPR)
30	Thymosin	Wuhan Jinyintan Hospital, China	Biological response modifier	Small protein isolated from the thymus ChiCTR2000029806 (ICTPR)
31	Solnatide	Medical University of Vienna, Vienna Austria	Reduces pulmonary edema	Synthetic Peptide Phase-II 2020-001244-26 (EU-CTR)
32	Procalcitonin	Assistance Publique – Hôpitaux de Paris(AP-HP), France	Precursor of the hormone calcitonin	Peptide, Phase-IV 2020-001324-33 (EU-CTR)
33	Peginterferon Lambda-1A (Interferon Lambda)	University Health Network, Toronto, Canada	Activates a STAT phosphorylation-dependent signaling cascade	Phase-II, NCT04354259 (ClinicalTrials.gov)
34	Alteplase (t-PA) (Activase or Actilyse)	Denver Health and Hospital Authority, USA, and University College, London, UK	Serine protease that facilitates conversion of plasminogen to plasmin	Glycoprotein Phase-II, NCT04357730 (ClinicalTrials.gov) 2020-001640-26 (EU-CTR)
35	XPro1595	INmune Bio Inc., USA	Soluble TNF (sTNF) inhibitor	Protein, Phase-II NCT04370236, (ClinicalTrials.gov)
36	Metenkefalin + Tridecactide	Bosnalijek, Bosnia Herzegovina	Immunomodulator	Opioid peptide Phase-II, NCT04374032 (ClinicalTrials.gov)
37	PUL-042 Inhalation Solution	Pulmotect Inc., USA	TLR 2/6/9 agonist	Mixture of oligodeoxynucleotide and lipopeptide Phase-II, NCT04313023 NCT04312997, (ClinicalTrials.gov)
38	Defibrotide	Research institutes inItaly and Spain	Increase t-PA function and decrease plasminogen activator inhibitor-1 activity	Mixture of single-stranded oligonucleotides NCT04335201 NCT04348383 (ClinicalTrials.gov) 2020-001409-21 (EU-CTR)
39	Enoxaparin	Tongji Medical College of Huazhong University of Science and Technology and The Third People's Hospital of Shenzhen, China	Irreversibly inactivates clotting factor Xa	Heparin (Polysaccharide) Phase-0 ChiCTR2000030700 ChiCTR2000030701 (ICTPR) NCT04359277 (ClinicalTrials.gov)
40	Tinzaparin	Assistance Publique - Hôpitaux de Paris, France	Accelerates the inhibition of factor Xa	Heparin (Polysaccharide) Phase-II NCT04344756 (ClinicalTrials.gov)
41	Aescin or escin	University of Catanzaro, Italy	Mixture of saponins with anti-inflammatory, vasoconstrictor and vasoprotective effects., Induces nitric oxide synthesis	Steroid tethered with trisaccharide's Phase-II, NCT04322344 (ClinicalTrials.gov)
42	Kolimycin	The First Affiliated Hospital of Harbin Medical University, China	Binds to the 30S subunit of the bacterial ribosome	Amino oligo-sugar Phase-0 ChiCTR2000032242, (ICTPR)
43	Dornase	University College, London, UK, and Fondation Ophtalmologique Adolphe de Rothschild, France	Highly purified solution of recombinant human deoxyribonuclease I	Deoxyribonuclease-I Phase-II, NCT04359654 Phase-III, NCT04355364 (ClinicalTrials.gov)
44	Vitamin A	Mostafakhomeini Medical Centre, Saveh, Iran	Boosts immunity	Phase –II IRCT20180520039738N2 (ICTPR)
45	Vitamin C (Ascorbic acid)	Zhongnan Hospital of Wuhan University and Université de Sherbrooke, Canada	Antioxidant and cofactor; Boosts immunity	NCT04264533, NCT03680274 NCT04357782, NCT04344184 (ClinicalTrials.gov) IRCT20190917044805N2 (ICTPR)
46	Vitamin D	University Hospital, Angers, France and Universidad de Granada, Spain	Boosts immunity	2020-001717-20 (EU-CTR), NCT04334005, NCT04344041 (ClinicalTrials.gov)
47	Calcifediol	Tehran University of Medical Sciences, Iran	Boosts immunity	Phase-III IRCT20200401046909N1 IRCT20200401046909N2 (ICTPR)
48	Zinc	University of Melbourne, The Cleveland Clinic and University Hospital, Lille, France	Intravenous high dose zinc alone and in combination with vitamin C or vitamin D	Phase-I/II ACTRN12620000454976 NCT04342728, NCT04351490 (ClinicalTrials.gov)
49	Lipoic acid	Maoming People's Hospital, Maoming, China	Antioxidant	Phase-IV ChiCTR2000030471
50	Vitamin A, B, C, D, and E	Imam Khomeini Hospital, Tehran, Iran	Boosts immunity	Phase-III IRCT20200319046819N1 (ICTPR)
51	Umbilical cord derived stem cells	Huangshi Hospital of Traditional Chinese Medicine and Guanggu District of Hubei Maternal and Child Health Hospital, China	MSCs are known to possess immunomod- ulatory and regenerative properties	Fight the inflammation and lung degeneration ChiCTR2000031494 ChiCTR2000031430s
52	Adipose-derived mesenchymal stem cells (HB-adMSCs)	Hope Biosciences, Texas, USA	MSCs are known to possess immunomodulatory and regenerative properties	Fight the inflammation and lung degeneration NCT04349631, (ClinicalTrials.gov)
53	Nest Cell®	Azidus, Brazil	Mesenchymal stem cell therapy	Phase-I, NCT04315987 (ClinicalTrials.gov)
54	NK cells	Universidad Nacional de Colombia	Involved in the early defense against infectious pathogens and	Allogeneic NK transfer Phase-I/II

Table 3 (*continued*)

S.N.	Drug Name	Company/Developer	Function	Comment
			Middle East Gene Therapy corporation	NCT04344548 (ClinicalTrials.gov) IRCT20200417047113N1 (ICTPR)
55	NK cells, IL15-NK cells, NKG2D CAR-NK cells, ACE2 CAR-NK cells, NKG2D-ACE2 CAR-NK cells	Chongqing Public Health Medical Center, China	Boost innate immunity and adaptive immunity	Phase-I/II NCT04324996 (ClinicalTrials.gov)
56	TAK-888 (Plasma-derived antibodies)	Takeda Pharmaceutical Co., Japan	Plasma which contains antibodies against the virus	Polyclonal hyperimmune globulin (H-IG)
57	Amniotic fluid	University of Utah, USA	Protective liquid contained in the amniotic sac of a gravid amniote	Phase-I, NCT04319731 (ClinicalTrials.gov)
58	Heat-killed Mycobacterium w	CSIR, India and Cadila Pharmaceuticals, India	Immunomodulator	Phase-III, NCT04353518 NCT04347174 (ClinicalTrials.gov)
59	Nitric oxide	Sanotize Research & Development Corp., University of British Columbia, Canada and Massachusetts General Hospital, USA	Interferon (IFN) mediated inhibition manifested by activated macrophage	Nitic oxide inhalation Phase-II, NCT04337918 NCT03331445 NCT04312243 NCT04338828 (ClinicalTrials.gov)
60	Sevoflurane	University of Zurich	NMDA receptor antagonist. Inhibits nAChR and 5-HT3 receptor currents	Inhalational anaesthetic Phase-III, NCT04355962 (ClinicalTrials.gov)
61	Stannous Protoporphyrin (RBT-9)	Renibus Therapeutics Inc., USA	Coordination compound	Phase-II, NCT04364763 (ClinicalTrials.gov)
62	Sodium Bicarbonate	Mansoura University, Egypy	Inhalable sodium bicarbonate	Phase-I, NCT04374591 (ClinicalTrials.gov)
63	MRx-4DP0004	4D Pharma plc, UK	Immunomodulator	Phase-II, NCT04363372 (ClinicalTrials.gov)
64	Pulmozyme/Dornase alpha aerosol	Hôpital Fondation Adolphe de Rothschild, France	It breaks down excess DNA in the pulmonary secretions of people with cystic fibrosis	Synthetic protein PhaseIII 2020-001492-33 (EU-CTR)
65	Rintatolimod in combination with IFN Alpha-2b	Roswell Park Cancer Institute, USA	TLR3 agonist	Double-stranded RNA molecule Phasel/II NCT04379518 (ClinicalTrials.gov)

study B (renin-angiotensin (RAS) blockade versus no RAS blockade), and sub-study C (clazakizumab versus standard care) [94].

3.4. Monoclonal antibodies

Antibodies are a promising new class of therapeutics that have shown good efficacy against many viruses. Monoclonal antibodies (mAB) are man-made synthetic antibodies that mimic natural antibodies and primarily target susceptible sites on viral surface proteins. In coronaviruses they act by targeting the trimeric spike (S) glycoproteins on the viral surface that mediates the entry of the virus into the host cells. Monoclonal antibody-based therapeutics could be used not only as a prophylactic treatment for individuals exposed to the virus but also to prevent disease progression in patients already infected by the virus [95].

The spike proteins of SARS-CoV (SARS-S, 1255 residues, strain Urbani) and SARS-CoV-2 (SARS2-S,1273 residues, strain Wuhan-Hu-1) show 77.5% identity in primary amino acid sequence and thus are structurally very similar. They predominantly bind to the host receptor, human angiotensin-converting enzyme 2 (ACE2) protein, through the receptor-binding domain ($S1_B$ domain), and trigger irreversible conformational changes in the coronavirus spike proteins leading to membrane fusion [96–98].

Actemra (tocilizumab), a humanized monoclonal antibody that suppresses the immune system by inhibiting interleukin-6 (IL-6), is used for the treatment of rheumatoid arthritis. It is manufactured by the pharmaceutical giant Roche under the brand name actemra. FDA has recently approved actemra for a double-blind, placebo-controlled, randomized Phase-III COVACTA trial (registered on May 25, 2020) to treat severely ill COVID-19 patients with high IL-6 levels in the blood. COVACTA trial will be useful for assessing the safety and efficacy of intravenous actemra plus standard of care (SOC), versus placebo plus SOC. 450 patients have been enrolled for this trail). On May 28, 2020, Roche and Gilead Sciences announced the initiation of another global, multi-center, double-blind, randomized Phase-III REMDACTA trial to evaluate the safety and efficacy of actemra in combination with remdesivir versus placebo plus remdesivir in hospitalized COVID-19 patients with severe pneumonia (Table 3, Entry 1). The data obtained in the REMDACTA trial will supplement the COVACTA study [99–102]. Likewise, Feinstein Institutes for Medical Research, New York, USA, in collaboration with Gilead Sciences and Regeneron Pharmaceuticals, New York, USA, are launching clinical trials with sarilumab, another humanized monoclonal antibody and effective inhibitor of IL-6 receptor (Table 3, Entry 2). A Phase IIb-III clinical trial with leronlimab, a humanized Ig4 monoclonal antibody, and a CCR5 antagonist, is being carried out by CytoDyn Inc. on critically ill COVID-19 patients. In this study patients will receive leronlimab for two weeks (Table 3, Entry 1). Alexion Pharmaceuticals, Boston, USA, announced another global Phase-III clinical study to investigate ultomiris (ravulizumab/-cwvz) as a treatment for adult COVID-19 patients with severe pneumonia or acute respiratory distress syndrome (ARDS) (Table 3, Entry 4). Kinevant Sciences GmbH, and Roivant Sciences, both based in Basel, Switzerland, are independently conducting Phase-II clinical trial with gimsilumn, a fully humanized monoclonal antibody (Table 3, Entry 5).

Another open-label, Phase-I-II clinical trial (NCT04275245) conducted by Tang-Du Hospital, China, with meplazumab on 17 patients (assigned to meplazumab group) between February 03 and February 10, 2020, found that meplazumab improved the recovery of patients with SARS-CoV-2 induced pneumonia. However, the study investigators have recommended the need for a more comprehensive clinical investigation of meplazumab for the treatment of COVID-19 (Table 3, Entry 6) [103].

A study evaluating lenzilumab (anti-human GM-CSF monoclonal antibody) on hospitalized COVID-19 patients with pneumonia showed 92% recovery (11 out of 12 patients), and significant improvement in oxygenation with a median time to discharge of 5 days. No adverse events were reported. In fact, after two days of treatment with lenzilumab, a significant reduction in inflammatory myeloid cells was observed [104]. Additionally, a large number of monoclonal antibody (mAB)-based drugs such as ixekizumab, bevacizumab (avastin), adalimumab (humira), clazakizumab,

siltuximab, nivolumab, IFX-1, TJ003234, LY3127804 and sirukumab are currently undergoing trials for COVID-19 treatment at different institutions around the world (Table 3, Entries 8–17).

3.5. Other recombinant proteins and peptides

On April 10, 2020, University Hospital, Ghent, Belgium, registered a Phase-III clinical trial with the drug anakinra, a recombinant, non-glycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra). The trial goal is to compare the safety and efficacy of the simultaneous blockade of the interleukin-6 pathway and interleukin-1 pathway in improving oxygenation and short- and long-term prognosis of COVID-19 patients with acute hypoxic respiratory failure and systemic cytokine release syndrome (Table 3, Entry 18).

Hunan Haiyao Hongxingtang Pharmaceutical Company, China, carried out an open-label, randomized, parallel-controlled trial for evaluating the efficacy of novaferon as a single agent, and in combination with lopinavir/ritonavir. They also tested the anti-SARS-CoV-2 effects of novaferon in cell-based assays. Study results confirmed the anti-SARS-CoV-2 effects of novaferon *in vitro,* and in COVID-19 patients (Table 3, Entry 19) [105].

Additionally, the Food and Drug Administration (FDA) has accepted ATyr Pharma's Investigational New Drug (IND) application for the Phase-II clinical investigation of ATYR1923 in COVID-19 patients with severe respiratory complications. ATYR1923, a fusion protein comprising of the immuno-modulatory domain of histidyl t-RNA synthetase fused to the fragment crystallization (Fc) region of a human antibody, directly binds to the neuropilin-2 (Nrp2) to modulate Nrp2 signaling and downregulate the innate and adaptive immune response in inflammatory conditions. Currently, ATyrPharma is conducting a Phase-Ib-IIa clinical trial withATYR1923 on patients with pulmonary sarcoidosis (Table 3, Entry 20) [106]. Likewise, several other proteins and peptide-based agents such as IFN-α2b, human recombinant ACE2 (APN01), sargramostim (leukine), CD24Fc, anti-programmed cell death-1 mAB, angiotensin (1–7), aviptadil, intravenous immunoglobulin, ulinastatin, thymosin, solnatide, procalcitonin, interferon lambda, alteplase, XPro1595, and metenkefalin in combination with tridecactide are currently registered for clinical trials and are being actively tested (Table 3, Entries 21–36).

3.6. Oligonucleotides and polysugars

Oligonucleotide and polysaccharide based therapeutic agents such as PUL-042AD, defibrotide, enoxaparin, tinzaparin, aescin, kolimycin, and dornase are also being actively pursued in multiple clinical trials for the treatment of COVID-19 (Table 3 Entry 37–43).

3.7. Vitamins and cofactors

Vitamins and other cofactors play a significant role in boosting the immune system. Therefore, clinical trials with vitamins A, B, C, D and E, and cofactor lipoic acid, calcifediol, and zinc are currently underway for the treatment of COVID-19 (Table 3 Entries 38–50).

3.8. Stem cells, plasma and, other body fluids-based therapy

To stimulate a robust host immune response against SARS-CoV-2, FDA has permitted the emergency use of antibody-laden blood plasma collected from the people who recovered from COVID-19 infection [107,108]. Towards this end, Takeda Pharmaceuticals Company, Tokyo, Japan, has started clinical trials with plasma-derived therapy called TAK-888, which involves isolation of coronavirus-specific antibodies from COVID-19 survivors and its administration to infected patients. The development of drugs and vaccines against COVID-19 is a time-consuming process, whereas blood plasma is readily accessible and relatively safe. Mayo Clinic recently conducted studies with convalescent plasma on 5000 hospitalized COVID-19 patients under the FDA's Expanded Access Program (EAP). The study found transfusion of convalescent plasma to be safe for the treatment of severely ill COVID-19 patients [109]. Currently, a large number of clinical trials based on convalescent plasma, amniotic fluid stem cells, and NK cells have been initiated worldwide (Table 3 Entries 51–57).

3.9. Miscellaneous

Heat-killed mycobacterium based vaccine against leprosy activates the toll-like receptor (TLR) pathway, modulates immune response, and explicitly enhances host-T cell functions [110]. Mycobacterium w vaccine is registered as an 'Mw vaccine' in India, and is currently undergoing clinical trial for the treatment of COVID-19 patients. Mw vaccine potentially mitigates the cytokine storm responsible for the severity of the symptoms, and fatality, in the majority of the COVID-19 patients (Table 3 Entry 58). In addition, clinical studies to evaluate the efficacy of nitric oxide inhalation, sevoflurane, stannous protoporphyrin (RBT-9), sodium bicarbonate, and MRx-4DP0004 in COVID-19 patients are also being carried out by several healthcare institutions (Table 3, Entries 59–65).

4. Preclinical research

For the development of a therapeutic agent for COVID-19 treatment, a variety of small molecules drugs, antibodies, cell-based or RNA-based compounds are undergoing preclinical studies. Besides, screening and reinvestigation of many existing drugs, especially antivirals and antibiotics, are ongoing as a post-infection treatment option against COVID-19 [43].

4.1. Antiviral drugs

As COVID-19 is a viral disease, considerable scientific attention has been focused on repurposing approved antiviral drugs (Fig. 8) [111]. In preclinical cell-based studies, ribavirin (a ribonucleoside analog) (**73**) showed activity against SARS-CoV-2 (EC_{50} = 109.50 μM, CC_{50} > 400 μM, selectivity index (SI) > 3.65) [65]. Molecular docking studies suggest that ribavirin, sofosbuvir (**26**), galidesivir (**16**), setrobuvir (**109**), IDX-184 (**110**), and tenofovir (**2**) tightly bind to the SARS-CoV-2 RdRp and can thus serve as potential candidates for drug repurposing studies against COVID-19 [112]. Another promising candidate is β-D-N^4-hydroxycytidine (NHC, EIDD-1931) (**111**). This orally bioavailable ribonucleoside analog exhibits broad-spectrum antiviral activity against several unrelated RNA viruses, such as influenza virus, coronavirus, Ebola virus, and Venezuelan equine encephalitis virus (VEEV). The University of North Carolina (UNC) led team recently reported promising antiviral activity of NHC against SARS-CoV-2, MERS-CoV, SARS-CoV, and related CoVs *in vitro*. NHC prodrug, β-D-N^4-hydroxycytidine-5′-isopropyl ester (EIDD-2801) (**112**), also yielded excellent results in the form of improved lung function, reduced virus load, and weight loss in mice infected with SARS-CoV or MERS-CoV [113].

Another antiviral drug, niclosamide (**113**), an FDA-approved anti-helminthic drug, is effective against the SARS-CoV-2 family of viruses such as SARS-CoV, MERS-CoV. Niclosamide exhibits activity in nanomolar to the micromolar range, highlighting its potential use as a suitable drug repurposing candidate for SARS-CoV-2 [114–116]. Koet et al. recently carried out a study wherein they

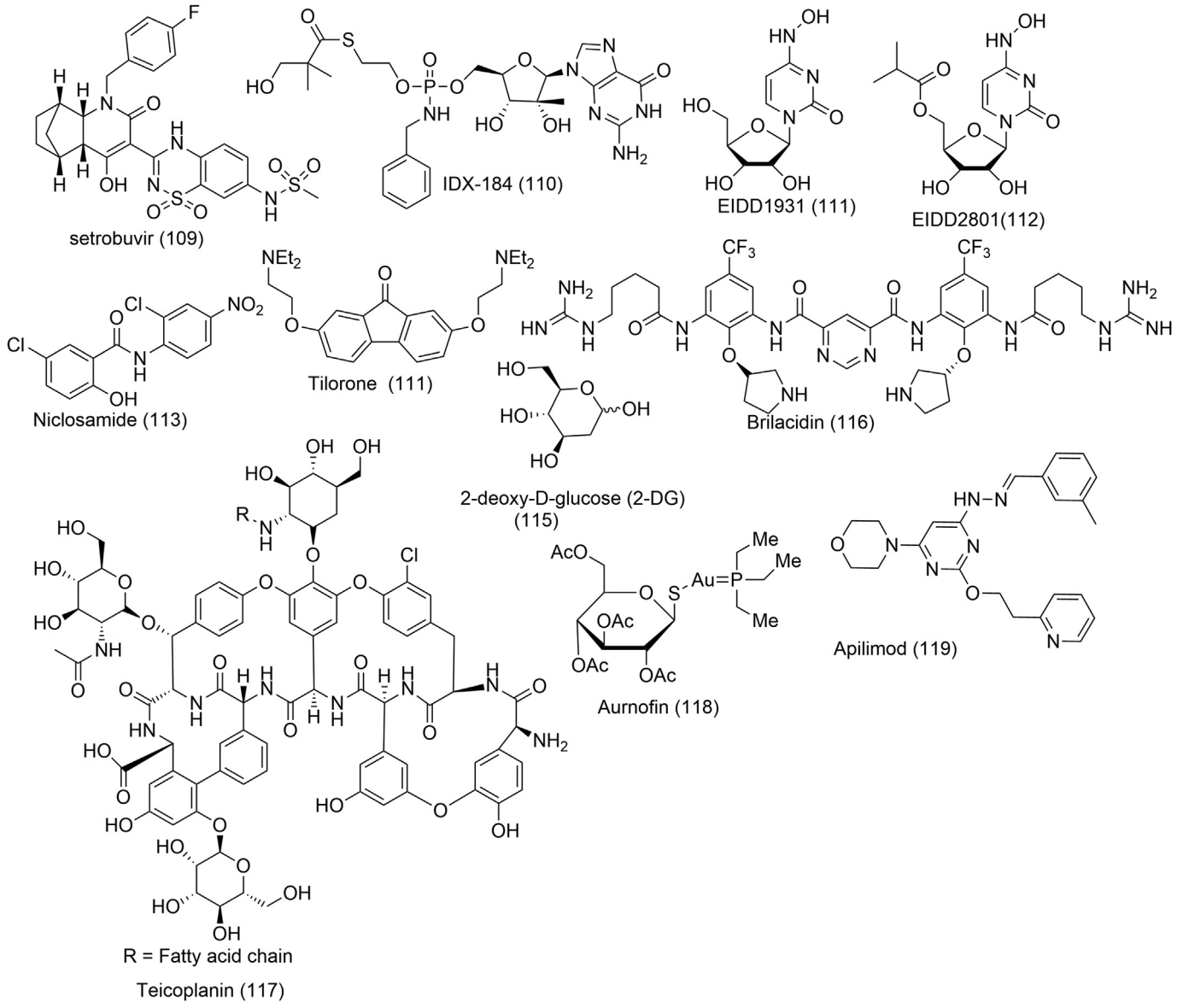

Fig. 8. Known drugs under preclinical investigation for treatment of COVID-19.(Drug repurposing)

evaluated the *in vitro* inhibitory activity of 50 FDA approved drugs in Vero cells to identify potential drug candidates against SARS-CoV-2. The screening led to the identification of two drugs, i.e., niclosamide, an anti-helminthic drug, and tilorone, an antiviral drug. Both these drugs showed encouraging results [117]. Niclosamide inhibited SARS-CoV-2 activity at IC_{50} = 0.28 μM In contrast, while tilorone (**114**) exhibited an IC_{50} value of 4.09 μM. Recently, N. C. Gassen and co-workers have shown that niclosamide blocks SKP2 activity, enhances autophagy and inhibits MERS-CoV replication [116,118]. A similar mechanism might be attributable to the inhibition of SARS CoV-2 infection by niclosamide. Likewise, human clinical studies of tilorone as a treatment for acute respiratory viral infections (ARVIs) have demonstrated 72% prophylactic efficacy in respiratory tract infections in humans [119].

4.2. Other miscellaneous drugs and drug like molecules

A recent study by researchers at Nanjing University, China, demonstrated that N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride (HTCC) possesses very good inhibitory activity against SARS-CoV-2 *in vitro* (CC_{50} = 158.0 μg/ml, IC_{50} 12.5 μg/ml, SI 12.6) and MERS-CoV (CC_{50} = 161.0 μg/ml, IC_{50} = 62.8 μg/ml, SI 2.6). These results suggest that HTCC can be a potential drug candidate for the treatment of COVID-19. However, HTCC drug is yet to be registered and approved for clinical use [120].

A team of researchers at the University of Frankfurt, Germany, reported that inhibition of glycolysis with low concentrations of 2-deoxy-D-glucose (2-DG, **115**) entirely blocked the replication of SARS-CoV-2 in Caco−2 cells, *in vitro*. The study found that infected host cells are manipulated by the virus to increase their dependence on glycolysis dramatically. However, the presence of 2-DG inhibits glycolysis as the decoy glucose, 2-DG, cannot be converted into energy. Thus the presence of low concentrations of 2-DG prevents the replication of SARS-CoV-2 [121].

Brilacidin (**116**) is an antibiotic currently being investigated for the treatment of inflammation of the oral mucosa (Phase-II clinical study) and inflammatory bowel disease. Brilacidin blocks VERO cells infection by the SARS-CoV-2 virus in a dose-dependent

manner relative to the control (DMSO) group. Brilacidin's ability to attack the outer envelope of the SARS-CoV2 appears to be the underlying mechanism by which it acts against SARS-CoV-2 [122,123].

Recently, another drug teicoplanin (**117**), a glycopeptide antibiotic, showed excellent *in vitro* inhibitory activity against SARS-CoV-2. Although the bactericidal activity of teicoplanin against gram-positive bacterial infections, especially staphylococcal infections is well-known, it has also shown efficacy against a variety of viruses such as Ebola virus, influenza virus, flavivirus, hepatitis C virus, HIV, and coronaviruses such as MERS-CoV and SARS-CoV. Teicoplanin showed a promising IC_{50} value of 1.66 μM against SARS-CoV-2, which is much lower than the concentration reached in human blood (8.78 μM for a daily dose of 400 mg). These initial results now need to be confirmed through a randomized clinical trial [124,125].

Many other approved antibiotics like ritavancin, dalbavancin, and monensin, and an anti-protozoal drug, emetine, have also been found to inhibit several coronaviruses and viruses belonging to other families, *in vitro,* and thus could be potentially repurposed for the treatment of COVID-19 [126].

Ivermectin, an FDA-approved, broad-spectrum anti-parasitic drug, was found to possess very good *in vitro* activity against SARS-CoV-2. A single dose of this drug in Vero-hSLAM cells, two hour post-SARS-CoV-2 infection was able to induce ~5000-fold reduction in viral RNA at 48 h. Antiviral activity of ivermectin is through inhibition of importin (IMP) Impα/β1 heterodimer mediated nuclear import of viral proteins [127].

Auranofin (118), an FDA-approved drug for the treatment of rheumatoid arthritis, has been investigated as a potential therapeutic agent for several diseases such as cancer, neurodegenerative disorders, HIV/AIDS, parasitic infections and bacterial infections. Recently, auranofin was approved by the FDA for Phase-II clinical trials in cancer patients [128]. In light of these developments, researchers studied the antiviral activity of aurnofin against SARS-CoV-2 and analysed its potential effect on virus-induced inflammation in human cells. Interestingly, the treatment of SARS-CoV-2 infected human cells with aurnofin resulted in a 95% reduction in the viral RNA load at 48 h. Auranofin treatment also attenuated the expression of SARS-CoV-2-induced cytokines in human cells [129].

Apilimod (LAM-002) (**119**), an inhibitor of the interleukins IL-12 and IL-23 production, was developed for the treatment of autoimmune conditions such as Crohn's disease and rheumatoid arthritis. However, apilimod gave disappointing results in clinical studies, and consequently further drug development was stopped. Apilimod is a phosphatidylinositol-3-phosphate 5-kinase (PIKfyve) lipid kinase inhibitor, and recent data suggests that inhibition of PIKfyve by apilimod significantly reduces SARS-CoV-2 pseudovirions entry into 293/hACE2 cells in a dose-dependent manner. Although apilimod exhibits activity as a single agent, it is more effective when used in combination with remdesivir [130,131].

5. Conclusion

This report provides a comprehensive review of the urgent global efforts, currently underway, towards the discovery and development of vaccines and therapeutic agents for the prevention and treatment of COVID-19. This review is specifically focused on the ongoing clinical and preclinical studies on the various vaccines, repurposed drugs, and other therapeutic agents being investigated as part of the urgent global response to control and combat the COVID-19 pandemic. The development of a vaccine seems to be the most promising approach in this respect. Drug repurposing is another important strategy for the development of an effective therapeutic against COVID-19 in a limited time-frame, and several known drugs, primarily antivirals, are currently undergoing clinical trials. Besides, researchers are also directing their efforts towards the identification of new targets for the discovery and development of vaccines and therapeutics against COVID-19. However, an effective vaccine or therapeutic is not expected anytime soon. We anticipate that in the coming months, biologists will identify new targets, and medicinal chemists will screen more drugs and molecular libraries against novel and existing targets in their efforts to find a cure for COVID-19.

Funding

The authors did not receive any specific funding for this work.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

References

[1] A.E. Gorbalenya, S.C. Baker, R.S. Baric, R.J. de Groot, C. Drosten, A.A. Gulyaeva, B.L. Haagmans, C. Lauber, A.M. Leontovich, B.W. Neuman, D. Penzar, S. Perlman, L.L.M. Poon, D.V. Samborskiy, I.A. Sidorov, I. Sola, J. Ziebuhr, The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2, Nat. Microbiol. (2020), https://doi.org/10.1038/s41564-020-0695-z.

[2] K. Kupferschmidt, J. Cohen, Will novel virus go pandemic or be contained? Science (80) (2020) https://doi.org/10.1126/science.367.6478.610.

[3] J.K. Taubenberger, D.M. Morens, Influenza: the mother of all pandemics, Emerg. Infect. Dis. (2006), https://doi.org/10.3201/eid1201.050979, 1918.

[4] P. Zhou, X. Lou Yang, X.G. Wang, B. Hu, L. Zhang, W. Zhang, H.R. Si, Y. Zhu, B. Li, C.L. Huang, H.D. Chen, J. Chen, Y. Luo, H. Guo, R. Di Jiang, M.Q. Liu, Y. Chen, X.R. Shen, X. Wang, X.S. Zheng, K. Zhao, Q.J. Chen, F. Deng, L.L. Liu, B. Yan, F.X. Zhan, Y.Y. Wang, G.F. Xiao, Z.L. Shi, A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature (2020), https://doi.org/10.1038/s41586-020-2012-7.

[5] Johns Hopkins Hospital and Medicine, Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU), Johns Hopkins Univ., 2020. https://coronavirus.jhu.edu/map.html.

[6] S.J. Anthony, C.K. Johnson, D.J. Greig, S. Kramer, X. Che, H. Wells, A.L. Hicks, D.O. Joly, N.D. Wolfe, P. Daszak, W. Karesh, W.I. Lipkin, S.S. Morse, J.A.K. Mazet, T. Goldstein, Global patterns in coronavirus diversity, Virus Evol (2017), https://doi.org/10.1093/ve/vex012.

[7] S. Su, G. Wong, W. Shi, J. Liu, A.C.K. Lai, J. Zhou, W. Liu, Y. Bi, G.F. Gao, Epidemiology, genetic recombination, and pathogenesis of coronaviruses, Trends Microbiol. (2016), https://doi.org/10.1016/j.tim.2016.03.003.

[8] G. Readfearn, How Did Coronavirus Start and where Did it Come from? Was it Really Wuhan's Animal Market? Guard, 2020. https://www.theguardian.com/world/2020/apr/28/how-did-the-coronavirus-start-where-did-it-come-from-how-did-it-spread-humans-was-it-really-bats-pangolins-wuhan-animal-market.

[9] D. Cyranoski, Mystery deepens over animal source of coronavirus, Nature (2020), https://doi.org/10.1038/d41586-020-00548-w.

[10] B. Tang, N.L. Bragazzi, Q. Li, S. Tang, Y. Xiao, J. Wu, An updated estimation of the risk of transmission of the novel coronavirus (2019-nCov), Infect. Dis. Model. (2020), https://doi.org/10.1016/j.idm.2020.02.001.

[11] Covid-19: One Third of Humanity under Virus Lockdown, Econ. Times, 2020. https://economictimes.indiatimes.com/news/international/world-news/covid-19-one-third-of-humanity-under-virus-lockdown/articleshow/74807030.cms.

[12] B. Shanmugaraj, K. Siriwattananon, K. Wangkanont, W. Phoolcharoen, Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19), Asian Pac. J. Allergy Immunol. (2020), https://doi.org/10.12932/AP-200220-0773.

[13] M. Cascella, M. Rajnik, A. Cuomo, S.C. Dulebohn, R. Di Napoli, Features, evaluation and treatment coronavirus (COVID-19) [Internet], in: In: StatPearls, StatPearls Publishing, Treasure Island (FL, 2020, https://www.ncbi.nlm.nih.gov/books/NBK554776/.

[14] A.R. Fehr, S. Perlman, Coronaviruses: an overview of their replication and pathogenesis, in: Coronaviruses Methods Protoc, 2015, pp. 1–23, https://doi.org/10.1007/978-1-4939-2438-7_1.

[15] World Health Organization, Q&A on Coronaviruses (COVID-19), Who, 2020. https://www.who.int/news-room/q-a-detail/q-a-on-on-covid-19-for-older-people.

[16] J.S. Morse, T. Lalonde, S. Xu, W.R. Liu, Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections

caused by 2019-nCoV, Chembiochem (2020), https://doi.org/10.1002/cbic.202000047.
[17] Landscape Analysis of Therapeutics as March 21 2020, 2020. https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1. (Accessed 21 June 2020).
[18] Draft Landscape of COVID-19 Candidate Vaccines, WHO, 2020. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. (Accessed 15 June 2020).
[19] A. Barlow, K.M. Landolf, B. Barlow, S.Y.A. Yeung, J.J. Heavner, C.W. Claassen, M.S. Heavner, Review of emerging pharmacotherapy for the treatment of coronavirus disease 2019, Pharmacotherapy (2020), https://doi.org/10.1002/phar.2398.
[20] M.P. Lythgoe, P. Middleton, Ongoing clinical trials for the management of the COVID-19 pandemic, Trends Pharmacol. Sci. (2020), https://doi.org/10.1016/j.tips.2020.03.006.
[21] J.M. Sanders, M.L. Monogue, T.Z. Jodlowski, J.B. Cutrell, Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review, JAMA, J. Am. Med. Assoc. (2020), https://doi.org/10.1001/jama.2020.6019.
[22] K. Thorlund, L. Dron, J. Park, G. Hsu, J.I. Forrest, E.J. Mills, A real-time dashboard of clinical trials for COVID-19, Lancet Digit. Heal. (2020), https://doi.org/10.1016/S2589-7500(20)30086-8.
[23] Y.F. Tu, C.S. Chien, A.A. Yarmishyn, Y.Y. Lin, Y.H. Luo, Y.T. Lin, W.Y. Lai, D.M. Yang, S.J. Chou, Y.P. Yang, M.L. Wang, S.H. Chiou, A review of sars-cov-2 and the ongoing clinical trials, Int. J. Mol. Sci. (2020), https://doi.org/10.3390/ijms21072657.
[24] T.S. Davis Js, D. Ferreira, J.T. Denholm, Clinical trials for the prevention and treatment of coronavirus disease 2019 (COVID-19): the current state of play, Med. J. Aust. — Prepr. (2020). https://www.mja.com.au/journal/2020/clinical-trials-prevention-and-treatment-coronavirus-disease-2019-covid-19-current.
[25] L.V. Tse, R.M. Meganck, R.L. Graham, R.S. Baric, The current and future state of vaccines, antivirals and gene therapies against emerging coronaviruses, Front. Microbiol. (2020), https://doi.org/10.3389/fmicb.2020.00658.
[26] Moderna Ships mRNA Vaccine against Novel Coronavirus (mRNA-1273) for Phase 1 Study, 2020. https://investors.modernatx.com/news-releases/news-release-details/moderna-ships-mrna-vaccine-against-novel-coronavirus-mrna-1273. (Accessed 5 June 2020).
[27] Moderna's Phase I Covid-19 mRNA Vaccine Has Manufacturing Edge but Many Obstacles to Confirm Protection Lay Ahead, 2020. https://www.clinicaltrialsarena.com/comment/modernas-phase-i-covid-19-mrna-vaccine-has-manufacturing-edge-but-many-obstacles-to-confirm-protection-lay-ahead/. (Accessed 5 June 2020).
[28] Moderna Announces Positive Interim Phase 1 Data for its mRNA Vaccine (mRNA-1273) against Novel Coronavirus, 2020. https://investors.modernatx.com/node/8986/pdf.
[29] Moderna Receives FDA Fast Track Designation for mRNA Vaccine (mRNA-1273) against Novel Coronavirus, 2020. https://investors.modernatx.com/news-releases/news-release-details/moderna-receives-fda-fast-track-designation-mrna-vaccine-mrna. (Accessed 21 June 2020).
[30] Moderna Announces First Participants in Each Age Cohort Dosed in Phase 2 Study of mRNA Vaccine (mRNA-1273) against Novel Coronavirus, 2020. https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-first-participants-each-age-cohort-dosed-phase. (Accessed 21 June 2020).
[31] CanSinoBIO's Investigational Vaccine against COVID-19 Approved for Phase 1 Clinical Trial in China, CanSinoBIO, 2020. http://www.cansinotech.com/homes/article/show/56/153.html. (Accessed 5 June 2020).
[32] China's CanSino Prepares to Advance COVID-19 Vaccine Candidate into Phase II, CanSinoBIO, 2020. http://www.cansinotech.com/homes/article/show/56/153.html. (Accessed 5 June 2020).
[33] CanSino Bio Enrols for Ph 2 Trial of COVID-19 Vaccine, 2020. https://www.biospectrumasia.com/news/37/15850/cansino-bio-enrols-for-ph-2-trial-of-covid-19-vaccine.html.
[34] Oxford COVID-19 Vaccine to Begin Phase II/III Human Trials, Univ. Oxford, 2020. http://www.ox.ac.uk/news/2020-05-22-oxford-covid-19-vaccine-begin-phase-iiiii-human-trials. (Accessed 5 June 2020).
[35] R. Carlson, INO-4800 DNA Coronavirus Vaccine, Precis. Vacciniation, 2020. https://www.precisionvaccinations.com/vaccines/ino-4800-dna-coronavirus-vaccine. (Accessed 5 June 2020).
[36] IVI and SNU Partner to Trial Inovio's Covid-19 Vaccine in Korea, 2020. https://www.clinicaltrialsarena.com/news/ivi-snu-inovio-vaccine-trial/. (Accessed 5 June 2020).
[37] Novavax Initiates Phase 1/2 Clinical Trial of COVID-19 Vaccine, 2020. http://ir.novavax.com/news-releases/news-release-details/novavax-initiates-phase-12-clinical-trial-covid-19-vaccine. (Accessed 5 June 2020).
[38] Sinovac Announces Positive Preliminary Results of Phase I/II Clinical Trials for Inactivated Vaccine Candidate against COVID-19, 2020. https://pipelinereview.com/index.php/2020061474985/Vaccines/Sinovac-Announces-Positive-Preliminary-Results-of-Phase-I/II-Clinical-Trials-for-Inactivated-Vaccine-Candidate-Against-COVID-19.html. (Accessed 17 June 2020).
[39] Q. Gao, L. Bao, H. Mao, L. Wang, K. Xu, M. Yang, Y. Li, L. Zhu, N. Wang, Z. Lv, H. Gao, X. Ge, B. Kan, Y. Hu, J. Liu, F. Cai, D. Jiang, Y. Yin, C. Qin, J. Li, X. Gong, X. Lou, W. Shi, D. Wu, H. Zhang, L. Zhu, W. Deng, Y. Li, J. Lu, C. Li, X. Wang, W. Yin, Y. Zhang, C. Qin, Development of an inactivated vaccine candidate for SARS-CoV-2, Science (2020), https://doi.org/10.1126/science.abc1932.
[40] S. Naylor, D.M. Kauppi, J.M. Schonfeld, Therapeutic Drug Repurposing, Repositioning and Rescue: Part II: Business Review, Drug Discov. World, 2015.
[41] S.L. Senanayake, Drug repurposing strategies for COVID-19, Futur. Drug Discov (2020), https://doi.org/10.4155/fdd-2020-0010.
[42] D. Guo, Old weapon for new enemy: drug repurposing for treatment of newly emerging viral diseases, Virol. Sin. (2020), https://doi.org/10.1007/s12250-020-00204-7.
[43] S. Pushpakom, F. Iorio, P.A. Eyers, K.J. Escott, S. Hopper, A. Wells, A. Doig, T. Guilliams, J. Latimer, C. McNamee, A. Norris, P. Sanseau, D. Cavalla, M. Pirmohamed, Drug repurposing: progress, challenges and recommendations, Nat. Rev. Drug Discov. (2018), https://doi.org/10.1038/nrd.2018.168.
[44] P. Zhai, Y. Ding, X. Wu, J. Long, Y. Zhong, Y. Li, The epidemiology, diagnosis and treatment of COVID-19, Int. J. Antimicrob. Agents (2020), https://doi.org/10.1016/j.ijantimicag.2020.105955.
[45] B. Cao, Y. Wang, D. Wen, W. Liu, J. Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, H. Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, H. Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, J. Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, C. Wang, A trial of lopinavir–ritonavir in adults hospitalized with severe covid-19, N. Engl. J. Med. (2020), https://doi.org/10.1056/NEJMoa2001282.
[46] I.F.N. Hung, K.C. Lung, E.Y.K. Tso, R. Liu, T.W.H. Chung, M.Y. Chu, Y.Y. Ng, J. Lo, J. Chan, A.R. Tam, H.P. Shum, V. Chan, A.K.L. Wu, K.M. Sin, W.S. Leung, W.L. Law, D.C. Lung, S. Sin, P. Yeung, C.C.Y. Yip, R.R. Zhang, A.Y.F. Fung, E.Y.W. Yan, K.H. Leung, J.D. Ip, A.W.H. Chu, W.M. Chan, A.C.K. Ng, R. Lee, K. Fung, A. Yeung, T.C. Wu, J.W.M. Chan, W.W. Yan, W.M. Chan, J.F.W. Chan, A.K.W. Lie, O.T.Y. Tsang, V.C.C. Cheng, T.L. Que, C.S. Lau, K.H. Chan, K.K.W. To, K.Y. Yuen, Triple combination of interferon beta-1b, lopinavir—ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial, Lancet (2020), https://doi.org/10.1016/S0140-6736(20)31042-4.
[47] R.U. Kadam, I.A. Wilson, Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol, Proc. Natl. Acad. Sci. U.S.A. (2017), https://doi.org/10.1073/pnas.1617020114.
[48] G. Li, E. De Clercq, Therapeutic options for the 2019 novel coronavirus (2019-nCoV), Nat. Rev. Drug Discov. (2020), https://doi.org/10.1038/d41573-020-00016-0.
[49] The Efficacy of Lopinavir Plus Ritonavir and Arbidol against Novel Coronavirus Infection, ELACOI, 2020. https://clinicaltrials.gov/ct2/show/NCT04252885. (Accessed 5 June 2020).
[50] Y. Li, Z. Xie, W. Lin, W. Cai, C. Wen, Y. Guan, X. Mo, J. Wang, Y. Wang, P. Peng, X. Chen, W. Hong, G. Xiao, J. Liu, L. Zhang, F. Hu, F. Li, F. Zhang, X. Deng, L. Li, Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial, Med (2020), https://doi.org/10.1016/j.medj.2020.04.001.
[51] S. De Meyer, D. Bojkova, J. Cinatl, E. Van Damme, C.B. Meng, M. Van Loock, B. Woodfall, S. Ciesek, Lack of antiviral activity of darunavir against SARS-CoV-2, Int. J. Infect. Dis. (2020), https://doi.org/10.1016/j.ijid.2020.05.085.
[52] J&J Says No Evidence Darunavir Works against Coronavirus, 2020. https://www.pharmaceutical-technology.com/news/jj-janssen-darunavir-coronavirus/. (Accessed 5 June 2020).
[53] Clinical Study for Safety and Efficacy of Favipiravir in the Treatment of Novel Coronavirus Pneumonia (COVID-19), 2020. http://www.chictr.org.cn/showprojen.aspx?proj=49042. (Accessed 5 June 2020).
[54] A. Maxmen, More than 80 clinical trials launch to test coronavirus treatments, Nature (2020), https://doi.org/10.1038/d41586-020-00444-3.
[55] Q. Cai, M. Yang, D. Liu, J. Chen, D. Shu, J. Xia, X. Liao, Y. Gu, Q. Cai, Y. Yang, C. Shen, X. Li, L. Peng, D. Huang, J. Zhang, S. Zhang, F. Wang, J. Liu, L. Chen, S. Chen, Z. Wang, Z. Zhang, R. Cao, W. Zhong, Y. Liu, L. Liu, Experimental treatment with favipiravir for COVID-19: an open-label control study, Engineering (2020), https://doi.org/10.1016/j.eng.2020.03.007.
[56] C. Chen, J. Huang, Z. Cheng, J. Wu, S. Chen, Y. Zhang, B. Chen, M. Lu, Y. Luo, J. Zhang, P. Yin, X. Wang, Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial, MedRxiv, 2020, https://doi.org/10.1101/2020.03.17.20037432.
[57] Russia's ChemRar Reports Positive Data of Favipiravir in Covid-19, Clin. Trials Arena, 2020. https://www.clinicaltrialsarena.com/news/chemrar-rdif-favipiravir-data/. (Accessed 8 June 2020).
[58] WHO Director-General's Opening Remarks at the Media Briefing on COVID-19 - 18 March 2020, 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—18-march-2020. (Accessed 5 June 2018).
[59] B.E. Young, S.W.X. Ong, S. Kalimuddin, J.G. Low, S.Y. Tan, J. Loh, O.T. Ng, K. Marimuthu, L.W. Ang, T.M. Mak, S.K. Lau, D.E. Anderson, K.S. Chan, T.Y. Tan, T.Y. Ng, L. Cui, Z. Said, L. Kurupatham, M.I.C. Chen, M. Chan, S. Vasoo, L.F. Wang, B.H. Tan, R.T.P. Lin, V.J.M. Lee, Y.S. Leo, D.C. Lye, Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore, JAMA, J. Am. Med. Assoc. (2020), https://doi.org/10.1001/jama.2020.3204.
[60] P.L.L.M. Chu C M, V.C.C. Cheng, I.F.N. Hung, M.M.L. Wong, K.H. Chan, K.S. Chan, R.Y.T. Kao, Y.K.Y. Wong C L P, Y. Guan, J.S.M. Peiris, Role of

lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings, Thorax 59 (2004) 252–256, https://doi.org/10.1136/thorax.2003.012658.
[61] The Hydroxychloroquine Debate Continues, Clin. Trials Arena, 2020. https://www.clinicaltrialsarena.com/comment/hydroxychloroquine-debate-covid-19/. (Accessed 19 June 2020).
[62] A. Cortegiani, G. Ingoglia, M. Ippolito, A. Giarratano, S. Einav, A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19, J. Crit. Care (2020), https://doi.org/10.1016/j.jcrc.2020.03.005.
[63] Efficacy and Safety of Hydroxychloroquine for Treatment of COVID-19, Clinicaltrials.Gov, 2020. https://www.clinicaltrials.gov/ct2/show/NCT04261517. (Accessed 15 June 2020).
[64] P. Gautret, J.-C. Lagier, P. Parola, V.T. Hoang, L. Meddeb, M. Mailhe, B. Doudier, J. Courjon, V. Giordanengo, V.E. Vieira, H.T. Dupont, S. Honoré, P. Colson, E. Chabrière, B. La Scola, J.-M. Rolain, P. Brouqui, D. Raoult, Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, Int. J. Antimicrob. Agents (2020), https://doi.org/10.1016/j.ijantimicag.2020.105949.
[65] M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, Z. Shi, Z. Hu, W. Zhong, G. Xiao, Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro, Cell Res. (2020), https://doi.org/10.1038/s41422-020-0282-0.
[66] J. Chen, D. Liu, L. Liu, P. Liu, Q. Xu, L. Xia, Y. Ling, D. Huang, S. Song, D. Zhang, Z. Qian, T. Li, Y. Shen, H. Lu, A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19, J. Zhejiang Univ. 49 (2020) 215–219.
[67] Z. Chen, J. Hu, Z. Zhang, S. Jiang, S. Han, D. Yan, R. Zhuang, B. Hu, Z. Zhang, Efficacy of Hydroxychloroquine in Patients with COVID-19: Results of a Randomized Clinical Trial, MedRxiv, 2020, https://doi.org/10.1101/2020.03.22.20040758.
[68] J. Magagnoli, S. Narendran, F. Pereira, T.H. Cummings, J.W. Hardin, S.S. Sutton, J. Ambati, Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19, Med (2020), https://doi.org/10.1016/j.medj.2020.06.001.
[69] J. Geleris, Y. Sun, J. Platt, J. Zucker, M. Baldwin, G. Hripcsak, A. Labella, D.K. Manson, C. Kubin, R.G. Barr, M.E. Sobieszczyk, N.W. Schluger, Observational study of hydroxychloroquine in hospitalized patients with covid-19, N. Engl. J. Med. (2020), https://doi.org/10.1056/nejmoa2012410.
[70] Q&A : Hydroxychloroquine and COVID-19, 2020. https://www.who.int/news-room/q-a-detail/q-a-hydroxychloroquine-and-covid-19.
[71] Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and.
[72] L.P. Jordheim, D. Durantel, F. Zoulim, C. Dumontet, Advances in the development of nucleoside and nucleotide analogues for cancer and viral diseases, Nat. Rev. Drug Discov. (2013), https://doi.org/10.1038/nrd4010.
[73] Early peek at data on Gilead coronavirus drug suggests patients are responding to treatment, Stat (2020). https://www.statnews.com/2020/04/16/early-peek-at-data-on-gilead-coronavirus-drug-suggests-patients-are-responding-to-treatment/.
[74] J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, H.C. Lane, Remdesivir for the treatment of covid-19 — preliminary report, N. Engl. J. Med. (2020), https://doi.org/10.1056/nejmoa2007764.
[75] Gilead Announces Results from Phase 3 Trial of Investigational Antiviral Remdesivir in Patients with Severe COVID-19, 2020. https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-covid-19. (Accessed 19 June 2020).
[76] Gilead's Suspension of Covid-19 Trials in China Should Serve as a Bellwether for Studies in Other Countries, Clin. Trials Arena, 2020. https://www.clinicaltrialsarena.com/comment/gilead-remdesivir-covid-19-china-trials/.
[77] Montefiore and Einstein Assess Remdesivir and Baricitinib for Covid-19, Clin. Trials Arena, 2020. https://www.clinicaltrialsarena.com/news/remdesivir-plus-baricitinib-covid-19/. (Accessed 17 June 2019).
[78] Global Coronavirus COVID-19 Clinical Trial Tracker, 2020. https://www.covid-trials.org/. (Accessed 29 June 2020).
[79] A.K. Singh, A. Singh, R. Singh, A. Misra, Remdesivir in COVID-19: a critical review of pharmacology, pre-clinical and clinical studies, Diabetes Metab. Syndr. Clin. Res. Rev. (2020), https://doi.org/10.1016/j.dsx.2020.05.018.
[80] Recovery: Randomized Evaluation of COVID-19 Therapy, 2020. https://www.recoverytrial.net/. (Accessed 19 June 2020).
[81] COVID-19 Treatments Could Be Fast-Tracked through New National Clinical Trial Initiative, Gov, UK, 2020. https://www.gov.uk/government/news/covid-19-treatments-could-be-fast-tracked-through-new-national-clinical-trial-initiative. (Accessed 5 June 2020).
[82] P. Horby, W.S. Lim, J. Emberson, M. Mafham, J. Bell, L. Linsell, N. Staplin, C. Brightling, A. Ustianowski, E. Elmahi, B. Prudon, C. Green, T. Felton, D. Chadwick, K. Rege, C. Fegan, L.C. Chappell, S.N. Faust, T. Jaki, K. Jeffery, A. Montgomery, K. Rowan, E. Juszczak, J.K. Baillie, R. Haynes, M.J. Landray, Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report, MedRxiv, 2020, https://doi.org/10.1101/2020.06.22.20137273.
[83] World Health Organization, WHO Director-General's Opening Remarks at the Media Briefing on COVID-19., 2020.
[84] E. Mahase, Covid-19: demand for dexamethasone surges as RECOVERY trial publishes preprint, BMJ 369 (2020) m2512, https://doi.org/10.1136/bmj.m2512.
[85] World First Coronavirus Treatment Approved for NHS Use by Government, 2020. https://www.gov.uk/government/news/world-first-coronavirus-treatment-approved-for-nhs-use-by-government. (Accessed 29 September 2020).
[86] B.S. Perappadan, Coronavirus | Government Approves Use of Dexamethasone, the Hindu, 2020. https://www.thehindu.com/news/national/coronavirus-india-approves-use-of-dexamethasone/article31934249.ece.
[87] BerGenBio Starts Bemcentinib Dosing in ACCORD Trial, Clin. Trials Arena, 2020. https://www.clinicaltrialsarena.com/news/bergenbio-bemcentinib-accord-dosing/. (Accessed 17 June 2020).
[88] Major COVID-19 Drugs Trial Begins in Birmingham, 2020. https://www.birmingham.ac.uk/news/latest/2020/05/major-covid-drugs-trial-begins-in-birmingham.aspx. (Accessed 15 June 2020).
[89] Namilumab and Infliximab Selected for CATALYST Trial in UK, Clin. Trials Arena, 2020. https://www.clinicaltrialsarena.com/news/catalyst-trial-first-two-candidates/. (Accessed 17 June 2020).
[90] A. Muehler, E. Peelen, H. Kohlhof, M. Gröppel, D. Vitt, Vidofludimus calcium, a next generation DHODH inhibitor for the Treatment of relapsing-remitting multiple sclerosis, Mult. Scler. Relat. Disord. (2020), https://doi.org/10.1016/j.msard.2020.102129.
[91] Immunic, Inc, Receives first regulatory approval from German health authority BfArM to initiate a phase 2 clinical trial of its selective oral DHODH inhibitor, IMU-838, in: COVID-19 Patients, 2020. https://www.immunic-therapeutics.com/2020/05/13/immunic-inc-receives-first-regulatory-approval-from-german-health-authority-bfarm-to-initiate-a-phase-2-clinical-trial-of-its-selective-oral-dhodh-inhibitor-imu-838-in-covid-19-patients/. (Accessed 15 June 2020).
[92] Germany's BfArM Approves Covid-19 Trial by Immunic, 2020. https://www.clinicaltrialsarena.com/news/immunic-covid-19-trial-germany/. (Accessed 15 June 2020).
[93] Immunic, Inc, Announces First Patients Dosed in its Phase 2, CALVID-1 Clinical Trial of IMU-838 in COVID-19, BioSpace, 2020. https://www.biospace.com/article/releases/immunic-inc-announces-first-patients-dosed-in-its-phase-2-calvid-1-clinical-trial-of-imu-838-in-covid-19/. (Accessed 17 June 2020).
[94] Austrian CoronaVirus Adaptive Clinical Trial (COVID-19) (ACOVACT), 2020. https://clinicaltrials.gov/ct2/show/NCT04351724. (Accessed 17 June 2020).
[95] C. Wang, W. Li, D. Drabek, N.M.A. Okba, R. van Haperen, A.D.M.E. Osterhaus, F.J.M. van Kuppeveld, B.L. Haagmans, F. Grosveld, B.J. Bosch, A human monoclonal antibody blocking SARS-CoV-2 infection, Nat. Commun. (2020), https://doi.org/10.1038/s41467-020-16256-y.
[96] D. Wrapp, N. Wang, K.S. Corbett, J.A. Goldsmith, C.L. Hsieh, O. Abiona, B.S. Graham, J.S. McLellan, Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation, Science (80) (2020), https://doi.org/10.1126/science.aax0902.
[97] A.C. Walls, Y.J. Park, M.A. Tortorici, A. Wall, A.T. McGuire, D. Veesler, Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein, Cell (2020), https://doi.org/10.1016/j.cell.2020.02.058.
[98] A.C. Walls, X. Xiong, Y.J. Park, M.A. Tortorici, J. Snijder, J. Quispe, E. Cameroni, R. Gopal, M. Dai, A. Lanzavecchia, M. Zambon, F.A. Rey, D. Corti, D. Veesler, Unexpected receptor functional mimicry elucidates activation of coronavirus fusion, Cell (2019), https://doi.org/10.1016/j.cell.2018.12.028.
[99] Roche Initiates Phase III Clinical Trial of Actemra/RoActemra Plus Remdesivir in Hospitalised Patients with Severe COVID-19 Pneumonia, 2020. https://www.roche.com/media/releases/med-cor-2020-05-28.htm. (Accessed 15 June 2020).
[100] Genentech Announces FDA Approval of Clinical Trial for Actemra to Treat Hospitalized Patients with Severe COVID-19 Pneumonia, 2020. https://www.gene.com/media/press-releases/14843/2020-03-23/genentech-announces-fda-approval-of-clin. (Accessed 15 June 2020).
[101] X. Xu, M. Han, T. Li, W. Sun, D. Wang, B. Fu, Y. Zhou, X. Zheng, Y. Yang, X. Li, X. Zhang, A. Pan, H. Wei, Effective treatment of severe COVID-19 patients with tocilizumab, Proc. Natl. Acad. Sci. U.S.A. (2020), https://doi.org/10.1073/pnas.2005615117.
[102] Actemra Use in Coronavirus Disease 2019 (COVID-19), 2020. https://medinfo.roche.com/content/dam/medinfo/documents/covid-19/Actemra_GL-019952.pdf.
[103] H. Bian, Z.-H. Zheng, D. Wei, Z. Zhang, W.-Z. Kang, C.-Q. Hao, K. Dong, W. Kang, J.-L. Xia, J.-L. Miao, R.-H. Xie, B. Wang, X.-X. Sun, X.-M. Yang, P. Lin, J.-J. Geng, K. Wang, H.-Y. Cui, K. Zhang, X.-C. Chen, H. Tang, H. Du, N. Yao, S.-S. Liu, L.-N. Liu, Z. Zhang, Z.-W. Gao, G. Nan, Q.-Y. Wang, J.-Q. Lian, Z.-N. Chen, P. Zhu, Meplazumab Treats COVID-19 Pneumonia: an Open-Labelled, Concurrent Controlled Add-On Clinical Trial, 2020, https://doi.org/10.1101/2020.03.21.20040691.
[104] Z. Temesgen, M. Assi, P. Vergidis, S.A. Rizza, P.R. Bauer, B.W. Pickering, R.R. Razonable, C.R. Libertin, C.D. Burger, R. Orenstein, H.E. Vargas, B.R.V. Palraj, A.S. Dababneh, G. Chappell, D. Chappell, O. Ahmed, R. Sakemura,

C. Durrant, S.S. Kenderian, A. Badley, First Clinical Use of Lenzilumab to Neutralize GM-CSF in Patients with Severe COVID-19 Pneumonia, MedRxiv, 2020, https://doi.org/10.1101/2020.06.08.20125369.
[105] F. Zheng, Y. Zhou, Z. Zhou, F. Ye, B. Huang, Y. Huang, J. Ma, Q. Zuo, X. Tan, J. Xie, P. Niu, W. Wang, Y. Xu, F. Peng, N. Zhou, C. Cai, W. Tang, X. Xiao, Y. Li, Z. Zhou, Z. Zhou, Y. Jiang, Y. Xie, W. Tan, G. Gong, A novel protein drug, novaferon, as the potential, Antiviral Drug for COVID-19 (2020), https://doi.org/10.1101/2020.04.24.20077735.
[106] aTyr Pharma Announces Phase 2 Study of ATYR1923 in COVID-19 Patients with Severe Respiratory Complications Following FDA Acceptance of IND Application, GlobeNewswire, 2020. https://www.globenewswire.com/news-release/2020/04/21/2019306/0/en/aTyr-Pharma-Announces-Phase-2-Study-of-ATYR1923-in-COVID-19-Patients-with-Severe-Respiratory-Complications-Following-FDA-Acceptance-of-IND-Application.html.
[107] A. Maxmen, How blood from coronavirus survivors might save lives, Nature (2020), https://doi.org/10.1038/d41586-020-00895-8.
[108] A. Casadevall, L.A. Pirofski, The convalescent sera option for containing COVID-19, J. Clin. Invest. (2020), https://doi.org/10.1172/JCI138003.
[109] US Study Finds Convalescent Plasma Safe for Covid-19 Patients, Clin. Trials Arena, 2020. https://www.clinicaltrialsarena.com/news/convalescent-plasma-early-data/. (Accessed 19 June 2020).
[110] Trials of Mw Vaccine for Treatment of Covid-19 Patients to Be Initiated Soon: PGIMER Chandigarh, India Today, 2020. https://www.indiatoday.in/india/story/trials-of-mw-vaccine-for-treatment-of-covid-19-patients-to-be-initiated-soon-pgimer-chandigarh-1671370-2020-04-26.
[111] L. Dong, S. Hu, J. Gao, Discovering drugs to treat coronavirus disease 2019 (COVID-19), Drug Discov. Ther. (2020), https://doi.org/10.5582/ddt.2020.01012.
[112] A.A. Elfiky, Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study, Life Sci. 253 (2020), https://doi.org/10.1016/j.lfs.2020.117592.
[113] T.P. Sheahan, A.C. Sims, S. Zhou, R.L. Graham, A.J. Pruijssers, M.L. Agostini, S.R. Leist, A. Schäfer, K.H. Dinnon, L.J. Stevens, J.D. Chappell, X. Lu, T.M. Hughes, A.S. George, C.S. Hill, S.A. Montgomery, A.J. Brown, G.R. Bluemling, M.G. Natchus, M. Saindane, A.A. Kolykhalov, G. Painter, J. Harcourt, A. Tamin, N.J. Thornburg, R. Swanstrom, M.R. Denison, R.S. Baric, An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice, Sci. Transl. Med. (2020), https://doi.org/10.1126/scitranslmed.abb5883.
[114] J. Xu, P.Y. Shi, H. Li, J. Zhou, Broad spectrum antiviral agent niclosamide and its therapeutic potential, ACS Infect. Dis. (2020), https://doi.org/10.1021/acsinfecdis.0c00052.
[115] C.C. Wen, Y.H. Kuo, J.T. Jan, P.H. Liang, S.Y. Wang, H.G. Liu, C.K. Lee, S.T. Chang, C.J. Kuo, S.S. Lee, C.C. Hou, P.W. Hsiao, S.C. Chien, L.F. Shyur, N.S. Yang, Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus, J. Med. Chem. (2007), https://doi.org/10.1021/jm070295s.
[116] N.C. Gassen, D. Niemeyer, D. Muth, V.M. Corman, S. Martinelli, A. Gassen, K. Hafner, J. Papies, K. Mösbauer, A. Zellner, A.S. Zannas, A. Herrmann, F. Holsboer, R. Brack-Werner, M. Boshart, B. Müller-Myhsok, C. Drosten, M.A. Müller, T. Rein, SKP2 attenuates autophagy through Beclin1-ubiquitination and its inhibition reduces MERS-Coronavirus infection, Nat. Commun. (2019), https://doi.org/10.1038/s41467-019-13659-4.
[117] S. Jeon, M. Ko, J. Lee, I. Choi, S.Y. Byun, S. Park, D. Shum, S. Kim, Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs, Antimicrob, Agents Chemother (2020), https://doi.org/10.1128/AAC.00819-20.
[118] C.J. Wu, J.T. Jan, C.M. Chen, H.P. Hsieh, D.R. Hwang, H.W. Liu, C.Y. Liu, H.W. Huang, S.C. Chen, C.F. Hong, R.K. Lin, Y.S. Chao, J.T.A. Hsu, Inhibition of severe acute respiratory syndrome coronavirus replication by niclosamide, Antimicrob. Agents Chemother. (2004), https://doi.org/10.1128/AAC.48.7.2693-2696.2004.
[119] S. Ekins, T.R. Lane, P.B. Madrid, Tilorone: a broad-spectrum antiviral invented in the USA and commercialized in Russia and beyond, Pharm. Res. (N. Y.) (2020), https://doi.org/10.1007/s11095-020-02799-8.
[120] A. Milewska, Y. Chi, A. Szczepanski, E. Barreto-Duran, K. Liu, D. Liu, X. Guo, Y. Ge, J. Li, L. Cui, M. Ochman, M. Urlik, S. Rodziewicz-Motowidlo, F. Zhu, K. Szczubialka, M. Nowakowska, K. Pyrc, HTCC as a highly effective polymeric inhibitor of SARS-CoV-2 and MERS-CoV, BioRxiv (2020), https://doi.org/10.1101/2020.03.29.014183.
[121] D. Bojkova, K. Klann, B. Koch, M. Widera, D. Krause, S. Ciesek, J. Cinatl, C. Münch, SARS-CoV-2 infected host cell proteomics reveal potential therapy targets, Res. Sq. (2020), https://doi.org/10.21203/rs.3.rs-17218/v1.
[122] Brilacidin, Background and Scientific Rationale for Brilacidin as a Potential Novel Coronavirus (COVID-19) Treatment, 2020. https://static1.squarespace.com/static/5715352e20c647639137f992/t/5e9cebd48660e44c2754fa00/1587342453349/Brilacidin+for+COVID-19+Overview+-+MOA%2C+PreClinical+Data%2C+Academic+Literature+-+4.20.20.pdf. (Accessed 15 June 2020).
[123] Vanquishing the Virus: 160+ COVID-19 Drug and Vaccine Candidates in Development, 2020. https://www.genengnews.com/a-lists/vanquishing-the-virus-160-covid-19-drug-and-vaccine-candidates-in-development/.
[124] J. Zhang, X. Ma, F. Yu, J. Liu, F. Zou, T. Pan, H. Zhang, Teicoplanin Potently Blocks the Cell Entry of 2019-nCoV, BioRxiv, 2020, https://doi.org/10.1101/2020.02.05.935387.
[125] S.A. Baron, C. Devaux, P. Colson, D. Raoult, J.M. Rolain, Teicoplanin: an alternative drug for the treatment of COVID-19? Int. J. Antimicrob. Agents (2020) https://doi.org/10.1016/j.ijantimicag.2020.105944.
[126] P.I. Andersen, A. Ianevski, H. Lysvand, A. Vitkauskiene, V. Oksenych, M. Bjørås, K. Telling, I. Lutsar, U. Dumpis, Y. Irie, T. Tenson, A. Kantele, D.E. Kainov, Discovery and development of safe-in-man broad-spectrum antiviral agents, Int. J. Infect. Dis. (2020), https://doi.org/10.1016/j.ijid.2020.02.018.
[127] L. Caly, J.D. Druce, M.G. Catton, D.A. Jans, K.M. Wagstaff, The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro, Antivir. Res. (2020), https://doi.org/10.1016/j.antiviral.2020.104787.
[128] C. Roder, M.J. Thomson, Auranofin: repurposing an old drug for a golden new age, Drugs R (2015), https://doi.org/10.1007/s40268-015-0083-y.
[129] H.A. Rothan, S. Stone, J. Natekar, P. Kumari, K. Arora, M. Kumar, The FDA-approved gold drug auranofin inhibits novel coronavirus (SARS-COV-2) replication and attenuates inflammation in human cells, Virology (2020), https://doi.org/10.1016/j.virol.2020.05.002.
[130] A. Billich, Drug evaluation: apilimod, an oral IL-12/IL-23 inhibitor for the treatment of autoimmune diseases and common variable immunodeficiency, Idrugs (2007).
[131] X. Ou, Y. Liu, X. Lei, P. Li, D. Mi, L. Ren, L. Guo, R. Guo, T. Chen, J. Hu, Z. Xiang, Z. Mu, X. Chen, J. Chen, K. Hu, Q. Jin, J. Wang, Z. Qian, Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV, Nat. Commun. (2020), https://doi.org/10.1038/s41467-020-15562-9.