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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Chapter 6

Therapeutic options in coronavirus treatment: COVID-19 drug discovery update

Suchetana Mukherjee[1] and Dwaipayan Sinha[2]
[1]*Department of Botany, Sripat Singh College, Jiaganj, Murshidabad, West Bengal, India;*
[2]*Department of Botany, Government General Degree College, Mohanpur, Paschim Medinipur, West Bengal, India*

Chapter outline

6.1 Introduction

Pandemics and epidemics have repeated itself several times in the history of human civilization causing a huge toll of life, of which novel coronavirus disease 2019 (nCOVID-19) needs a special mention due to the severe damage caused by it to human population. It is a threat that has put the entire world to a

Coronavirus Drug Discovery. https://doi.org/10.1016/B978-0-323-85156-5.00021-3
Copyright © 2022 Elsevier Inc. All rights reserved.

turmoil. Bats and pangolins are proposed to be its possible biotic reservoir. The extreme contagiousness of the virus promotes its rapid spread and continuous evolution in human population [1].

Coronavirus (CoV) is a member of the enveloped, single-stranded, positive-sense RNA viruses. It was first reported in humans in the mid-1960s mostly causing respiratory tract infection [2]. In the 21st century, three coronaviruses—the severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—have been a global threat to human health.

SARS-CoV-2 which causes COVID-19 is the product of natural evolution [3]. COVID-19 was reported for the first time on December 27, 2019 at Wuhan hospital, China. Till mid 2020, no vaccine has been reported for the management of the infection, but some treatment options based on previous experiences of viral threats have been proposed for COVID-19.

The RNA genome of SARS-CoV-2 contains a 5′-methyl-guanosine cap, poly (A)-tail, and 29,903 nucleotides according to WH-Human 1 coronavirus. It is classified as a beta-coronavirus (βCoV) (lineage B) and is the seventh coronavirus to infect humans, following 2 αCoV (HCoV-229E and HKU-NL63) and 4 βCoV (HCoV-OC43 [lineage A], HCoV-HKU1 [lineage A]), whereas SARS-CoV and MERS-CoV belong to lineage B and lineage C, respectively [1]. This chapter is an attempt to highlight the initial treatment pattern and strategies to combat COVID-19 . The chapter elaborates the transmission of SARS-CoV and various drugs which acted as initial resort for the treatment of the disease.

6.2 Novel coronavirus 2019

Coronaviruses belong to the *Coronaviridae* family and the order *Nidovirales*. They have the capacity of infecting a wide range of hosts namely birds, wild, and domesticated animal species [4]. These viruses have the capability of rapid mutation, alteration of tissue tropism, crossing of species barrier, and adapting to different epidemiological conditions [5]. Coronaviruses are the causal agent of gastrointestinal tract and respiratory infections and are represented by four genera, namely, alpha-CoV, beta-CoV, gamma-CoV, and delta-CoV. Among them, alpha- and beta-coronaviruses are known to infect mammals, gamma-coronavirus infect avians, and delta-coronavirus infects both mammals and avians. Representatives of alpha-coronavirus comprise of HCoV-NL63, TGEV, porcine epidemic diarrhea virus (PEDV), and PRCV, whereas SARS-CoV, MERS-CoV, bat coronavirus HKU4, MHV, BCoV, and human coronavirus OC43 belong to the group of beta-coronavirus. The bronchitis CoV (IBV) and porcine delta CoV (PdCV) falls in the group of delta-coronaviruses [6]. Among all the coronavirus variants, the SARS-CoV and MERS CoV have posed serious public health concerns due to their zoonotic emergence and the

ability to cross species barrier, resulting in high pathogenicity and mortality in humans [5]. SARS-CoV-2 is a positive-sense RNA virus that performs its replication through multi-subunit replication/transcription complex composed of nonstructural proteins (NSPs). The NSP12 is the catalytic subunit and forms the core of the complex which is composed of an RNA-dependent RNA polymerase (RdRp). It requires accessory factors such as NSP7 and NSP8 for its full activity [7]. The coronaviruses possess the largest genomes among all RNA viruses with G + C content varying for 32%−43% [8]. The genome of coronavirus ranges from 26,000 bases to 32,000 bases and includes 6−11 open reading frame (ORF). The first ORF is composed of about 67% of the total genome encoding 16 NSPs while the remaining ORFs encode structural and accessory proteins. The crucial structural proteins encoded by the virus are S (spike surface glycoprotein), E (small envelope protein), M (matrix protein), and N (nucleocapsid protein) proteins. The S proteins help in host cell receptor binding and determine the tropism of the host [9]. The spike protein contains three parts, namely, an ectodomain, a membrane spanning anchor, and an intracellular tail. The ectodomain is further cleaved into two parts, namely S1, which helps in attachment to the receptor, and S2, which is responsible for membrane fusion during the process of molecular maturation. The spike proteins either bind to the protein receptors or glycans in different species of coronavirus [10]. The recent pandemic can be traced back to Wuhan, Hubei Province of China, where reports of cluster of patients having pneumonia of undetermined reason which were epidemiologically linked to sea food and wet animal wholesale market of Wuhan in December 2019. Consequently, an unknown beta-coronavirus was discovered from human respiratory epithelial cells through unbiased sequencing in samples of patients suffering from pneumonia. This led to the isolation of a distinct biological group which falls in the subgenus of *Sarbecovirus* and subfamily *Orthocoronavirinae* and named as 2019-nCoV, a novel coronavirus [10].

6.2.1 Spread of COVID-19

On December 8, 2019, many patients with pneumonia of unknown cause were reported in Wuhan, Hubei province, China. It was further observed that most of the affected patients were associated to a local wholesale market in Huanan selling seafood and other wet animals. The patients suffered from pneumonia, respiratory infections, and some patients got affected by acute respiratory distress syndrome accompanied by severe respiratory failure. On January 7, novel coronavirus was identified from a throat swab of a patient at the Chinese Center for Disease Control and Prevention [11]. Furthermore, WHO declared the disease a health emergency of global concern in January 2020 and officially named the disease as coronavirus disease 2019 (COVID-19) on February 12, 2020 [12]. During the month of January 2020, about 33 Chinese provinces reported approximately 5900 confirmed and 9000 suspected COVID

cases with a death toll of 106 [13]. On January 31, 2020, China reported 11,791 confirmed cases and 17,988 suspected cases in 34 provinces [14]. The spread of COVID-19 was rapid and it crossed the geopolitical borders of China in January 2020 itself and confirmed cases were reported in 19 countries across the globe namely Australia, Canada, Cambodia, France, Finland, Germany, India, Italy, Japan, Nepal, Malaysia, the Philippines, the Republic of Korea, Singapore, Sri Lanka, Thailand, United Arab Emirates, United States of America, and Vietnam [15]. The world experienced a rapid growth of COVID-19 pandemic with 85,403 confirmed cases on a global scale out of which 79,394 confirmed cases were from China with 2838 deaths [16].

Presently, COVID-19 has spread to almost all the countries of the globe and as of July 8, 2020 there is a whopping 11,669,259 cases and 539,906 fatalities across the globe [17]. The present global scenario as of July 8, 2020 is tabulated in Table 6.1.

6.2.2 Symptoms of COVID-19

COVID-19 positive patients exhibit flu-like symptoms characterized by dry coughs, sore throat, high fever, and breathing problems. These may also be accompanied by fatigue, muscle pain, and sneezing. Under severe condition, there are reports of pneumonia, serious respiratory syndrome, and kidney failure ultimately leading to death [18]. Epidemiological studies suggest that the mortalities are higher in elder populations and the incidence is much lower in children [19]. Respiratory troubles along with elevated white blood cell (WBC) and cytokine levels are reported in patients suffering from COVID-19 [20]. One of the COVID-19 patients reported 5 days of fever accompanied by cough, coarse breathing sounds of both lungs with a body temperature of 39 °C.

TABLE 6.1 Continent wise count of COVID-19 cases as on July 8, 2020 [17].

Continents	Total confirmed cases	Total new cases	Total deaths	Total new deaths
Africa	397,942	15,379	7415	276
Americas	6,004,685	89,134	268,828	2092
Eastern Mediterranean	1,204,698	17,078	28,664	562
Europe	2,827,789	17,941	201,255	604
South-East Asia	1,001,655	27,266	26,224	605
Western Pacific	231,749	2159	7507	8
Global	11,669,259	168,957	539,906	4147

The WBC differential count exhibited 70.0% neutrophils and 0.1% eosinophils along with elevations in levels of C-reactive protein (16.16 mg/L; normal range 0−10 mg/L), erythrocyte sedimentation rate (29 mm/h; normal range <20 mm/h), and D-dimer (580 ng/mL; normal range 500 ng/mL). Multiple peripheral ground-glass opacities were observed in the lungs through unenhanced chest CT. Analysis of the sputum of the patient showed positive real-time polymerase chain reaction results which confirmed COVID-19 infection [21].

6.2.3 Transmission of COVID-19

Infective particles may spread from their natural hub to a vulnerable host through a variety of pathways which includes the transmission from a human to another human, transmission through air, endogenous infection, common vehicle, and vector spread [22]. The respiratory viruses are assumed to transmit over multiple routes, out of which transmission through droplets and aerosols is of immense significance [23]. There are three potential pathways of transmission of SARS-CoV-2 from an infected host to a susceptible host. The first pathway is transmission from person to person (direct contact) through respiratory droplets. These droplets are capable of traveling a distance of 6 feet through air. The second pathway is transmission through fomites (indirect contact) for the duration it is viable in the surfaces of which it is present. The aerosols form the third way of viral transmission through indirect contact mode for a distance of over six feet in air. To affect a successful infection, SARS-CoV-2 requires to lodge on specific regions namely the eyes, nose, and mouth of a host [24].

As of now, preventive measures are the most effective strategy in limiting the spread of infection of SARS-CoV-2. In this regard, early screening, diagnosis, isolation, and treatment are required to prevent further spread of the disease. In this regard, the most important strategy is frequently washing of hands by soaps and use of alcohol-based hand sanitizers, in addition to avoiding contact with other persons and covering of face and mouth in order to minimize chances of entry of virus through the body opening [25]. The important preventive measures for spread of SARS-CoV are tabulated in Table 6.2.

6.3 Drug discovery for COVID

The term “drug” originates from “drogue” which means dried herbs in French. Drugs are chemical substances that have the capability to modulate the mental, emotional, and physical state of oneself and have a profound effect on the functions of the brain [26]. Chemicals bind to the protein and are absorbed in the systemic circulation. The efficacy of a drug is due to the difference in pharmacokinetics and pharmacodynamics between ethnicity, age, genetic

TABLE 6.2 Measures required to be followed for preventing spread of SARS-CoV.

Quarantine	Other preventive measures
Self-quarantine (practicing lockdown) **(a)** Mandatory quarantine **(b)** Private residence **(c)** Hospitals **(d)** Public institutions **(e)** Others (ships)	**1.** Avoidance of crowding
	2. Frequent hand wash with soaps and use of hand sanitizers
	3. Practicing isolation
	4. Use of personal protective equipment
	5. Closure of schools and colleges (as a protective measure)
	6. Social distancing
	7. Closure of workplaces or measured activities in workplace

makeup, and disease state [27]. A group of medicines which have similar molecular structures, the same mechanism of action, a related mode of action, and are used to treat the same disease forms a drug class.

6.3.1 Sources of drug

Drugs are derived mainly from natural sources, but synthetic and semi-synthetic drugs are also manufactured owing to their higher yield, purity, quality, and low price [28]. Crude drugs are naturally occurring raw substances obtained from minerals, plants, and animals. It contains pharmacologically active ingredients which do not require any further refinement. Natural sources of drugs comprise plants, animals, microbes, and minerals. Plants as a whole are sources of crude drugs. Whereas, in the case of animals, drugs are mostly obtained from glandular secretions, liver, venoms (polypeptide), nonpeptide toxins, etc. Many life-saving drugs like penicillin, chloramphenicol, streptomycin, etc., are obtained from microbes. Coral (eleutherobin), sponges (discodermolide), and marine microorganisms (curacin A) synthesize biochemical compounds which can attenuate inflammations, inhibit viruses, and prevent cancer. Drugs obtained from minerals may include compounds constituting both metals and nonmetals and are used for treating number of ailments. New drugs are the result of microbiological conversion of precursor molecule, aberrant synthesis in higher plants, as well as through culture of cells and organs. Semisynthetic preparation of drugs involves alteration in chemical structure without any modification of the nucleus, thereby improving the efficiency of natural drugs. Drugs are also prepared synthetically and are also genetically engineered [29].

6.3.2 Antiviral drugs and other alternatives

The application of antiviral drugs includes treating viral infections without harming the host cell by identifying viral proteins, or parts of proteins, that can be disabled. Herpes virus was the first to be treated with an antiviral compound which was produced in 1960s. Various drugs are being developed at an extremely quick pace and new drug targets are being exploited along with clinical trials of newly formulated drugs.

Most of the viral diseases (except HIV) are self-limited illnesses not requiring specific antiviral therapy. Current antiviral drugs target 3 groups of viruses—herpes, hepatitis, and influenza [30].

Natural products such as lycorine, silvestrol, tylophorine, ouabain, and homoharringtonine can interact with key viral proteins that are associated with virulence in nanomolar concentration. These may help in future drug development strategies or may act as drug design templates [31].

Indian medicinal herbs are a promising alternative to combat viral infections. Indian herbs are used as a prophylaxis for a number of viral infections related to respiratory distress. These herbs help to stimulate immune system and modulate inflammatory effects, thereby rendering overall protection against the virus infection.

The homeopathy medicine, Arsenicum album 30, may be a possible preventive against coronavirus infection. It affects HT29 cells and human macrophages. It also showed NF-κB hyperactivity and TNF-α release in macrophage [32].

6.3.3 Role of medicinal plants

In India, the study is rather minimal, where antimouse coronaviral activity is manifested by certain plants such as *Allium sativum* [33], which target the viral replication of SARS-CoV. *Clerodendrum inerme* having the potential to inactivate the viral ribosomes may be utilized as a drug targeting SARS-CoV-2 protein translation [34]. *Strobilanthes cusia* [35] attenuates the RNA synthesis of virus and induces protease activity targeting the HCoV. *Andrographis paniculata* can treat viral respiratory infections in ayurvedic and medicinal systems [36,37]. *Sambucus ebulus* [38] has been known to inhibit the activity of enveloped viruses. Methanolic extracts of plants were derived from 22 families and their MIC (minimum inhibitory concentration) values were evaluated. Some of the extracts exhibited antiviral activities which included mouse coronavirus (the surrogate of human SARS virus). Most potent extracts were from *Gymnema sylvestre*, *Pergularia daemia*, *Sphaeranthus indicus*, *Cassia alata*, *Evolvulus alsinoides*, *Clitoria ternatea*, *Indigofera tinctoria*, *Abutilon indicum*, *Vitex trifolia*, *C. inerme*, and *Leucas aspera* which revealed anti-MCV and anti-HSV properties at a concentration of 0.4 μg/mL [39].

Camellia japonica, *Saposhnikovia divaricata*, and *Dryopteris crassirhizoma* showed potential inhibitory effects on PEDV replication by targeting key structural protein synthesis and relevant gene expression. The anti-PEDV molecules obtained may help in investigating the deadly human coronaviruses, as they share some similar replication mechanisms [40].

6.3.4 Molecular biology and drug target

SARS-CoV-2 targets cells through viral structural spike proteins which binds to angiotensin-converting enzyme 2 (ACE-2) receptor followed by entry into the host using host cell receptors and endosomes [41,42]. S1 unit of S protein helps in adherence of the virus to the surface of the target cells. Serine protease TMPRSS2 promotes viral entry by S protein priming [41]. RdRp, coronavirus main protease, and papain-like protease are nonstructural proteins which are encoded by viral genome. Upon entry to the cell, the virus synthesizes RNA via RdRp. A TMPRSS2 inhibitor thus may be an important target for drugs [41,42]. It is translated to polyproteins of virus within the host cell using the host translation apparatus. They are then broken into effector proteins by coronavirus main protease and papain-like protease which deubiquinates a number of host cell proteins such as interferon factors and NF-κB, which results in suppression of immune system. The cryo-EM structure analysis revealed that the S protein−ACE-2 binding in case of SARS-CoV-2 is in many folds higher than in SARS-CoV [43]. However, drugs that inhibit ACE trigger the expression of ACE-2, thereby intensifying the infection. Thus, drugs that promote ACE inhibition may not be therapeutic in coronavirus treatment [44].

6.4 Drug discovery related to COVID-19

As SARS-CoV-2 wreaks havoc throughout the globe, extensive research was initiated for drug discovery for treating the disease in the first half of 2020. It was revealed that a number of candidates from western medicines, natural substances, and conventional Chinese medicines have potentials to counteract the virus [45−47]. Interferon α (IFN-α), chloroquine phosphate, lopinavir/ritonavir, ribavirin, and Arbidol are the antivirals which are considered as preventive medicine for treatment of SARS-CoV-2 induced pneumonia by the National Health Commission of the People's Republic of China (Table 6.3) [48].

Though a number of antiviral formulations have been recommended for the treatment of SARS-CoV-2, no specific vaccine or therapeutic drugs for COVID-19 were established till the middle of 2020 [49]. This remained a major challenge to narrow down the potential therapeutic regimens for COVID-19 treatment. A potent vaccine is extremely essential for the treatment and cure for ever-increasing cases of COVID-19. From 2020 onwards, a lot of research was being undertaken to develop vaccines throughout the world.

TABLE 6.3 Names of antivirals recommended by the National Health Commission, People's Republic of China for the treatment of SARS-CoV-2.

Name of the drug	Dosage to be administered	Mode of administration
IFN-α	5 million units or equivalent, twice a day	Vapor inhalation
Lopinavir/ritonavir	200 mg/50 mg/capsule, 2 capsules each time twice a day	Oral
Ribavirin	500 mg in combination with IFN-α or lopinavir/ritonavir, 2−3 times a day	Intravenous infusion
Chloroquine phosphate	500 mg, 2 times a day	Oral
Chloroquine	300 mg, 2 times a day	Oral
Arbidol	200 mg each time, 3 times a day	Oral
The tenure of treatment is recommended for not more than 10 days.		

Until the development of vaccines, some common antiviral drugs were used for treatment. This section will summarize the status of pharmacotherapeutics that were used for COVID-19 therapy during initial stages of transmission.

6.4.1 Antiviral agents

6.4.1.1 Remdesivir

Remdesivir (Fig. 6.1) is one of the potential candidates for treating patients infected with SARS-CoV-2. Chemically, remdesivir is a phosphoramidate prodrug of an adenosine C-nucleoside that functions as broad-spectrum antiviral agent produced by Gilead Sciences in 2017. It was initially used to treat patients infected with Ebola virus [50]. Remdesivir is converted into its active form within the cell which is responsible for obscuring viral RNA polymerase and blocking proofreading by exonuclease of virus. This results in decrease of RNA production of virus. The mechanism by which remdesivir acts is by the delay of chain cessation of nascent viral RNA [51]. Fig. 6.2 depicts the action of remdesivir within the cell.

After diffusion, remdesivir is metabolized into nucleoside triphosphate via a series of changes. The nucleoside triphosphate is the active form that inhibits RdRp [52]. In order to evaluate the effectiveness, phase III clinical trials of remdesivir kick-started in China on February 5, 2020 [53]. The trial took place at the Capital Medical University with 308 participants with mild and moderate SARS-CoV infection, but was suspended on April 15, 2020

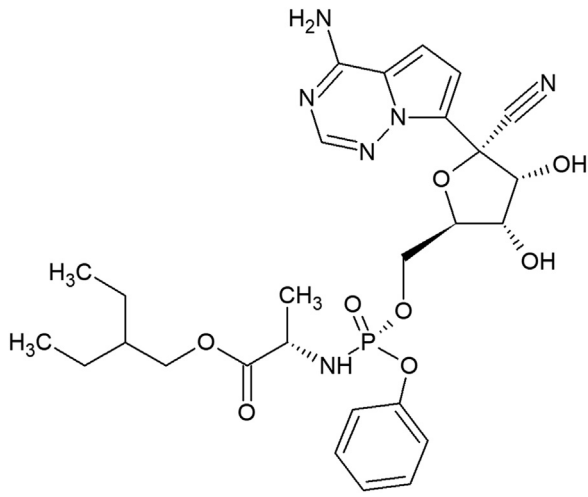

FIGURE 6.1 Molecular structure of remdesivir.

(NCT04252664, since suspended). A day later, a second trial was also registered on the same location focusing on patients with advanced SARS-CoV-2 related respiratory disease. This trial was undertaken with 237 participants and was terminated in mid-April 2020 (NCT04257656, since terminated). Both trials were designed to monitor the primary outcome of administration of remdesivir in normalization of fever, oxygen saturation, respiratory rate, and remission of cough which is sustained for 72 h [52]. The recommended dose includes a 10-day course of 200 mg loading dose on day 1 followed by 100 mg once-daily maintenance doses of remdesivir for 9 days in both studies [54].

6.4.1.2 Hydroxychloroquine and chloroquine

Hydroxychloroquine and chloroquine (Figs. 6.3 and 6.4) are drugs that are commonly used as a remedy of lupus erythematosus [55], rheumatoid arthritis [56], and malaria [57]. Compared to chloroquine, hydroxychloroquine is less toxic as it possesses a hydroxyl group and performs the same function [58]. Hydroxychloroquine and chloroquine target the lysosomes and are useful to control graft-versus-host disease in humans [59,60]. Chloroquine accumulation in lysosomes results in significant change of pH [61], thereby affecting the activity of protease. This affects degradation of glycosaminoglycans [62,63]. It was reported from several investigations that chloroquine possess the capacity to inhibit the entry of SARS-CoV-2, fusion of virus with cell through interference of glycosylation of ACE-2 receptor, and attachment with spike protein [64–66]. This indicated that chloroquine and hydroxychloroquine are more effective in the early stages of COVID-19 infection (Fig. 6.5) [67,68].

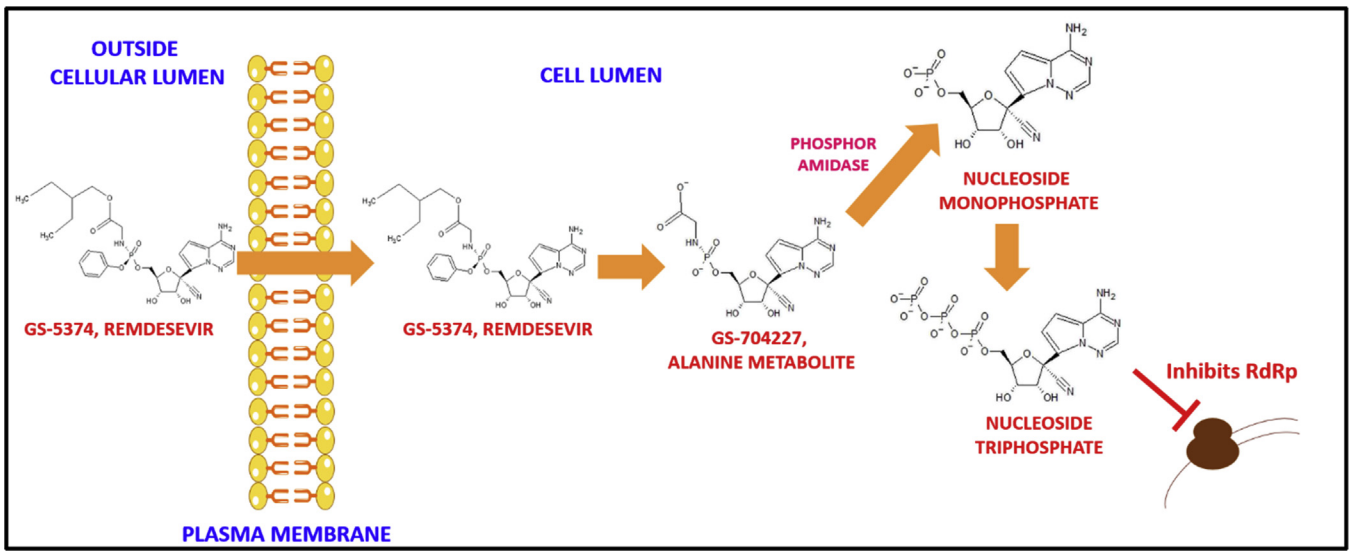

FIGURE 6.2 Schematic representation of action of remdesivir inside the cell.

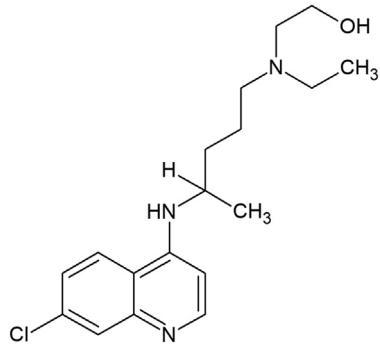

FIGURE 6.3 Molecular structure of hydroxychloroquine.

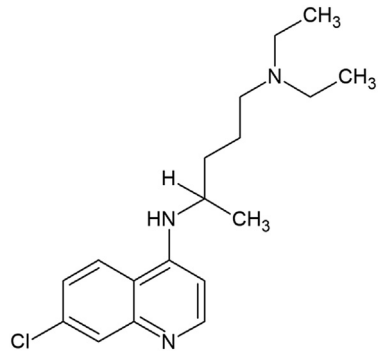

FIGURE 6.4 Molecular structure of chloroquine.

There is evidence that chloroquine and hydroxychloroquine resulted in reduction of cytokine storms which contributed to acute respiratory distress which resulted in majority of deaths among COVID-19 patients [69,70]. There were also reports that hydroxychloroquine effectively inhibits infection of SARS-CoV in vitro [71]. An in vitro study reported that zinc inhibits the activity of RNA polymerase in SARS-CoV and retroviruses [72]. There was also a report that zinc can improve the actions of chloroquine during COVID-19 treatment [73]. In a study conducted at Méditerranée Infection University Hospital Institute in Marseille, France, it was reported that the daily administration of 600 mg of hydroxychloroquine resulted in significant reduction or disappearance of viral load in COVID-19 patients and the effect was further reinforced by azithromycin [74]. A study recommended an initial higher dose of 400 mg two times daily of hydroxychloroquine sulfate followed by a fixed dose of 200 mg, two times a day for 4 days in case of SARS-CoV-2 infection. It was also found that hydroxychloroquine was stronger than chloroquine in

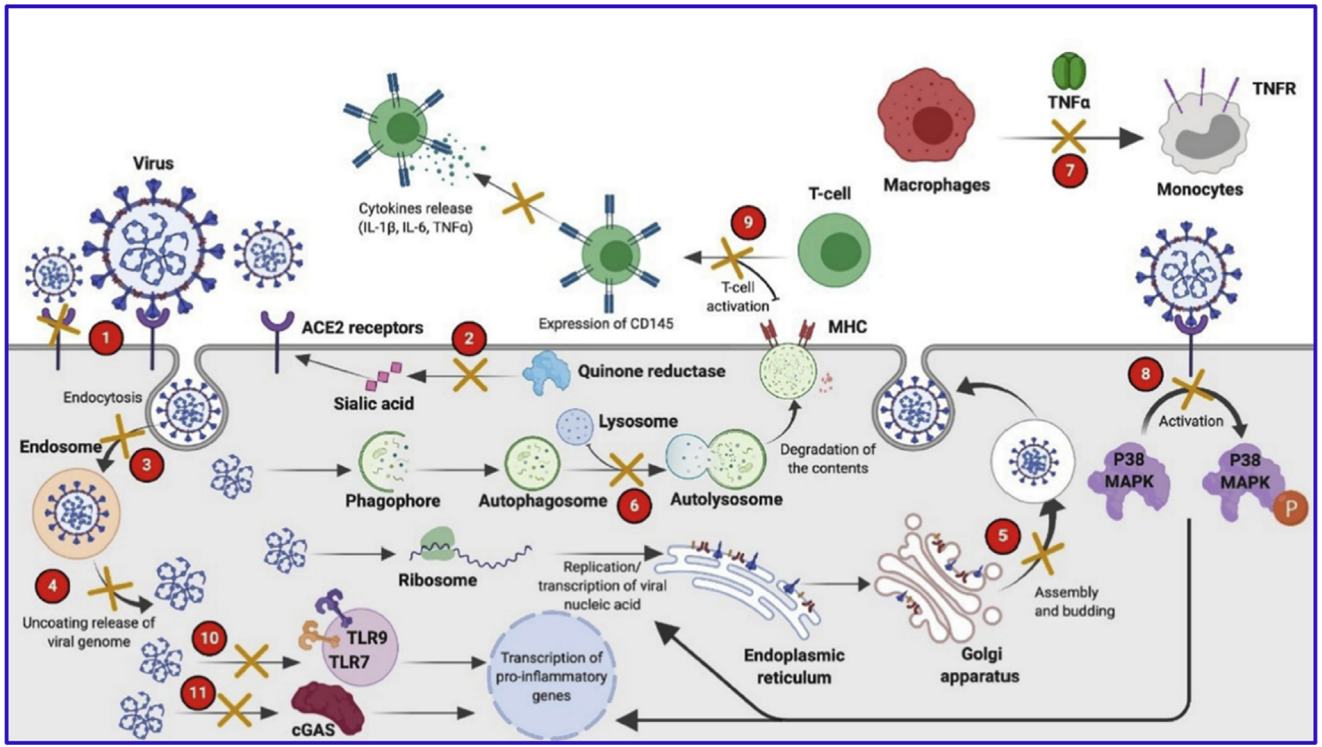

FIGURE 6.5 Probable sites of action of chloroquine (CQ) and hydroxychloroquine (HCQ). (X) Sites of inhibition by CQ and HCQ. (1) **CQ and HCQ:** inhibition of binding of virus to the specific receptor on cell surface, (2) **CQ:** inhibition of sialic acid biosynthesis by suppressing activity of quinone reductase 2 which affect activity of ACE-2 receptor, (3) **CQ and HCQ:** inhibition of pH-dependent endocytosis of virus through increase of pH, (4) **CQ:** intervention with uncoating of viral particles, (5) **CQ:** intervention with assembly/budding which results in accumulation of viral vesicles in trans-Golgi network, (6) **CQ:** interference with degradation of lysosomal protein and fusion of lysosome with autophagosomes. **HCQ:** Interferes with activity of lysosome which prevents expression of class II MHC, (7) **CQ:** interference with release of TNF and binding from macrophages and/to monocytes, (8) **CQ**: attenuation of phosphorylation of P38 MAPK and caspase in Th1 cells thereby inhibiting production of proinflammatory cytokines and replication of virus, (9) **HCQ**: blocking of MHC expression thereby preventing T cell activation, expression of CD145, and release of cytokines, (10) **HCQ:** disables TLR signaling through increase of pH of endosomes and interfering with binding of TLR7 and TLR9 to their DNA/RNA ligands, thereby inhibiting transcription of proinflammatory genes, and (11) **HCQ**: inhibition of binding of DNA to the cGAS resulting in reduction of transcription and production of cytokines [66].

inhibiting SARS-CoV-2 in vitro [71]. However, there were reports that hydroxychloroquine exhibited some side effects such as cardiac failure, blindness, and toxicity of kidney [75]. Thus, clinicians are required to be conscious of risks associated with the administration of these drugs for treatment of SARS-CoV infections.

6.4.1.3 Lopinavir-ritonavir

Lopinavir (Fig. 6.6) inhibits protease [76] and is reported to possess high affinity for HIV protease I [77]. It is administered in combination with ritonavir and was first launched by Abbott as Kaletra in 2000 [78]. Lopinavir has a poor bioavailability and extensive metabolism [79]. It is thus co-administered with ritonavir to enhance its exposure. Ritonavir (Fig. 6.7) boosts the plasma concentration of lopinavir by suppressing its metabolism, thereby increasing the potential of lopinavir [80]. In a trial performed with lopinavir/ritonavir on 199 patients with confirmed SARS-CoV-2 infection, 99 patients were administered with 400 and 100 mg of lopinavir and ritonavir, respectively, twice daily for 2 weeks along with standard care. No significant improvement was observed with lopinavir/ritonavir treatment. Further trials were required to be performed on patients with severe illness in future to determine the best combination of drugs [81]. However, a report from Korea stated that lopinavir/ritonavir administered to a 54-year-old male patient infected with SARS-CoV-2 significantly decreased coronavirus titers [82]. A randomized phase II trial was performed on patients infected with SARS-CoV-2 who were admitted to healthcare facilities in Hong Kong. Out of 127 patients, 86 patients were administered with a combination of 400 mg of lopinavir and 100 mg of ritonavir along with 400 mg of ribavirin every 12 h with three doses of interferon

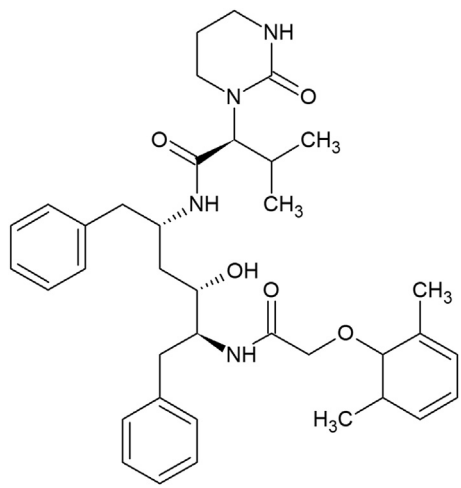

FIGURE 6.6 Molecular structure of lopinavir.

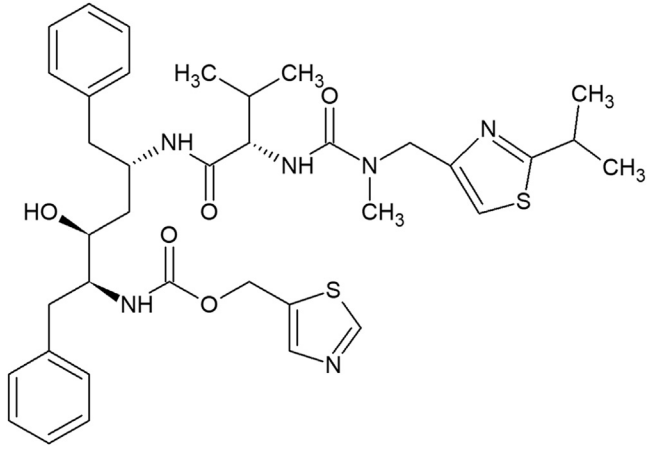

FIGURE 6.7 Molecular structure of ritonavir.

beta-1b (8 million international units) on alternate days. It was observed that the combination group exhibited significantly shorter median time from initiation of study treatment to absence of coronavirus in nasopharyngeal swab which was considered to be the end point of study [83].

6.4.1.4 Umifenovir (Arbidol)

Umifenovir is a hydrophobic drug with an indole-based chemical structure (Fig. 6.8). It is a dual-acting antiviral and host targeting agent which is used for the prevention of influenza and related respiratory infections. It has been in use in Russia for more than two decades and in China from 2006 onwards [84]. It is an oral antiviral drug that is marketed as Arbidol [85]. Umifenovir was also reported to have in vitro antiviral efficacy against Ebola virus, human herpes virus 8, hepatitis C virus, and *Tacaribe arenavirus* [86]. The main mechanism of umifenovir is blocking of the virus-cell membrane fusion through inhibiting clathrin-mediated endocytosis, thus preventing the virus infection [87]. An

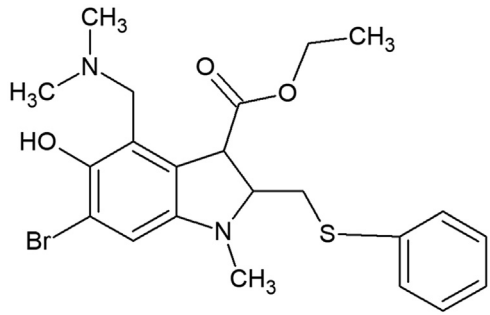

FIGURE 6.8 Molecular structure of umifenovir.

in vitro study reported that Arbidol effectively inhibits SARS-CoV-2 infection by blocking the viral entry obstructing attachment of virus and release from endolysosomes [88]. A retrospective cohort study indicates combination of Arbidol with lopinavir/ritonavir resulted in a higher recovery rate (75%) as evident from absence of virus in the nasopharyngeal swab after 7 days of treatment as compared to monotherapy of lopinavir/ritonavir (35%) [89]. Two randomized and open level trials were undertaken in China. A phase IV clinical trial was performed in Guangzhou Eighth People's Hospital which explored the effectiveness of combination of lopinavir, ritonavir, and Arbidol in treating novel coronavirus infection. This trial was initiated on February 5, 2020 and is still on recruitment mode [90]. A second study was initiated on February 7, 2020. It is an interventional clinical trial to study the potential of Arbidol Hydrochloride Tablets along with standard treatment versus standard treatment for pneumonia caused by the novel coronavirus [91].

6.4.1.5 *Favipiravir*

Favipiravir (Fig. 6.9) is a derivative of pyrazinecarboxamide and is inhibitory to RNA viruses. Within the host, Favipiravir is modified to ribofuranosyl-triphosphate derivative by host's enzyme and this is responsible for the inhibition of RdRp of influenza virus. Toyama Chemical Co Ltd, Japan, introduced Favipiravir and got approval for treating resistant cases of influenza [92]. Favipiravir selectively targets conservative catalytic domains of RdRp, thus preventing nucleotide incorporation replication and transcription of virus [93]. The impairment in replication of virus results in increased number and frequency of transition and transversion mutations inducing lethal mutagenesis in virus [94]. Favipiravir is administered to treat infectious disease such as influenza [95], Ebola [96], and norovirus [97]. A study reported that Favipiravir is effective in SARS-CoV-2 infection of Vero E6 cells (ATCC-1586) with half maximal effective concentration of 61.88 μmol per liter and half maximal cytotoxic concentration (CC50) $>$ 400 μmol per liter and selectivity index $>$ 6.46 [98]. Clinical trials exploring the effectivity of Favipiravir against COVID-19 infection were extensively performed in China and Japan during initial stages of drug developement against COVID-19. The details of the trial were tabulated in Table 6.4.

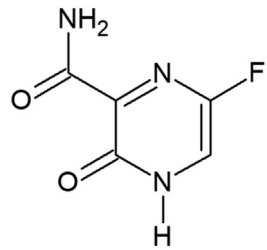

FIGURE 6.9 Molecular structure of Favipiravir.

TABLE 6.4 Selected trials on efficacy of Favipiravir against COVID-19 infection.

Trial registration code	Trial type	Total number of patients enrolled	Objective/Outcome	References
ChiCTR200030254	Randomized control trial	240 120—Favipiravir 120—Arbidol	Comparison of safety and efficacy of Arbidol and Favipiravir in treatment of patients with COVID-19 infection. Higher recovery rate in patients treated with Favipiravir along with faster relief from cough and pyrexia.	[99]
ChiCTR2000030113	Interventional study	15—Control group **Intervention**: Ritonavir 15—Experimental group **Intervention**: Favipiravir	Observing the safety and effectiveness of Favipiravir for treating novel coronavirus—related pneumonia with poorly responsive ritonavir.	[100]
ChiCTR2000029600	Interventional study	**30—Group A** **Intervention:** Alpha-interferon atomization **30—Group B** **Intervention:** Combination of lopinavir/ritonavir along with Alpha-interferon **30—Group C** **Intervention:** Favipiravir + alpha-interferon atomization	Monitoring safety and effectiveness of Favipiravir for treatment of SARS-CoV-2 infection associated pneumonia.	[101]

Continued

TABLE 6.4 Selected trials on efficacy of Favipiravir against COVID-19 infection.—cont'd

Trial registration code	Trial type	Total number of patients enrolled	Objective/Outcome	References
ChiCTR2000029544	Interventional study	**10—Group 1** **Intervention:** Current antiviral treatment + baloxavir marboxil tablets **10—Group 2** **Intervention:** Current antiviral treatment + Favipiravir tablets **10—Group 3** **Intervention:** Current antiviral treatment	Evaluating the effectiveness and safety of combination of baloxavir marboxil or Fabiravir dipivoxil for treating patients having SARS-CoV-2 infection.	[102]
ChiCTR2000029548	Interventional study	**10—Group A** **Intervention**: 80 mg of baloxavir marboxil on first day, 80 mg on fourth day, and 80 mg on seventh day if required. Not to be administered more than three times in total. **10—Group B** 600 mg of Favipiravir, three times a day along with 1600 mg first loading up to 14 days. **10—Group C** **Intervention:** 200 mg of lopinavir and 50 mg of ritonavir two times a day for 14 days	Evaluating the effectiveness and safety of baloxavir marboxil, lopinavir/ritonavir, and Favipiravir for treating patients having SARS-CoV-2 infection.	[103]
ChiCTR2000030894	Interventional study	**90—Group 1** **Intervention:** Combination of Favipiravir with tocilizumab **30—Group 2** **Intervention:** Favipiravir **30—Group 3** **Intervention:** Tocilizumab	Evaluating the effectiveness and safety of Favipiravir in combination with tocilizumab for treating patients having SARS-CoV-2 infection.	[104].

6.4.1.6 Oseltamivir

Oseltamivir (Fig. 6.10) is a drug used to treat influenza A and B [105]. It is a cyclohexene carboxylate ester. Oseltamivir blocks neuraminidases present on the surfaces of influenza viruses and interferes with the release of complete viral particles in the host cell [106]. Several trials were undertaken to check the effectivity of oseltamivir against SARS-CoV-2 (Table 6.5).

6.4.2 Supporting agents

Many concomitant therapies were in use as supporting agents due to the nonavailability of vaccines or antiviral drugs for the treatment of SARS-CoV-2 during the initial months of the pandemic. These included a number of compounds, antibiotics, and antibodies. The mechanism of actions of these therapeutic agents and their role in COVID-19 treatment are tabulated in Table 6.6 while the clinical trials and other scientific studies related to them are tabulated in Tables 6.7 and 6.8, respectively.

6.5 Plasma therapy

Plasma therapy was first introduced in the 19th century to treat diphtheria [129]. Clinical trials using antibody-rich plasma from recovered COVID-19 patients to treat COVID-19 positive ones gained a lot of popularity in COVID-19 therapy in some countries including India. Potentiality and lack of side effects in clinical trials related to COVID-19 vaccine development are the main motives of FDA. In India, West Bengal government is collaborating with Council of Scientific and Industrial Research (CSIR), India, and they are conducting clinical trials to cure patients with convalescent plasma therapy (CPT) [130,131].

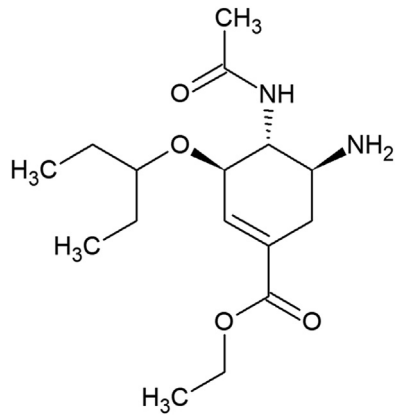

FIGURE 6.10 Molecular structure of oseltamivir.

TABLE 6.5 Selected trials for checking the efficacy of oseltamivir against SARS-CoV-2 infection.

Trial registration code	Trial type	Total number of patients enrolled with drug interventions	Objective/Outcome	References
NCT04255017	Interventional (clinical trial)	400 (estimated and recruiting). **Intervention**: Oseltamivir with various combinations of lopinavir/ritonavir and Arbidol hydrochloride at different doses.	Relief from fever cough and associated symptoms related to SARS-CoV-2 infection along with improvement in lung CT.	[107]
NCT04303299	Interventional (clinical trial)	320 (not recruiting) **Intervention**: Oseltamivir with various combinations of hhydroxychloroquine, lopinavir, ritonavir, and Favipiravir at different doses.	Eradication of nasopharyngeal SARS-CoV-2.	[108]

TABLE 6.6 Selected supporting agents which are in use for treating SARS-CoV infection.

Name of the supporting agent	IUPAC nomenclature	Mode of action	References
Compounds			
Azithromycin	(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-[(2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-2-ethyl-3,4,10-trihydroxy-13-[(2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-3,5,6,8,10,12,14-heptamethyl-1-oxa-6-azacyclopentadecan-15-one	Interferes bacterial translation process by attaching to 50S subunit of ribosome, thereby inhibiting translation of mRNA	[109]
Ascorbic acid	(2R)-2-[(1S)-1,2-dihydroxyethyl]-3,4-dihydroxy-2H-furan-5-one	Enhances development and proliferation of T lymphocytes and NK (natural killer) cells Involved in the immune response to viral agents	[110]
Corticosteroids (methylprednisolone)	(6S,8S,9S,10R,11S,13S,14S,17R)-11,17-dihydroxy-17-(2-hydroxyacetyl)-6,10,13-trimethyl-7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[a]phenanthren-3-one	Attenuation of cytokine response. Accelerate resolution of pulmonary and systemic inflammation	[111,112]
Nitric oxide	Nitric oxide	Vasodilator	[113]
Sirolimus	(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-[(2R)-1-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]propan-2-yl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.04,9]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentone	Immunosuppressant Inhibition of mTOR	[114,115]

Continued

TABLE 6.6 Selected supporting agents which are in use for treating SARS-CoV infection.—cont'd

Name of the supporting agent	IUPAC nomenclature	Mode of action	References
Antibodies			
Tocilizumab	Monoclonal antibody developed by Roche and Chugai Pharmaceutical	IL-6 receptor antagonist	[116]
Sarilumab	Full human anti—IL-6R monoclonal IgG1 antibody	Binds to both soluble and membrane-bound IL-6Rα, thus blocking the cis- and trans-inflammatory signaling cascades of IL-6	[117,118]

TABLE 6.7 Clinical trials performed with the supporting agents.

Trial registration code	Trial type	Total number of patients enrolled/participants	Objective/Outcome	References
2020-000890-25	Randomized clinical trial	36	Azithromycin added to hydroxychloroquine exhibited significantly more efficiency in eliminating virus.	[74,119]
NCT04264533	Randomized trial	140	Number of ventilation-free days determined on the 28th day of enrollment. 28 days mortality monitoring of patient survival. Duration of stay in ICU.	[120]
NCT04341675	Randomized trial	30	Number of patients who are alive and not dependent on advanced respiratory support on 28th day. Number of patients requiring intensification in care. Change in specific biomarkers such as LDH, ferritin, D-dimer, lymphocyte count over time. Number of surviving patients to discharge from hospital.	[121]
NCT03901001	Randomized trail	160	In time frame of 28 days: **(a)** Respiratory status to normalcy **(b)** Copies of viral ribonucleic acid (RNA) per milliliter.In time frame of 10 days: Levels of interleukin, chemokine ligand 9, soluble tumor necrosis factor receptor-1, phospho-p38, and phospho-ERK.	[122]

Continued

TABLE 6.7 Clinical trials performed with the supporting agents.—cont'd

Trial registration code	Trial type	Total number of patients enrolled/participants	Objective/Outcome	References
NCT04305457	Randomized, interventional (clinical trial)	240	Decrease in requirement of intubation and mechanical ventilation in patients having mild to moderate COVID-19 symptoms.	[123]
NCT04306393	Randomized, interventional (clinical trial)	200	Change of arterial oxygenation at 48 h from enrollment. Time to reach normoxemia during the first 28 days after enrollment. Proportion of SARS-nCoV-2–free patients during the first 28 days after enrollment.	[124]
ChiCTR2000029765	Interventional study	188	Evaluation of safety and effectiveness of tocilizumab in treatment of regular patients with NCP (including severe risk factors) and critical NCP patients. Outcome: Ventilator utilization.	[125]
NCT04315298	Randomized interventional clinical trial	2500	Evaluation of change in C-reactive protein (CRP) (%) levels in patients with serum interleukin-6 level greater than the upper limit. Proportion of patients with at least 1-point improvement in clinical status using the 7-point ordinal scale in patients with critical COVID-19 treated with mechanical ventilation at baseline.	[126]

TABLE 6.8 Other investigations performed with the supporting agents.

Name of the compound	Objectives	Outcome	References
Methylprednisolone	To describe the clinical characteristics and outcomes in patients who have developed ARDS from COVID-19 infection related pneumonia.	Methylprednisolone reduced the mortality incidence among COVID-19 infected patients. Death rate of patients treated with methylprednisolone-46%.	[127]
Methylprednisolone	To evaluate the potential and safety of corticosteroid for treatment of severe COVID-19 pneumonia.	Methylprednisolone administration resulted in improvement of SpO2. Betterment in absorption degree of the focus in chest CT. Less number of days required to normalize body temperature upon treatment with methylprednisolone.	[128]

6.6 Future projections

The unbridled spread of COVID-19 on one hand and the lack of authentic drug or vaccine have put forward a challenge to scientists throughout the world. Immense research is being carried out globally at present to find possible therapeutic options. Thus, this chapter has tried to act as a depository of data for the developments of drug/vaccine formulation against novel coronavirus till June, 2020 .

The chapter has highlighted on different antiviral drugs and supportive agents which undoubtedly created a database for the researchers for its further improvement and administration.

It has also emphasized on natural sources of drugs especially those obtained from medicinal plants to combat COVID-19. This would open up new possibilities for researchers to explore the wide range of phytochemical compounds, acting either directly or after modifications, to formulate drugs or immune booster in the near future.

The chapter also highlighted the recent development in alternative treatments such as homeopathy and plasma therapy which may open up new horizon for researchers to investigate them further.

6.7 Conclusion

SARS-CoV-2 that causes COVID-19 is a single-stranded positive-sense enveloped coronavirus which causes respiratory tract infection in humans. It is closely related to SARS-CoV and MERS-CoV. Being highly contagious, it has caused a global health threat. Till June, 2020, no specific drug or vaccine against this virus is available. During that period, the strategies to combat this deadly virus included:

1. Targeting SARS-CoV-2 attachment to the host.
2. Targeting SARS-CoV-2 replication inside the host.
3. Repurposing of already approved drugs which mainly include
   a. Anti-HIV drugs inhibiting the HIV protease (lopinavir/ritonavir, darunavir/cobicistat).
   b. Hydroxychloroquine, a derivative of chloroquine, inhibiting lysosomal functioning.
   c. Inhibition of RdRp—remdesivir.
   d. Favipiravir (Glenmark).

In addition, CPT is an alternative therapy toward SARS-CoV infection and was also investigated. Also, drugs from medicinal plants may be applied for COVID-19 treatment. The ongoing research in this field is also a ray of hope in fighting COVID-19.

The Central Council for Research in Homeopathy under the ministry of AYUSH, Govt. of India, had also proposed the administration of Arsenicum album 30 to boost immunity in order to combat COVID-19.

Moreover, India's first indigenous COVID-19 vaccine "COVAXIN" has been approved for clinical trials (phase I and phase II) by the Drug Controller General of India (DCGI) throughout the country in the month of July 2020. The vaccine is an inactivated one prepared from infectious SARS-CoV-2 virus and is developed by Bharat Biotech with scientific assistance from Indian Council of Medical Research and National Institute of Virology, Pune [132,133].

Although no drug against COVID-19 was certified till the mid of 2020, vigorous research/clinical trials were in full motion for the formulation of a potent drug/vaccine to cure COVID-19. This effort bloomed into success through rolling out of a number of vaccines by several pharmaceutical companies throughout the world. From the last quarter of 2020, the world experienced a massive vaccination drive in stages whose disbursement and administration were meticulously formulated through the concept of 'equitable disbursement of vaccines'. Till 2022, the world experienced several waves of infection accompanied by transmission with mutant strains of the SARS-CoV surfacing out intermittently. Though the virus has affected the global population but with an efficient vaccination drive coupled with strict precautionary measures, an optimistic condition leading to substantial recovery from the pandemic seems not far off.

List of abbreviations

ACE Angiotensin-converting protein
AYUSH Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy
BCoV Bovine coronavirus
c-GAS Cyclin GMP-AMO synthase
CDC Chinese Center for Disease Control and Prevention
CEST Central European Summer Time
CoV Coronavirus
CPT Convalescent plasma therapy
CQ Chloroquine
CRP C-reactive protein
Cryo-EM Cryo-electron microscopy
DNA Deoxyribonucleic acid
EC Effective concentration
FDA Food and Drug Administration
HCoV Human coronavirus
HCV Hepatitis C virus
HIV Human immunodeficiency virus
HSV Herpes simplex virus
HVV Human herpes virus
IL Interleukin
MAPK Mitogen-activated protein kinase
MCV Mouse coronavirus
MERS-CoV Middle East respiratory syndrome coronavirus
MHC Major histocompatibility complex
MHV Mouse hepatitis coronavirus
nCOVID-19 Novel coronavirus 2019
NF-κB Nuclear factor kappa light chain enhancer of activated B cells
NK Neutral killer
NSPs Nonstructural proteins
ORF Open reading frame
PdCV Porcine delta coronavirus
PRCV Porcine respiratory coronavirus
RdRp RNA-dependent RNA polymerase
RNA Ribonucleic acid
SARS-CoV Severe acute respiratory syndrome coronavirus
TGEV Transmissible gastroenteritis coronavirus
TLR Toll-like receptor
TMPRSS2 Transmembrane serine protease 2
TNF Tumor necrosis factor
UAE United Arab Emirates
US United States
WHCV WH-human coronavirus
WHO World Health Organization

References

[1] Liu YC, Kuo RL, Shih SR. COVID-19: the first documented coronavirus pandemic in history. Biomed J May 5, 2020;43(4):328−33.

[2] Kahn JS, McIntosh K. History and recent advances in coronavirus discovery. Pediatr Infect Dis J 2005;24(11 Suppl. l):S223−6.
[3] COVID-19 coronavirus epidemic has a natural origin. Science Daily March 17, 2020. Available from: https://www.sciencedaily.com/releases/2020/03/200317175442.htm. [Accessed 26 June 2020].
[4] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet February 15, 2020;395(10223): 497−506.
[5] Helmy YA, Fawzy M, Elaswad A, Sobieh A, Kenney SP, Shehata AA. The COVID-19 pandemic: a comprehensive review of taxonomy, genetics, epidemiology, diagnosis, treatment, and control. J Clin Med April 24, 2020;9(4):1225.
[6] Li F. Structure, function, and evolution of coronavirus spike proteins. Annu Rev Virol September 29, 2016;3(1):237−61.
[7] Yin W, Mao C, Luan X, Shen DD, Shen Q, Su H, et al. Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by remdesivir. Science May 1, 2020:eabc1560.
[8] Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID-19: their roles in pathogenesis. J Microbiol Immunol Infect March 31, 2020;54(2):159−63.
[9] Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, et al. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe March 11, 2020;27(3):325−8.
[10] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. China novel coronavirus investigating and research team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med February 20, 2020;382(8):727−33.
[11] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet February 15, 2020;395(10223):507−13.
[12] Srivastava N, Baxi P, Ratho RK, Saxena SK. Global trends in epidemiology of coronavirus disease 2019 (COVID-19). Coronavirus Dis April 30, 2020:9−21.
[13] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet February 22, 2020;395(10224):565−74.
[14] Adhikari SP, Meng S, Wu YJ, Mao YP, Ye RX, Wang QZ, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. Infect Dis Poverty March 17, 2020;9(1):29.
[15] WHO. Novel coronavirus (2019-nCoV) situation report−11. 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200131-sitrep-11-ncov.pdf?sfvrsn=de7c0f7_4. [Accessed 10 June 2020].
[16] WHO. Novel coronavirus (2019-nCoV) situation report−40. 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200229-sitrep-40-covid-19.pdf?sfvrsn=849d0665_2. [Accessed 10 June 2020].
[17] WHO. Coronavirus disease (COVID-19) situation report−170. 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200708-covid-19-sitrep-170.pdf?sfvrsn=bca86036_2. [Accessed 9 July 2020].
[18] Ali I, Alharbi OML. COVID-19: disease, management, treatment, and social impact. Sci Total Environ August 1, 2020;728:138861.

[19] Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. Clin Immunol June 2020;215:108427.
[20] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun May 2020;109:102433.
[21] Lei J, Li J, Li X, Qi X. CT imaging of the 2019 novel coronavirus (2019-nCoV) pneumonia. Radiology April 2020;295(1):18.
[22] Jayaweera M, Perera H, Gunawardana B, Manatunge J. Transmission of COVID-19 virus by droplets and aerosols: a critical review on the unresolved dichotomy. Environ Res September 2020;188:109819.
[23] Morawska L, Cao J. Airborne transmission of SARS-CoV-2: the world should face the reality. Environ Int June 2020;139:105730.
[24] Galbadage T, Peterson BM, Gunasekera RS. Does COVID-19 spread through droplets alone? Front Public Health April 24, 2020;8:163.
[25] Güner R, Hasanoğlu I, Aktaş F. COVID-19: prevention and control measures in community. Turk J Med Sci April 21, 2020;50(SI-1):571−7.
[26] What are drugs? Australian Government Department of Health. Available from: https://www.health.gov.au/health-topics/drugs/about-drugs/what-are-drugs. Accessed from: 26.06.2020.
[27] Health Engine, Pharmacology. Available from: https://healthengine.com.au/info/what-are-drugs-introduction-to-pharmacology. Accessed on: 26.06.2020.
[28] Arivazhahan A. Sources and nature of drugs. In: Raj GM, Raveendran R, editors. Introduction to basics of pharmacology and toxicology. Singapore: Springer; 2019.
[29] Alamgir ANM. Drugs: their natural, synthetic, and biosynthetic sources. In: Therapeutic use of medicinal plants and their extracts, progress in drug research. Springer; 2017.
[30] Razonable RR. Antiviral drugs for viruses other than human immunodeficiency virus. Mayo Clin Proc 2011;86(10):1009−26.
[31] Islam MT, Sarkar C, El-Kersh DM, et al. Natural products and their derivatives against coronavirus: a review of the non-clinical and pre-clinical data [published online ahead of print, 2020 Apr 4]. Phytother Res 2020. https://doi.org/10.1002/ptr.6700.
[32] Homoeopathic perspectives in covid-19 coronavirus infection-fact sheet. Central Council for Research in Homoeopathy, New Delhi, India. (An autonomous body of the ministry of Ayush, Government of India). 2020. Available from: https://www.ccrhindia.nic.in/showimg.aspx?ID=15677. [Accessed 26 June 2020].
[33] Keyaerts E, Vijgen L, Pannecouque C, Van Damme E, Peumans W, Egberink H, et al. Plant lectins are potent inhibitors of coronaviruses by interfering with two targets in the viral replication cycle. Antiviral Res September 2007;75(3):179−87.
[34] Olivieri F, Prasad V, Valbonesi P, Srivastava S, Ghosal-Chowdhury P, Barbieri L, et al. A systemic antiviral resistance-inducing protein isolated from Clerodendrum inerme Gaertn. is a polynucleotide:adenosine glycosidase (ribosome-inactivating protein). FEBS Lett November 4, 1996;396(2−3):132−4.
[35] Tsai YC, Lee CL, Yen HR, Chang YS, Lin YP, Huang SH, et al. Antiviral action of tryptanthrin isolated from Strobilanthes cusia leaf against human coronavirus NL63. Biomolecules February 27, 2020;10(3):366.
[36] Yarnell E. Herbs for viral respiratory infections. Altern Complement Ther 2018;24:1.
[37] Coon JT, Ernst E. Andrographis paniculata in the treatment of upper respiratory tract infection: a systematic review of safety and efficacy. Planta Med 2004;70(4):293−8.

[38] Ganjhu RK, Mudgal PP, Maity H, Dowarha D, Devadiga S, Nag S, et al. Herbal plants and plant preparations as remedial approach for viral diseases. Virusdisease December 2015;26(4):225–36.
[39] Vimalanathan S, Ignacimuthu S, Hudson JB. Medicinal plants of Tamil Nadu (Southern India) are a rich source of antiviral activities. Pharmaceutical Biol 2009;47(5):422–9.
[40] Yang JL, Kim T, Ha Q, Oh WK. Discovery of inhibitory materials against PEDV corona virus from medicinal plants. Jpn J Vet Res 2016;64(S1):S53–63.
[41] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE-2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell April 16, 2020;181(2):271–80. e8.
[42] Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review [published online ahead of print, 2020 Apr 13]. JAMA 2020. https://doi.org/10.1001/jama.2020.6019.
[43] Liu C, Zhou Q, Li Y, Garner LV, Watkins SP, Carter LJ, et al. Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases. ACS Cent Sci March 25, 2020;6(3):315–31.
[44] Giavina-Bianchi P, Aun MV, Agondi RC, Kalil J. Debate on drugs that may aggravate COVID-19. J Allergy Clin Immunol Pract April 25, 2020;8(7):2452–3.
[45] Ren X, Shao XX, Li XX, Jia XH, Song T, Zhou WY, et al. Identifying potential treatments of COVID-19 from Traditional Chinese Medicine (TCM) by using a data-driven approach. J Ethnopharmacol August 10, 2020;258:112932.
[46] Pan X, Dong L, Yang L, Chen D, Peng C. Potential drugs for the treatment of the novel coronavirus pneumonia (COVID-19) in China. Virus Res June 9, 2020;286:198057.
[47] Mani JS, Johnson JB, Steel JC, Broszczak DA, Neilsen PM, Walsh KB, et al. Natural product-derived phytochemicals as potential agents against coronaviruses: a review. Virus Res July 15, 2020;284:197989.
[48] Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther 2020;14(1):58–60.
[49] Amanat F, Krammer F. SARS-CoV-2 vaccines: status report. Immunity April 14, 2020;52(4):583–9.
[50] Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L, et al. Discovery and synthesis of a phosphoramidate prodrug of a Pyrrolo[2,1-f][triazin-4-amino] adenine C-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses. J Med Chem March 9, 2017;60(5):1648–61.
[51] Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. Travel Med Infect Dis 2020 ;34:101615.
[52] Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, et al. Remdesivir: a review of its discovery and development leading to emergency use authorization for treatment of COVID-19. ACS Cent Sci May 27, 2020;6(5):672–83.
[53] Cao YC, Deng QX, Dai SX. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: an evaluation of the evidence. Travel Med Infect Dis April 2, 2020:101647.
[54] Wu R, Wang L, Kuo HD, Shannar A, Peter R, Chou PJ, et al. An update on current therapeutic drugs treating COVID-19. Curr Pharmacol Rep May 11, 2020:1–15.
[55] Takezawa K, Ueda-Hayakawa I, Yamazaki F, Kambe N, Son Y, Okamoto H. Successful treatment with Hydroxychloroquine for systemic lupus erythematosus with cutaneous involvement accompanied by a xanthomatous reaction. Lupus 2020;29(1):79–82.

[56] Sebastiani S, Fresina M, Cellini M, Campos EC. Hydroxychloroquine for treatment of rheumatoid arthritis: multifocal electroretinogram and laser flare-cell photometry study. Clin Ophthalmol April 11, 2017;11:689−96.

[57] Ben-Zvi I, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: from malaria to autoimmunity. Clin Rev Allergy Immunol 2012;42(2):145−53.

[58] Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of Chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov March 18, 2020;6:16.

[59] Shukla AM, Wagle Shukla A. Expanding horizons for clinical applications of chloroquine, hydroxychloroquine, and related structural analogues. Drugs Context November 25, 2019;8. 2019-9-1.

[60] Ren L, Xu W, Overton JL, Yu S, Chiamvimonvat N, Thai PN. Assessment of chloroquine and hydroxychloroquine safety profiles: a systematic review and meta-analysis. Front Pharmacol 2020;11:562777.

[61] Lu S, Sung T, Lin N, Abraham RT, Jessen BA. Lysosomal adaptation: how cells respond to lysosomotropic compounds. PLoS One March 16, 2017;12(3):e0173771.

[62] Schultz KR, Gilman AL. The lysosomotropic amines, chloroquine and hydroxychloroquine: a potentially novel therapy for graft-versus-host disease. Leuk Lymphoma 1997;24(3−4):201−10.

[63] Mauthe M, Orhon I, Rocchi C, Zhou X, Luhr M, Hijlkema KJ, et al. Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion. Autophagy 2018;14(8):1435−55.

[64] Singh AK, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: a systematic search and a narrative review with a special reference to India and other developing countries. Diabetes Metab Syndr 2020 ;14(3):241−6.

[65] Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents May 2020;55(5):105938.

[66] Hashem AM, Alghamdi BS, Algaissi AA, Alshehri FS, Bukhari A, Alfaleh MA, et al. Therapeutic use of Chloroquine and Hydroxychloroquine in COVID-19 and other viral infections: a narrative review. Travel Med Infect Dis May 6, 2020;35:101735.

[67] Das S, Bhowmick S, Tiwari S, Sen S. An updated systematic review of the therapeutic role of hydroxychloroquine in coronavirus disease-19 (COVID-19). Clin Drug Investig 2020;40:591−601.

[68] Andreani J, Le Bideau M, Duflot I, Jardot P, Rolland C, Boxberger M, et al. In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect. Microb Pathog August 2020;145:104228.

[69] Yu B, Li C, Chen P, Zhou N, Wang L, Li J, et al. Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19. Sci China Life Sci May 15, 2020:1−7.

[70] Zhao M. Cytokine storm and immunomodulatory therapy in COVID-19: role of chloroquine and anti-IL-6 monoclonal antibodies. Int J Antimicrob Agents June 2020;55(6):105982.

[71] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis March 9, 2020:ciaa237.

[72] te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog 2010;6(11):e1001176. Published 2010 Nov 4.
[73] Rahman MT, Idid SZ. Can Zn be a critical element in COVID-19 treatment? Biol Trace Elem Res May 26, 2020:1−9.
[74] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents March 20, 2020:105949.
[75] Alanagreh L, Alzoughool F, Atoum M. Risk of using Hydroxychloroquine as a treatment of COVID-19 [published online ahead of print, 2020 May 27]. Int J Risk Saf Med 2020. https://doi.org/10.3233/JRS-200024.
[76] Tan D, Walmsley S. Lopinavir plus ritonavir: a novel protease inhibitor combination for HIV infections. Expert Rev Anti Infect Ther 2007;5(1):13−28.
[77] Hurst M, Faulds D. Lopinavir Drugs 2000;60(6):1371−81.
[78] Drugbank. Available from: https://www.drugbank.ca/drugs/DB01601. Accessed on: 10.06. 2020.
[79] Crommentuyn KM, Kappelhoff BS, Mulder JW, Mairuhu AT, van Gorp EC, Meenhorst PL, et al. Population pharmacokinetics of lopinavir in combination with ritonavir in HIV-1-infected patients. Br J Clin Pharmacol October 2005;60(4):378−89.
[80] Li F, Lu J, Ma X. CYP3A4-mediated lopinavir bioactivation and its inhibition by ritonavir. Drug Metab Dispos January 2012;40(1):18−24.
[81] Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. N Engl J Med May 7, 2020;382(19):1787−99.
[82] Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, et al. Case of the index patient who caused tertiary transmission of COVID-19 infection in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR. J Korean Med Sci February 17, 2020;35(6):e79.
[83] Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, et al. 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 May 30, 2020;395(10238):1695−704.
[84] National Center for Biotechnology Information. PubChem Database. Arbidol, CID=131411. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Arbidol. Accessed on June 25, 2020.
[85] Proskurnina EV, Izmailov DY, Sozarukova MM, Zhuravleva TA, Leneva IA, Poromov AA. Antioxidant potential of antiviral drug umifenovir. Molecules March 30, 2020;25(7):1577.
[86] Pécheur EI, Borisevich V, Halfmann P, Morrey JD, Smee DF, Prichard M, et al. The synthetic antiviral drug arbidol inhibits globally prevalent pathogenic viruses. J Virol January 6, 2016;90(6):3086−92.
[87] McKee DL, Sternberg A, Stange U, Laufer S, Naujokat C. Candidate drugs against SARS-CoV-2 and COVID-19. Pharmacol Res July 2020;157:104859.
[88] Wang X, Cao R, Zhang H, Liu J, Xu M, Hu H, et al. The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 in vitro. Cell Discov May 2, 2020;6:28.
[89] Deng L, Li C, Zeng Q, Liu X, Li X, Zhang H, et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: a retrospective cohort study. J Infect July 2020;81(1):e1−5.

[90] The Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection (ELACOI). U.S. National Library of medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT04252885. Accessed on: 26.06.2020.
[91] Clinical Study of Arbidol Hydrochloride Tablets in the Treatment of Pneumonia Caused by Novel Coronavirus. U.S. National Library of medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT04260594. Accessed on: 26.06.2020.
[92] National Center for Biotechnology Information. PubChem Database. Favipiravir, CID=492405. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Favipiravir. Accessed on June 25, 2020.
[93] Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad-spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci 2017;93(7):449−63.
[94] Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol Ther May 2020;209:107512.
[95] Smee DF, Tarbet EB, Furuta Y, Morrey JD, Barnard DL. Synergistic combinations of Favipiravir and oseltamivir against wild-type pandemic and oseltamivir-resistant influenza A virus infections in mice. Future Virol November 2013;8(11):1085−94.
[96] Coomes EA, Haghbayan H. Favipiravir, an antiviral for COVID-19? J Antimicrob Chemother July 1, 2020;75(7):2013−4.
[97] Rocha-Pereira J, Jochmans D, Dallmeier K, Leyssen P, Nascimento MS, Neyts J. Favipiravir (T-705) inhibits in vitro norovirus replication. Biochem Biophys Res Commun 2012;424(4):777−80.
[98] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and Chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res March 2020;30(3):269−71.
[99] Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, et al. Favipiravir versus arbidol for clinical recovery rate in moderate and severe adult COVID-19 patients: aa prospective, multicenter, open-label, randomized controlled clinical trial. Front Pharmacol Sep 2, 2021;12:683296.
[100] Chinese Trial Registry. Randomized controlled trial for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19) with poorly responsive ritonavir/ritonavir. Available from: http://www.chictr.org.cn/showprojen.aspx?proj=49988. Accessed on: 10.06.2020.
[101] Chinese Trial Registry. Clinical study for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19). Available from: http://www.chictr.org.cn/showprojen.aspx?proj=49042. Accessed on: 10.06.2020.
[102] Chinese Trial Registry. A randomized controlled trial for the efficacy and safety of Baloxavir Marboxil, Favipiravir tablets in novel coronavirus pneumonia (COVID-19) patients who are still positive on virus detection under the current antiviral therapy. Available from: http://www.chictr.org.cn/showprojen.aspx?proj=49013. Accessed on: 10.06.2020.
[103] Chinese Trial Registry. Randomized, open-label, controlled trial for evaluating of the efficacy and safety of Baloxavir Marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of novel coronavirus pneumonia (COVID-19) patients. Available from: http://www.chictr.org.cn/showprojen.aspx?proj=49015. Accessed on: 10.06.2020.
[104] Chinese Trial Registry. Favipiravir combined with tocilizumab in the treatment of novel coronavirus pneumonia (COVID-19) - A multicenter, randomized, controlled trial. Available from: http://www.chictr.org.cn/showprojen.aspx?proj=51126. Accessed on: 10.06.2020.

[105] Allen UD, Aoki FY, Stiver HG. The use of antiviral drugs for influenza: recommended guidelines for practitioners. Can J Infect Dis Med Microbiol September 2006; 17(5):273–84.
[106] National Center for Biotechnology Information. PubChem Database. Oseltamivir, CID=65028. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Oseltamivir. Accessed on: June 26, 2020.
[107] Prospective/Retrospective, Randomized Controlled Clinical Study of Antiviral Therapy in the 2019-nCoV Pneumonia. ClinicalTrials.gov Identifier: NCT04255017. Available from: https://clinicaltrials.gov/ct2/show/study/NCT04255017. Accessed on: June 26, 2020.
[108] Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Hydroxychloroquine for Treatment of COVID-19: A Randomized Control Trial (THDMS-COVID-19). ClinicalTrials.gov Identifier: NCT04303299. Available from: https://clinicaltrials.gov/ct2/show/NCT04303299. Accessed on: 26.06.2020.
[109] Bakheit AH, Al-Hadiya BM, Abd-Elgalil AA. Azithromycin. Profiles Drug Subst Excip Relat Methodol 2014;39:1–40.
[110] van Gorkom GNY, Klein Wolterink RGJ, Van Elssen CHMJ, Wieten L, Germeraad WTV, Bos GMJ. Influence of vitamin C on lymphocytes: an overview. Antioxidants March 10, 2018;7(3):41. https://doi.org/10.3390/antiox7030041. PMID: 29534432; PMCID: PMC5874527.
[111] Cheng KC, Chen CM, Tan CK, Chen HM, Lu CL, Zhang H. Methylprednisolone reduces the rates of postextubation stridor and reintubation associated with attenuated cytokine responses in critically ill patients. Minerva Anestesiol May 2011;77(5):503–9.
[112] Meduri GU, Siemieniuk RAC, Ness RA, Seyler SJ. Prolonged low-dose methylprednisolone treatment is highly effective in reducing duration of mechanical ventilation and mortality in patients with ARDS. J Intensive Care August 24, 2018;6:53.
[113] Kitaura H, Uozumi N, Tohmi M, et al. Roles of nitric oxide as a vasodilator in neurovascular coupling of mouse somatosensory cortex. Neurosci Res 2007;59(2):160–71.
[114] Sheng L, Jun S, Jianfeng L, Lianghui G. The effect of sirolimus-based immunosuppression vs. conventional prophylaxis therapy on cytomegalovirus infection after liver transplantation. Clin Transplant 2015;29(6):555–9.
[115] Dancey JE. Inhibitors of the mammalian target of rapamycin. Expert Opin Investig Drugs 2005;14(3):313–28.
[116] Snir A, Kessel A, Haj T, Rosner I, Slobodin G, Toubi E. Anti-IL-6 receptor antibody (tocilizumab): a B cell targeting therapy.
[117] Raimondo MG, Biggioggero M, Crotti C, Becciolini A, Favalli EG. Profile of sarilumab and its potential in the treatment of rheumatoid arthritis. Drug Des Devel Ther May 24, 2017;11:1593–603.
[118] Huizinga TW, Fleischmann RM, Jasson M, Radin AR, van Adelsberg J, Fiore S, Huang X, et al. Sarilumab, a fully human monoclonal antibody against IL-6Rα in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. Ann Rheum Dis September 2014;73(9):1626–34.
[119] Clinical trials for 2020-000890-25. Treatment of Coronavirus SARS-CoV-2 Respiratory Infections with Hydroxychloroquine. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2020-000890-25. Accessed on: 26.06.2020.
[120] Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia. ClinicalTrials.gov Identifier: NCT04264533. Available from: https://clinicaltrials.gov/ct2/show/NCT04264533. Accessed on: 26.06.2020.

[121] Sirolimus Treatment in Hospitalized Patients With COVID-19 Pneumonia (SCOPE). ClinicalTrials.gov Identifier: NCT04341675. Available from: https://clinicaltrials.gov/ct2/show/NCT04341675. Accessed on: 26.06.2020.
[122] Adjunctive Sirolimus and Oseltamivir Versus Oseltamivir Alone for Treatment of Influenza. ClinicalTrials.gov Identifier: NCT03901001. Available from: https://clinicaltrials.gov/ct2/show/NCT03901001. Accessed on: 26.06.2020.
[123] Nitric Oxide Gas Inhalation Therapy for Mild/Moderate COVID-19 (NoCovid). ClinicalTrials.gov Identifier: NCT04305457. Available from: https://clinicaltrials.gov/ct2/show/NCT04305457. Accessed on: 26.06.2020.
[124] Nitric Oxide Gas Inhalation in Severe Acute Respiratory Syndrome in COVID-19 (NOSARSCOVID). ClinicalTrials.gov Identifier: NCT04306393. Available from: https://clinicaltrials.gov/ct2/show/NCT04306393. Accessed on: 26.06.2020.
[125] Chinese Trial Registry. A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19). Available from: http://www.chictr.org.cn/showprojen.aspx?proj=49409. Accessed on: 10.06.2020.
[126] Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19. ClinicalTrials.gov Identifier: NCT04315298. Available from: https://clinicaltrials.gov/ct2/show/NCT04315298. Accessed on: 26.06.2020.
[127] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med March 13, 2020:e200994.
[128] Wang Y, Jiang W, He Q, Wang C, Wang B, Zhou P, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. medRxiv 2020. 2020.03.06.20032342.
[129] Cohut M, Using convalescent blood to treat COVID-19: The whys and hows. Medical News Today. Available from: https://www.medicalnewstoday.com/articles/using-convalescent-blood-to-treat-covid-19-is-it-possible#A-therapy-used-for-over-100-years. Accessed on: 26.06.2020.
[130] COVID-19: Clinical trial for plasma therapy to begin in Kolkata. India TV. Avaiable from: https://www.indiatvnews.com/news/india/covid-19-plasma-therapy-clinical-trial-kolkata-617754. Accessed on: 26.06.2020.
[131] What is the status of convalescent plasma in the treatment of coronavirus disease 2019 (COVID-19)? Medscape. Available from: https://www.mesape.com/answers/2500122-197490/what-is-the-status-of-convalescent-plasma-in-the-treatment-of-coronavirus-disease-2019-covid-19. Accessed on: 29.06.2020.
[132] COVAXIN, India's first COVID-19 vaccine candidate set for phase I,II human trials. NDTV. Available from: https://www.ndtv.com/india-news/coronavirus-vaccine-india-covaxin-india-s-first-covid-19-vaccine-candidate-set-for-phase-i-ii-human-trials-2254189]. Accessed on: 29.06.2020.
[133] India's first COVID-19 vaccine candidate 'COVAXIN' gets DCGI approval for human clinical trials. The New Indian Express. Available from: https://www.newindianexpress.com/nation/2020/jun/29/indias-first-covid-19-vaccine-candidate-covaxin-gets-dcgi-approval-for-human-clinical-trials-2163105.html. Accessed on: 29.06.2020.].