JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS
https://doi.org/10.1080/07391102.2020.1802345

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Current status and strategic possibilities on potential use of combinational drug therapy against COVID-19 caused by SARS-CoV-2

Arif Jamal Siddiqui[a], Sadaf Jahan[b], Syed Amir Ashraf[c], Mousa Alreshidi[a], Mohammad Saquib Ashraf[d], Mitesh Patel[e], Mejdi Snoussi[a,f], Ritu Singh[g] and Mohd Adnan[a]

[a]Department of Biology, College of Science, University of Hail, Hail, Saudi Arabia; [b]Department of Medical Laboratory, College of Applied Medical Sciences, Majmaah University, Al Majma'ah, Saudi Arabia; [c]Department of Clinical Nutrition, College of Applied Medical Sciences, University of Hail, Hail, Saudi Arabia; [d]Department of Clinical Laboratory Sciences, College of Applied Medical Science, Shaqra University, Al Dawadimi, Saudi Arabia; [e]Bapalal Vaidya Botanical Research Centre, Department of Biosciences, Veer Narmad South Gujarat University, Surat, Gujarat, India; [f]Laboratory of Genetics, Biodiversity and Valorization of Bio-resources, Higher Institute of Biotechnology of Monastir, University of Monastir, Monastir, Tunisia; [g]Department of Environmental Sciences, School of Earth Sciences, Central University of Rajasthan, Ajmer, India

Communicated by Ramaswamy H. Sarma

ABSTRACT

The spread of new coronavirus infection starting December 2019 as novel SARS-CoV-2, identified as the causing agent of COVID-19, has affected all over the world and been declared as pandemic. Approximately, more than 8,807,398 confirmed cases of COVID-19 infection and 464,483 deaths have been reported globally till the end of 21 June 2020. Until now, there is no specific drug therapy or vaccine available for the treatment of COVID-19. However, some potential antimalarial drugs like hydroxychloroquine and azithromycin, antifilarial drug ivermectin and antiviral drugs have been tested by many research groups worldwide for their possible effect against the COVID-19. Hydroxychloroquine and ivermectin have been identified to act by creating the acidic condition in cells and inhibiting the importin (IMPα/β1) mediated viral import. There is a possibility that some other antimalarial drugs/antibiotics in combination with immunomodulators may help in combatting this pandemic disease. Therefore, this review focuses on the current use of various drugs as single agents (hydroxychloroquine, ivermectin, azithromycin, favipiravir, remdesivir, umifenovir, teicoplanin, nitazoxanide, doxycycline, and dexamethasone) or in combinations with immunomodulators additionally. Furthermore, possible mode of action, efficacy and current stage of clinical trials of various drug combinations against COVID-19 disease has also been discussed in detail.

ARTICLE HISTORY
Received 26 May 2020
Accepted 21 July 2020

KEYWORDS
Coronavirus; COVID-19; SARS-CoV-2; ACE2 receptor; immunomodulators

Introduction

Human coronaviruses are a group of spherical or pleomorphics medium size (100–150 nm), enveloped RNA viruses containing petal or club shaped peplomers on the surface. They belong to the family coronaviridae. These viruses infect mammals and birds causing diseases of the respiratory tract, gastrointestinal tract, liver, kidney and nervous system. Human coronavirus is responsible for human respiratory disease and a causative agent of common cold. The US National Institute of Allergy and Infectious Diseases (NIAID) research efforts build on earlier research on severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which also are caused by coronaviruses (Acter et al., 2020). MERS was firstly erupted in Saudi Arabia in September 2012. According to WHO, this disease has since spread to 27 countries (Chafekar & Fielding 2018). Patients infected with MERS coronavirus (MERS-CoV) develop severe acute respiratory illness, consisted with shortness of breath, cough and fever. Infection with SARS coronavirus (SARS-CoV) can also cause a severe viral respiratory illness. It was first reported in China in February 2003 though cases subsequently were noticed from November 2002 (Rabaan et al., 2020). By the time it was being contained, SARS spreaded to 26 countries in the span of four months.

The evidence of research suggested that MERS-CoV and SARS-CoV are originated from bats and in the same manner as COVID-19 was spread as well (Rabaan et al., 2020). Furthermore, SARS-CoV spreads from infected civets to the human, while MERS-CoV spreads from infected dromedary camels to human. Scientists are still trying to find out how SARS-CoV-2 spread from an animal reservoir to human (Mahanta et al., 2020; Rabaan et al., 2020). Currently, the world is suffering from a pandemic disease COVID-19 caused by a novel strain of coronavirus, called as SARS-CoV-2 (Aanouz et al., 2020).

According to World Health Organization (WHO), as of 21 June 2020, approximately 8,807,398 confirmed cases have been estimated globally with surpassing 464,483 deaths spanning over 216 countries (WHO 2020). These numbers of cases might be contrary to the real number of cases or would have been underestimated. This can be due to the

CONTACT Arif J. Siddiqui arifjamal13@gmail.com Department of Biology, College of Science, University of Hail, Hail 2440, Saudi Arabia

availability of number of COVID-19 diagnostic test/kits or poor health services and sectors in lower income countries (Mahanta et al., 2020). Currently till date (21 June 2020), countries with the most number of recorded infected cases are United States (2,255,119 cases, 119,719 deaths and 975,038 recovered), followed by Brazil (1,067,579 cases, 49,976 deaths and 543,186 recovered), Russia (576,952 cases, 8002 deaths and 339,711 recovered), India (410,461 cases, 13,254 deaths and 235,328 recovered), United Kingdom (303,110 cases, 42,589 deaths), Spain (245,938 cases, 28,322 deaths), Peru (251,338 cases, 7861 deaths and 138,763 recovered), Italy (238,275 cases, 34,610 deaths and 182,893 recovered), Chile (236,748 cases, 4295 deaths and 196,609 recovered), Iran (202,584 cases, 9507 deaths and 163,591 recovered) and Germany (189,822 cases, 8882 deaths and 174,900 recovered) (ECDC 2020; WHO 2020; WorldOmeter 2020) (Figure 1). According to this data, it can be concluded that infection rate due to COVID-19 is spreading exponentially in new hotspots like United States and Europe, when compared to first epicenter China, where the number of new cases is rapidly declining. Therefore, at this stage, the urge and requirement of effective drug or vaccine to control the COVID-19 disease is at its peak (Islam et al., 2020; K et al., 2020).

Discovery of new drug or vaccine development after all trials for human use will take approximately further time of 1–2 years or more. However, some countries have already started efforts in making vaccine or chemoprophylaxis against COVID-19 disease, even initiation of human trials are on track (Choudhary & Sharma 2020; Khan et al., 2020; Muralidharan et al., 2020). While some drugs have shown therapeutic effect against COVID-19 infection such as hydroxychloroquine (Al-Kofahi et al., 2020; Choudhary & Sharma 2020; Liu et al., 2020; Sinha & Balayla 2020), azithromycin, (Andreani et al., 2020a; Choudhary & Sharma 2020) ivermectin (Caly et al., 2020; Chaccour et al., 2020; Choudhary & Sharma 2020) and some other antivirals (Asai et al., 2020; Boopathi et al., 2020; Lian et al., 2020). However, it is still not clear that whether these drugs have a better therapeutic effect, when compared to other drugs or combination therapy of multiple drugs with immunomodulators will prove to provide us with better results. Consequently, this review will provide an insight and comprehensive view on different therapeutic approaches including combining of different known anti-parasitic drugs, as well as proposing novel suggestions of chemoprophylaxis drug therapy, which can be used in the current treatment and vaccine development strategies against COVID-19 disease.

Survey methodology

All peer reviewed scientific papers were used for this review article. Extensive literature searches have been performed using various literature search engines, including Science Direct, PubMed, Web of Science, Google Scholar, Scopus and ResearchGate with several terms: *(1) MERS-CoV, SARS-CoV-1 and SARS-CoV-2 related articles; (2) Antimalarial drugs usages in COVID-19 disease; (3) Antiviral drugs; and (4) Immunomodulators and vaccine related compounds*. All relevant studies meeting search criteria were included in this review.

Drug therapy in use against MERS-CoV and SARS-CoV

Lacking specific antiviral treatment, both SARS-CoV and MERS-CoV pose major clinical management challenges (Lu et al., 2015). Many drugs and therapies are still under clinical trials and substantial efforts are underway to discover new therapeutic agents for coronavirus infections (Lin et al., 2018; Zumla et al., 2016). The ISARIC (International Severe Acute Respiratory & Emerging Infection Consortium), collected drugs list in July 2013 which are easily available for the treatment of pandemic influenza, MERS-CoV, SARS-CoV-1. SARS-CoV-1 came into picture first time in Southern China and quickly spreaded around the globe in 2002–2003 (Rabaan et al., 2020). With high rate of nosocomial transmission having symptoms of high fever and unusual epidemic of a typical pneumonia to health care workers was happened in Foshan, Guangdong, China on November 2002 (Sims et al., 2008). The most promising and clinically available drugs were ribavirin and interferon (IFN), or a combination of the two. The combination of drugs have shown the efficacy in an *in vivo* model for MERS-CoV infection (Figure 2) (Falzarano et al., 2013). Although, the combination could not fulfill the recovery criteria in the small number of severely ill MERS-CoV patients (Dyall et al., 2017). In an *in vitro* study, mycophenolic acid (MPA) and IFN-β were also found to be highly effective against MERS-CoV infection (Hart et al., 2014). MPA was found to be effective and specific to MERS-CoV, and also with some activity were detected against SARS-CoV infection (Chan et al., 2015; Hart et al., 2014). Clinical trials have demonstrated the expression of IP-10, IFN-γ, IL-8 and IL-6 and these cytokines are denoted the severity of the disease (Russell et al., 2020). Three FDA-approved broad-spectrum inhibitors (chlorpromazine, chloroquine, toremifene) that were shown to be effective against MERS-CoV infection in immortalized cell lines and evaluated their antiviral activities (Cong et al., 2018). Among all three drugs, toremifene is known as an estrogen receptor modulator which has been found to restrict filoviruses and thus inhibit both MERS-CoV and SARS-CoV (Cong et al., 2018).

Previously, chloroquine (CQ), a well-established anti-parasitic agent, showed strong inhibition on MERS-CoV and SARS-CoV with low toxicity (Cong et al., 2018). CQ likely accumulates in lysosomes, where it sequesters protons and increases the pH. The drug interacts with a variety of host proteins and cellular processes, resulting in modulation of immune response (Cong et al., 2018). CQ has also been reported to inhibit replication of multiple viruses such as flaviviruses, influenza viruses, human immunodeficiency virus (HIV), Ebola and Nipah viruses *in vitro* (Dyall et al., 2014). However, in other study CQ had showed the least anti-MERS activity with very low toxicity during the treatment of coronavirus (Cong et al., 2018). Although, another drug chlorpromazine, belongs to neurotransmitter inhibitor, considered as first established antipsychotic drug and was used for schizophrenia treatment (de Wilde et al., 2014). In addition,

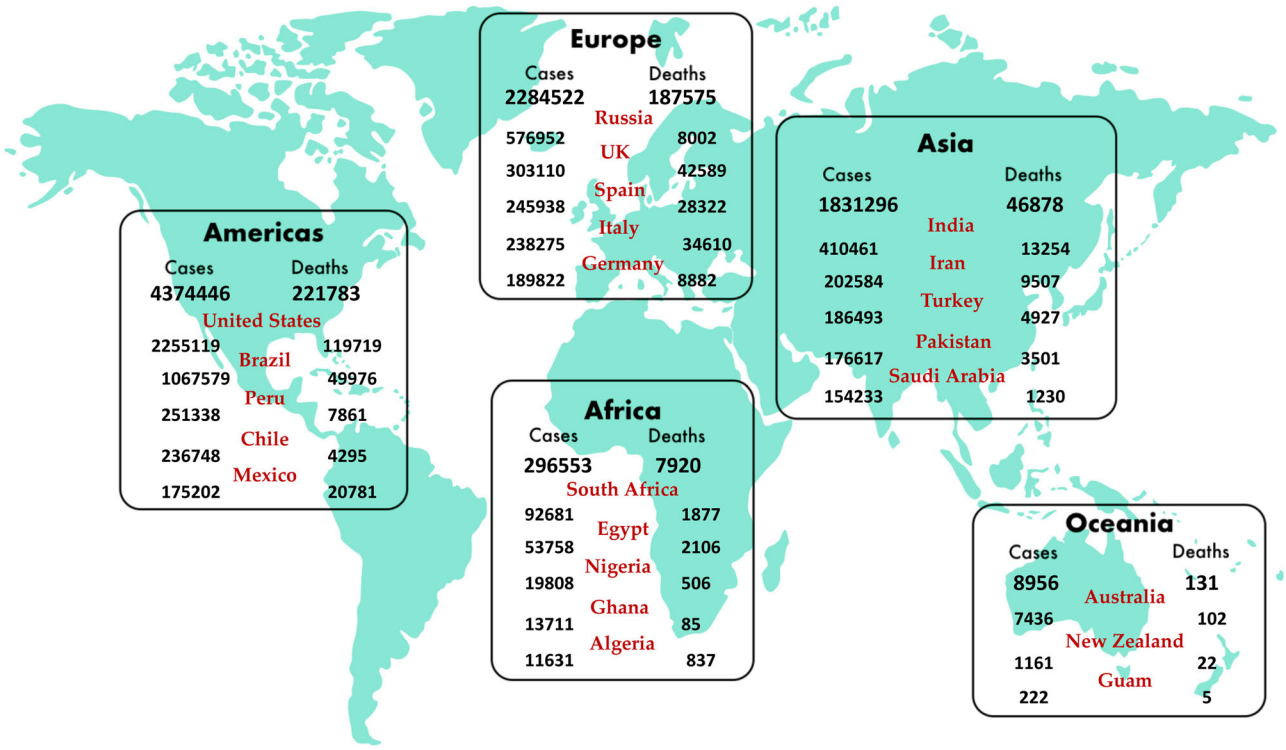


Figure 1. Pictorial world map representation of continent wise total number of cases and deaths with top affected countries until 21st June 2020. Data retrieved from (ECDC 2020).

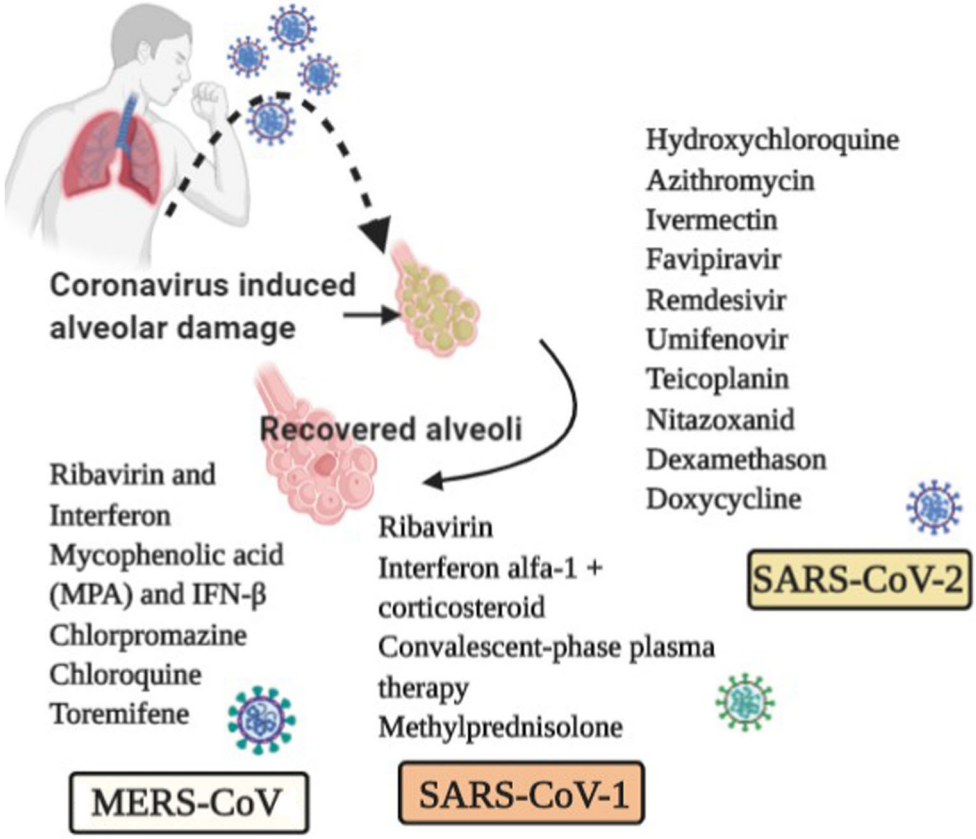


Figure 2. Diagrammatic representation of the MERS-CoV, SARS-CoV-1 and SARS-CoV-2 spread by coughing, and the possible effective drugs used against these viruses. During infection lungs alveoli get damaged, and the possible drugs can reverse the damage and restore the normal functioning of the lungs.

the mode of action of chlorpromazine is by inhibiting the clathrin-mediated endocytosis via blocking the formulation of clathrin-coated pits at the plasma membrane (de Wilde et al., 2014). According to earlier work, which has stated that

chlorpromazine have potential to inhibit MERS-CoV infection of Huh 7 cells with an EC_{50} of 4.9, vs CC_{50} of 21.3 μM (Cong et al., 2018). However, all these studies determined the tested compounds, each of which were shown to be efficacious in continuous cell lines, and could be a promising therapeutic drugs to treat the coronaviruses related diseases.

Current status of various drug therapy in use for the treatment of COVID-19 with their possible antiviral effects and mechanism of action

There are many drugs which are currently in use for the treatment of COVID-19 disease and most of the drugs are under clinical trials (Table 1).

Hydroxychloroquine (HCQ)

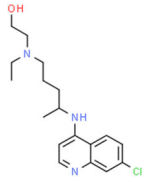
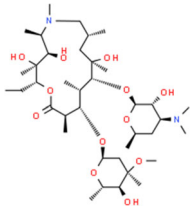
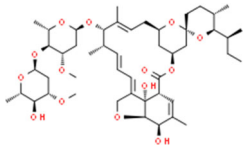
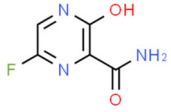
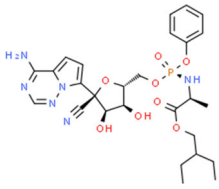
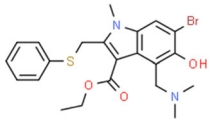
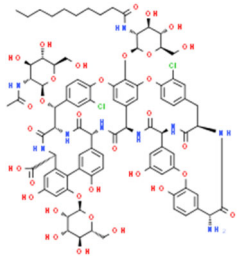
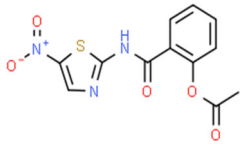
The HCQ is the derivative of CQ, and is the first category drug which is working as a therapeutic agent against COVID-19 infection (Beura & Prabhakar 2020; Choudhary & Sharma 2020; Sinha & Balayla 2020). This drug has also been previously used for the treatment of rheumatoid arthritis and systemic lupus erythematosus (Adeoye et al., 2020; Sinha & Balayla 2020) and is a first line drug for malaria treatment (Azad et al., 2017; Bhardwaj et al., 2016; Roesch et al., 2020; Siddiqui et al., 2015). Effect of HCQ on viral replication goes beyond cytokines inhibition (Asai et al., 2020; Bhardwaj et al., 2015; Siddiqui, Bhardwaj, et al., 2020; Siddiqui, Adnan, et al., 2020; Sinha & Balayla 2020). It acts as weak base and tend to increase the pH within the intracellular vacuole (Choudhary & Sharma 2020; Hasan et al., 2020; Sinha & Balayla 2020). Due to the weak base of this medication, it may affect acid balance and can inhibit many enzymes. This specific feature of HCQ possibly inhibits the viral entry to the cell (Asai et al., 2020; Sinha & Balayla 2020). It is also known to obstruct the viral post-translational modifications and glycosyl-transferases (Choudhary & Sharma 2020). Furthermore, it has been known to modify the processes such as degradation of protein through acidic hydrolases in the lysosome (Figure 3) (Choudhary & Sharma 2020). The impact of antiretroviral has been considered due to inhibition of viral glycosylation; a significant antiviral mechanism of HCQ (Asai et al., 2020). Additionally, it also inhibits the protein replication of viruses by blocking/distracting the pathway of endosome/lysosome or viral protein maturation. Some studies have revealed the possible mechanism of HCQ and its activity against COVID-19 (Liu et al., 2020; Sinha & Balayla 2020).

Most of the countries are currently using HCQ for the treatment and management of COVID-19. However, many recent studies showed that the use of HCQ in hospitalized COVID-19 patients had no impact on the risk of the most severe outcomes from the disease (Ferner & Aronson 2020a; Geleris et al., 2020). Furthermore, latest published data showed that, treatment with HCQ in 97 hospitalized patients of COVID-19, reduced the risk of mechanical ventilation. Although, mortality rate was higher in patients who got the treatment with HCQ alone (Magagnoli et al., 2020). Another study also showed similar data that high dose of HCQ drug is not of any apparent benefit and also the mortality rate is still high (Borba et al., 2020). Likewise, Joshua Geleris et al., also treated 811 COVID-19 patients with HCQ (600 mg twice on day 1, then 400 mg daily for a median of 5 days), and the authors said the results should not be rule out either benefit or harm from HCQ use, however, the finding of this study do not support continued use of HCQ drug in COVID-19 patients (Geleris et al., 2020). Furthermore, Gautret et al., study showed that HCQ treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients (Gautret et al., 2020a). Similarly, Zhaowei Chen et. al, study showed that the use of HCQ drug in patients with COVID-19 was just providing a significant recovery in the short period (Chen et al., 2020). Data collected by WHO, regarding safety and efficacy of HCQ as the treatment of COVID-19, the team of Executive Group of the Solidarity Trial decided to implement a temporary pause on HCQ trials as a precautionary measure. However, HCQ has been registered for clinical trial in more than 13 different countries and approximately 40 randomized clinical trials started giving answer about HCQ's efficacy against COVID-19 (Bienvenu et al., 2020). We need to wait to shed more light, based on clinical evidences for using HCQ against COVID-19 patients.

Azithromycin

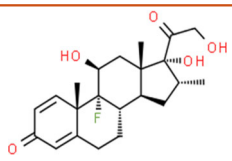
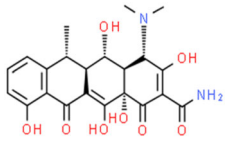
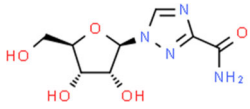
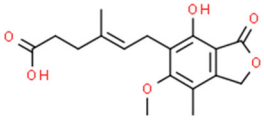
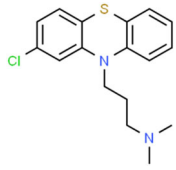
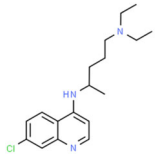
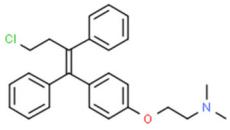
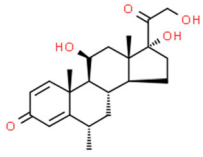
Azithromycin is the **s**econd choice of antimalarial drug to use against COVID-19 and it belongs to the class of antibiotics (Andreani et al., 2020a; Bakheit et al., 2014; Soni et al., 2015). Many studies have recently revealed the therapeutic effect of azithromycin against the COVID-19 infection (Andreani et al., 2020a; Asai et al., 2020; Choudhary & Sharma 2020). However, the exact mechanism is still unknown, but multiple mechanisms have been proposed for the putative antiviral properties determined with azithromycin drug. Some researches states that azithromycin acts as acidotropic lipophilic weak base, which changes (increase) the pH level of endosome maturation and trans-golgi network (Asai et al., 2020; Choudhary & Sharma 2020). Moreover, it can potentially inhibit endocytosis and viral genetic shedding from lysosomes, ultimately restricting viral replication (Gravesen & Judy 2020). Similarly, influenza and HIV also needs an acidic environment for the uncoating of the envelop. However, coronavirus also belongs to enveloped virus and it might have similar mechanism (Choudhary & Sharma 2020; Thanh Le et al., 2020). Likewise, these kinds of mechanisms have also been found inHCQ. Furthermore, azithromycin directly acts on bronchial epithelial cells by decreasing mucus secretion to enable and enhances the lung function (Choudhary & Sharma 2020). Recently, quantum mechanical modeling proposed a possible role of azithromycin drug in interfering with viral entry through binding collaboration between the COVID-19 spike protein and host receptor ACE2 protein (Angiotensin Converting Enzyme 2) (Figure 3) (Basit et al., 2020; Choudhary & Sharma 2020; Lobo-Galo et al., 2020). However, clinical trials are still necessary to confirm the role of the drug and its work as prophylaxis in reducing the infection rate. Azithromycin is currently

Table 1. List of drugs used in the treatment of MERS-CoV, SARS-CoV-1 and SARS-CoV-2 with their chemical structure, biological activity and possible mechanism.

Drugs name	Chemical structure	Biological activity/Therapeutic effect	Mode of action	References
Hydroxychloroquine		Used in the treatment of malarial and inflammatory activities. It is also now often used as an anti-rheumatologic agent in systemic lupus erythematosis and rheumatoid arthritis. Currently, this drug is used against SARS-CoV-2.	Inhibits terminal glycosylation of ACE2, the receptor that SARS-CoV-2 target for cell entry. ACE2 that is not in the glycosylated state may less efficiently interact with the SARS-CoV-2 spike protein, further inhibiting viral entry.	(Gautret et al. 2020a; Liu et al. 2020)
Azithromycin		It is used orally in children for the treatment of acute otitis media, malaria and also against SARS-CoV-2	Interferes with viral entry through binding collaboration between the COVID-19 spike protein and host receptor ACE2 and block the viral entry.	(Andreani et al. 2020b; Asai et al. 2020)
Ivermectin		It is a macrocyclic lactone derived from *Streptomyces avermitilis* with antiparasitic activity such as nematodes, scabies and onchocerciasis (river blindness). Now this drug is also used against SARS-CoV-2.	Acts and prevents the import (integrase protein and importin (IMP) $\alpha/\beta1$ heterodimer) through the rise in antiviral response, inhibits the nuclear import of viral and host protein	(Caly et al. 2020; Choudhary & Sharma 2020)
Favipiravir		It is a pyrazinecarboxamide derivative with activity against RNA viruses. It has been investigated for the treatment of life-threatening viruses such as Ebola virus, Lassa virus, and now COVID-19.	Targets RNA-dependent RNA polymerase (RdRp) enzymes that are important for the transcription and replication of viral genomes.	(Asai et al. 2020; Coomes & Haghbayan 2020)
Remdesivir		It belongs to prodrug of an adenosine triphosphate (ATP) analog. Its activity against viruses such as Lassa fever, Nipah, Hendra, respiratory syncytial, Junin, MERS, SARS-CoV-1 and SARS-CoV-2 coronaviruses.	Inhibits RNA-dependent RNA polymerases, conceivably through the interruption of RNA chain termination in the host cells.	(Augustin et al. 2020; Hendaus 2020)
Umifenovir		It is a derivative of indole carboxylic acid and is commonly used for the treatment of influenza A and B viruses and hepatitis C virus. Currently this drug has shown potential efficacy against COVID-19 disease.	Obstructs viral cell membrane fusion as well as virus endosome fusion with the host cell membrane and also this drug interferes with hydrogen bonding network of phospholipid.	(Costanzo et al. 2020; Pshenichnaya et al. 2019)
Teicoplanin		It is a glycopeptide antibiotic complex isolated from the bacterium *Actinoplanes teichomyceticus* and commonly used for the treatment of bacterial infections cause by Gram positive bacteria. It has also showed efficacy against HIV, Ebola virus, HCV, flavivirus, influenza virus and coronaviruses infection	Act on early stage of the viral life cycle by blocking or inhibiting the low-pH cleavage of the viral spike protein through cathepsin L in the late endosome, thus stopping the release of genomic viral RNA and preventing virus replication cycle inside the host cell.	(Pandey et al. 2020; Zhang, Ma, et al. 2020a)
Nitazoxanide		Activity against several parasitic worms and protozoa that is used predominantly in the United States in treatment of giardiasis and cryptosporidiosis. Also effective against viral diseases (HIV, HCV, HBV, rotavirus, influenza virus, MERS-CoV)	Enhance the production of interferon-α and interferon-β, It also selectively inhibit the maturation of the hemagglutinin glycoprotein at the post-translation stage.	(Calderon et al. 2020; Pepperrell et al. 2020)

(*continued*)

Table 1. Continued.

Drugs name	Chemical structure	Biological activity/Therapeutic effect	Mode of action	References
Dexamethasone		It is a synthetic adrenal corticosteroid with potent anti-inflammatory properties. It is used for a long time to treat arthritis and asthma. Currently, this drug is used in the treatment of COVID-19 infected patients in United Kingdom	The mechanism of action of this drug is not clear against SARS-CoV-2. However, it may inhibit phospholipase A2, which decreases the formation of arachidonic acid derivatives; they inhibit NF-Kappa B and other inflammatory transcription factors; they promote anti-inflammatory genes like interleukin-10.	(Al Saleh et al. 2020; Theoharides & Conti 2020)
Doxycycline		It is a synthetic, broad-spectrum tetracycline antibiotic exhibiting antimicrobial activity. Currently, it is also in use for treatment against COVID-19 disease.	Chelate zinc from MMPs and on the basis of chelating activity of this antibiotic, it might help in inhibiting SARS-CoV-2.	(Conforti et al. 2020; Malek et al. 2020; Szolnoky 2020)
Ribavirin		It is a nucleoside analogue and antiviral agent used in therapy of chronic hepatitis C, other flavivirus and coronavirus infections.	Ribavirin is incorporated into viral RNA, thereby inhibiting viral RNA synthesis, and inhibiting normal viral replication.	(Dyall et al. 2017; Falzarano et al. 2013)
Mycophenolic acid		It is an antineoplastic antibiotic derived from various *Penicillium* fungal species. It is an active metabolite of the prodrug mycophenolate mofetil and has antibacterial, antifungal, and antiviral activities.	The mechanism of action of this drug is still unknown for SARS-CoV-2. However, in case of MERS-CoV, they synergistically inhibit the papain-like protease (PLpr).	(Chan et al. 2015; Hart et al. 2014)
Chlorpromazine		It is a phenothiazine that was once the most commonly prescribed antipsychotic agent, but it is now rarely used.	Coronaviruses has been using clathrin-mediated endocytosis pathway to enter human cells. This drug has potential to inhibit clathrin-mediated endocytosis pathway for entry of viruses.	(Cong et al. 2018; de Wilde et al. 2014)
Chloroquine		It is an aminoquinoline used for the prevention and therapy of malaria. It is also effective in extraintestinal amebiasis and act as an anti-inflammatory agent for therapy of rheumatoid arthritis and lupus erythematosus	Does not affect the level of ACE2 expression on cell surfaces, but inhibits terminal glycosylation of ACE2, the receptor that SARS-CoV and SARS-CoV-2 target for cell entry	(Cong et al. 2018; Dyall et al. 2014)
Toremifene		It is a non-steroidal antiestrogen that is used in the treatment of estrogen receptor positive breast cancer. Long term toremifene therapy has been associated with development of fatty liver, steatohepatitis, cirrhosis, and rare instances of clinically apparent acute liver injury	Inhibits the spike protein and NSP14 (methyltransferase non-structural protein) of SARS-CoV-2.	(He et al. 2020; Zhou et al. 2020)
Methylprednisolone		It is a synthetic corticosteroid with anti-inflammatory and immunomodulating properties.	Methylprednisolone binds to and activates specific nuclear receptors, resulting in altered gene expression and inhibition of proinflammatory cytokine production.	(Wang et al. 2020; Zhu et al. 2020)

under clinical trial and has reached phase IV with promising results (NCT02048007).

Ivermectin

Ivermectin is generally used for the treatment and control of filarial diseases (Murthy 2019). Recently, its usage against COVID-19 infection showed some positive results and patients response. *In vitro* study on ivermectin have also been found very effective against positive-sense single-stranded RNA viruses, such as dengue, Zika and yellow fever, via inhibiting the viral replication (Azeem et al., 2015; Choudhary & Sharma 2020; Gotz et al., 2016; Mastrangelo et al., 2012). Similarly, recent report suggested that Ivermectin have a potential to inhibit COVID-19 replication *in vitro* (Caly et al., 2020). Moreover, the treatment of

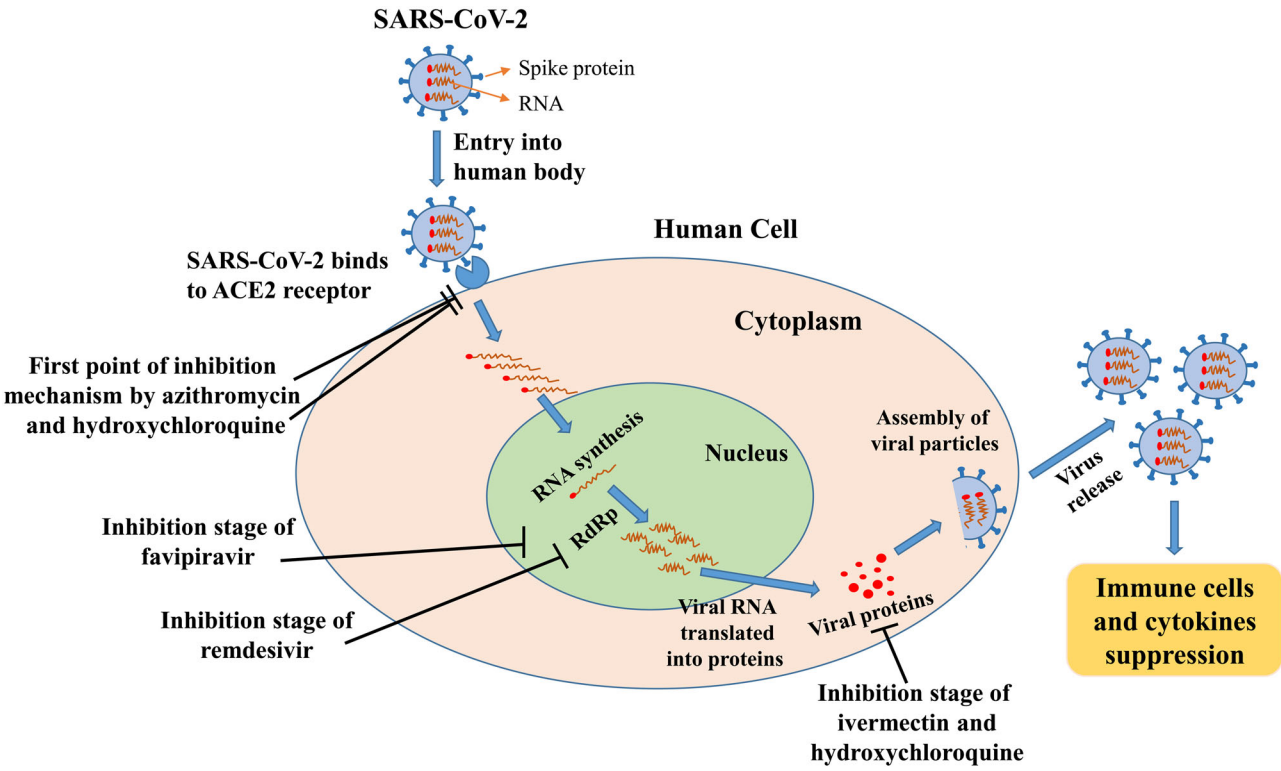


Figure 3. Model depicting the proposed drugs (hydroxychloroquine, azithromycin, ivermectin, favipiravir, remdesivir) with their possible acting points and mechanism* against SARS-CoV-2.

*SARS-CoV-2 enters the human cell and initiate its replication cycle. First stage starts with the binding of SARS-CoV-2 virus with ACE2 receptor, followed by transfer of viral RNA in to the human cell. RNA-dependent RNA polymerase (RdRp) enzyme initiates the production of viral RNAs. During RNA methylation, RNA cap is formed, which protects against the innate immune responses. Furthermore, during the process of viral RNA synthesis, translation of proteins is associated with pH-dependent membrane stress, which possibly elicits adverse effects against immune cells and cytokines. During this stage, if the viral replication cycle is not inhibited or infected cells are not eradicated; packed/assembled viruses will get disseminated and transfect other healthy host cells.

COVID-19 by the single dose of Ivermectin was found to reduce the viral load up to 5000 fold *in vitro* culture within 48 h (Caly et al., 2020). However, the best part of this drug is that no toxicity was observed during *in vitro* culture. Mechanism of action of this drug against COVID-19 is still unknown, though researchers believed that this drug is working in a similar way it acts on other viruses. Single stranded RNA viruses are mostly dependent on integrase protein and importin (IMP) $\alpha/\beta1$ heterodimer during infection, and this drug acts and prevents the import through the rise in antiviral response that ivermectin inhibits the nuclear import of viral and host protein (Caly et al., 2020; Choudhary & Sharma 2020) (Figure 3). Ivermectin has passed the phase I of clinical trial and now 200 mcg/kg dose of ivermectin is under phase II clinical trial (NCT04407130).

Favipiravir

Favipiravir is generally used for the treatment and control of influenza virus (Delang et al., 2018; Elfiky 2020; Furuta et al., 2017). This medicine was first licensed by Japan and largely used as an anti-influenza drug. It's efficacy in inhibiting other viruses such as Ebola, Lassa and rabies have been seen effectively (Asai et al., 2020). This drug is a derivative of pyrazinecarboxamide and it is being developed and manufactured by Fujifilm group. It targets RdRp enzymes, that is important for the transcription and replication of viral genomes (Coomes & Haghbayan 2020). Furthermore, favipiravir also has a potential to use for the treatment of avian influenza and other influenza strains that are resistant to neuramidase inhibitors (Coomes & Haghbayan 2020). The mechanism of action of favipiravir is described previously; it acts on viral RNA synthesis as a chain terminator at the specific site, where the RNA is incorporated into the host cell (Figure 3). Furthermore, this drug is not effective against DNA based viruses. Conversely, this specific property of favipiravir proves to have a positive outcome in the treatment of COVID-19 disease (Asai et al., 2020). Currently, favipiravir is under clinical trial and it has passed phase I and II with promising results (NCT04359615). Significantly, some study showed that the treatment of COVID-19 patients with favipiravir showed reduction in the load of SARS-CoV-2 when compared with control groups (Cai et al., 2020; Coomes & Haghbayan 2020; Lu et al., 2020). The pharmaceutical company Glenmark, India launched antiviral drug favipiravir under the brand name FabiFlu on 20th June 2020 for the treatment of mild to moderate COVID-19 patients. However, FabiFlu is the first oral favipiravir drug approved medication in India for the treatment of COVID-19 infected patients. Dose of favipiravir is administrated orally, 1800 mg twice daily on day 1 than 800 mg twice daily up to 14 days.

Remdesivir

Remdesivir is generally used for the treatment and control of Ebola and Marburg virus (Babadaei et al., 2020; Tchesnokov et al., 2019). Remdesivir belongs to prodrug of an adenosine

triphosphate (ATP) analog. Furthermore, after administration it gets metabolized into its active form GS-441,524 (Cao et al., 2020). Its activity against many other viruses such as Lassa fever, Nipah, Hendra, respiratory syncytial, Junin, MERS and SARS coronaviruses has also be seen (Asai et al., 2020; Hendaus 2020). However, the mechanism of action of this drug is shown by the inhibition of RdRp enzymes, conceivably through the interruption of RNA chain termination in the host cells (Figure 3) (Augustin et al., 2020). Consequently, it has been suggested that, remdesivir may be one of most useful and effective drug for the treatment of COVID-19 disease (Asai et al., 2020; Ferner & Aronson 2020b). *In vitro* testing with remdesivir has showed good results with significant reduction in SARS-CoV-2 load (Grein et al., 2020). Moreover, remdesivir has already reached phase III clinical trials against SARS-CoV-2 (NCT04365725) after encouraging pre-clinical results against SARS-CoV (Agostini et al., 2018; Sheahan et al., 2017) and MERS-CoV (de Wit et al., 2020).

Umifenovir

Umifenovir is commonly used for the treatment of influenza A and B viruses and hepatitis C virus (Pshenichnaya et al., 2019). Umifenovir is a derivative of indole carboxylic acid. This drug was firstly developed by Russia in 1988 (Pshenichnaya et al., 2019). However, after *in vitro* demonstration, this drug showed some potential to treat Ebola virus, human herpes virus, Tacaribe arenavirus (Pshenichnaya et al., 2019). The mechanism of action of umifenovir is known, it obstructs viral cell membrane fusion as well as virus endosome fusion with the host cell membrane. It also interferes with hydrogen bonding network of phospholipid (Costanzo et al., 2020). However, in other diseases caused by influenza virus, umifenovir directly interacts with virus particles to stabilize hemagglutinin. Blaising et.al 2020 first showed the *in vitro* activity of umifenovir with good results against SARS-CoV-1 and SARS-CoV-2 (Wu et al., 2020). Currently, umifenovir is undergoing clinical trials as a single agent (NCT04260594, NCT04255017) and also in randomized human clinical trial for comparison with favipiravir (ChiCTR2000030254).

Teicoplanin

Teicoplanin is a glycopeptide antibiotic and basically used in the prophylaxis and treatment of bacterial infections caused by Gram positive bacteria such as *Staphylococcus aureus* and *Enterococcus faecalis* (Shea & Cunha 1995). However, teicoplanin have also showed good efficacy against many viruses such as HIV, Ebola virus, hepatitis C virus (HCV), flavivirus, influenza virus, as well as MERS-CoV and SARS-CoV infection (Baron et al., 2020). Recently, *in vitro* study suggests that, teicoplanin has potential efficacy to inhibit the virus activity and reduces the load of SARS-CoV-2 (Pandey et al., 2020; Zhang, Ma, et al., 2020). Furthermore, Zhang et al., 2020 suggested that the concentration of teicoplanin antibiotic requires to inhibit the viral activity that is IC_{50} value of 1.66 uM (Zhang, Ma, et al., 2020). It acts on early stage of the viral life cycle by blocking or inhibiting the low-pH cleavage of the viral spike protein through cathepsin L in the late endosome. Thus, this way it stops the releasing of genomic viral RNA and preventing the viral replication cycle inside the host cell (Pandey et al., 2020). Therefore, teicoplanin needs to be further investigated for its potential effect against SARS-CoV-2 by randomized clinical trials, and hopefully this antibiotic will come out with some promising results.

Nitazoxanide (thiazolide)

Nitazoxanide is used for the treatment of parasitic diseases (cryptosporidiosis and giardiasis) that cause diarrhea, and viral diseases (HIV, HCV, hepatitis B virus (HBV), rotavirus, influenza virus, MERS-CoV) (Pepperrell et al., 2020; Simsek Yavuz & Unal 2020). Previous *in vitro* study suggested that, tizoxanide; the active circulating metabolite of nitazoxanide, inhibits the replication of the viruses (Calderon et al., 2020). The amount of drug required to inhibit viral replication by 50% (IC50s) are between 0.2 and 1.5 μg/ml in human and canine cell lines (Pepperrell et al., 2020). Furthermore, nitazoxanide has a potential capacity to enhance the production of interferon-α and interferon-β, which has been previously shown *in vitro* to exhibit activity against MERS-CoV, rotavirus, HBV, HCV, influenza virus and SARS-CoV-1 (Calderon et al., 2020). This drug has been shown to selectively inhibit the maturation of the hemagglutinin glycoprotein at the post-translation stage (Calderon et al., 2020). Nitazoxanide is currently under clinical trial to confirm its effectiveness with a dose of 500 mg alone or in combination with other drugs against COVID-19 (NCT04406246). Nitazoxanide is known for its safety in humans. Research showed the tolerability of single doses up to 4 g with minimal gastrointestinal side effects (Rajoli et al., 2020).

Doxycycline (tetracycline)

Doxycycline belongs to tetracycline antibiotic, that work against and inhibit various bacterial infections such as urinary tract infection, intestinal infection, gonorrhea, chlamydia and others (Ali et al., 2017). Currently, doxycycline is also under use for the treatment against COVID-19, because coronavirus is well-known to bind with metalloproteases (MMPs) of the host cells, in particular to ensure viral survival (Conforti et al., 2020). Furthermore, doxycycline is known to chelate zinc from MMPs, and on the basis of chelating activity of this antibiotic might help in inhibiting SARS-CoV-2 (Conforti et al., 2020; Szolnoky 2020). On the other hand, it is also known that these class of antibiotics have the ability to inhibit the replication of positive polarity single stranded RNA viruses (Szolnoky 2020). It is also used for the treatment of inflammatory skin diseases for long time, due to modulatory activity of innate immune response generation by this antibiotic (Malek et al., 2020). Due to modulating effect, it can decrease the expression of NF-κB and releases the inflammatory cytokines such as tumor necrosis factor-α, interleukin-1β and interleukin-6, which can inhibit granulomas inflammatory response and release free radicals (Malek et al., 2020). Therefore, due to these properties, possibility to inhibit the viral replication of SARS-CoV-2 inside the human

cells is high (Malek et al., 2020). Currently, doxycycline has already reached phase III clinical trials with 200 mg of daily dose given to patients that are infected with SARS-CoV-2 (NCT04371952).

Dexamethasone

The drug dexamethasone is used since long time for the treatment of arthritis and asthma. Currently, it is used in treatment of COVID-19 infected patients in United Kingdom and under clinical trials. According to one research team, they got effectual and promising results (Al Saleh et al., 2020). However, it is known that patients with advance stage of COVID-19 infection have severe lung inflammation, but clinicians are checking for the dexamethasone effectiveness results in last stage of infection (Theoharides & Conti 2020). 2104 COVID-19 infected patients were randomly selected for clinical trial and all patients were administrated with 6 mg dexamethasone once a day for 10 days (Theoharides & Conti 2020). In addition, it has reduced the death rate by one third in ventilated patients, according to press release from the recovery trial organizers (NCT04381936).

Current status or possible strategies in vaccine development

More than 80 countries have started the development strategies to make a vaccine against COVID-19. Currently, over 90 different vaccines are being developed by these countries using various approaches and novel technologies (Mandal 2020; Thanh Le et al., 2020). However, some groups are already in a stage of human trials, while others are still testing on animals (Thanh Le et al., 2020). Presently, formulation of vaccines against COVID-19 are divided into eight categories i.e. virus-weakened form, virus-inactivated form, replicating viral vector vaccine, non-replicating viral vector vaccine, nucleic acid based vaccine (DNA and RNA), protein based vaccine (protein sub-unit vaccine and virus like particles vaccine) (Thanh Le et al., 2020).

Possible suggested immunomodulators and combinational therapies against COVID-19

Currently, there are many drugs which are in use and trials for curing this pandemic disease COVID-19. Many studies have showed and determined that COVID-19 infection suppresses the immune system (Aziz et al., 2020; Yaqinuddin & Kashir 2020). Therefore, we need to ponder over other options which might have therapeutic potential: (1) use of combinational therapy with effective immunomodulators with known mechanism of action, which can enhance the functioning and response of immune system. Some important immunomodulators with their pharmacological effects have been listed in Table 2; (2) use of some other anti-malarial drugs such as artemisinin derivative and amodiaquine, because artemisinin has also shown antiviral activity. Mode of action of artemisinin is still not clear, but there is a possibility that it interferes with the viral replication, because of its usage for the treatment of severe malaria, helminths parasites and cancer. However, amodiaquine's mode of action is similar to HCQ, (3) similarly, we must think of new drug approaches which can act on ACE 2 receptor, because COVID-19 virus uses its surface of spike protein to block onto ACE 2 receptor on the surface of host receptor, (4) another possible suggestion is to use two or three different combination of drugs i.e. ivermectin, HCQ and azithromycin antimalarial drug in combination with favipiravir or remdesivir antiviral drug with immunomodulators or BCG vaccine for the treatment of COVID-19 infection. However, researchers have already started using combination therapy for treating the COVID-19 patients, but new approaches and combination of drugs are still needed, which can work in multiple way to cure the patients infected with SARS-CoV-2.

Current combination drug therapies against SARS-CoV-2

Clinicians all over the world using combination drug therapy for the treatment of COVID-19, which includes varieties of drugs in combination with different drugs and immunomodulators or natural remedies. Some drugs work well, while others not. Below are some drug combinations which are currently in use to treat COVID-19 infected patients.

Hydroxychloroquine (HCQ) plus azithromycin (AZ)

HCQ + AZ based treatment showed an apparent accelerated virus load clearance in the patients. This combination is already in use with phase III clinical trials underway (Andreani et al., 2020b; Gautret et al., 2020b). Administration of HCQ + AZ in the COVID-19 patients are given for 5 days with loading dose of 400 mg (HCQ) + 500 mg (AZ) for first day and 200 mg (HCQ) + 250 mg (AZ) for the next four days (NCT04347512). Fruitful results have been observed.

Hydroxychloroquine (HCQ) plus nitazoxanide (NZ)

Another combination for the treatment of COVID-19 patients has reached phase II clinical trials. In this combination (HCQ + NZ), both drugs have different mode of action and both works in two different sites of virus. However, the administration of HCQ + NZ drugs for COVID-19 patients are given for 10 days, three times daily with loading dose of 200 mg (HCQ) and 500 mg (NZ) given orally twice daily for 6 days (NCT04361318). Still, we need to wait further for the evaluation and efficacy of clinical results of this combination.

Nitazoxanide (NZ) plus ivermectin (IV)

This combination of drugs (NZ + IV) have also been in use for the treatment of COVID-19 infected patients (Pepperrell et al., 2020; Simsek Yavuz & Unal 2020), and is in phase II of clinical trial with 100 participants. Both drugs have the potential to inhibit SARS-CoV-2 infection. In addition, mode of action of both drugs is different, they inhibit viral protein synthesis and viral replication respectively. However, the administration of these two drugs are orally with 200 mcg/kg

Table 2. List of some important and possible immunomodulators with their pharmacological effects for activated or enhance immunity against SARS-CoV-2.

Family	Immunomodulators	Pharmacological effect
Bacterial products	Muramyl dipeptide (MDP)	Activation of macrophage (APC and phagocytosis)
	Bacillus Calmette-Guerin (BCG)	Activation of macrophage (APC) NK cells, B-lymphocytes.
	Lipopolysaccharides (LPS)	Activation of macrophage and B-lymphocytes
Synthetic drug	Levamisole	Maturation and activation T-lymphocytes, phagocytosis and chemotaxis.
Recombinant cytokines	Interferon-gamma	Proliferation of monocytes, activation of macrophage, lymphocytes, NK cells, increase expression of MHC-II
	Interleukin-12	Proliferation of monocytes, activation of macrophage, lymphocytes, NK cells, increase expression of MHC-II
Synthetic DNA molecule	CpG-ODN	TLR-9, Activation macrophage, dendritic cells, T & B lymphocytes
Plant extract	Echinacea species extract	Uses in respiratory tract infections and inflammatory conditions, including common cold, coughs, bronchitis, and inflammation of mouth and pharynx

ivermectin on empty stomach plus 500 mg nitazoxanide twice daily with food for 6 days (NCT04360356).

Azithromycin (AZ) plus nitazoxanide (NZ)

Another important combination will soon be going for clinical trials. These two drugs (AZ and NZ) have shown good efficacy against SARS-CoV-2 (Kelleni 2020), while acting on different sites of virus life cycle as described in Table 1. Administered dose is 600 mg of NZ drug alone is currently in use for the treatment of COVID-19 (Kelleni 2020). This combination needs to be considered and tested for positive and effective results.

Ivermectin (IV) plus doxycycline (DX)

IV and DX showed good results in using alone administered treatment in COVID-19 patients. Due to the effective response, this combination is under phase II clinical trial. Here, the mode of action of these two drugs is different and doxycycline also increases the pro-inflammatory response after inhibiting NF-κB pathway (Malek et al., 2020). Administration dose of these two drugs is 200 mcg/kg ivermectin as single dose with 200 mg doxycycline on day 1, followed by 100 mg doxycycline at every12 hour for 4 days (NCT04407130). However, this is still in very initial phase of clinical trials, thus we need to wait more for the outcome of this combination clinically.

Favipiravir (FV) plus hydroxychloroquine (HCQ) and favipiravir (FV) plus azithromycin (AZ)

The new way of combination drug therapy in use for the treatment of COVID-19 such as antiviral and antimalarial drugs FV + HCQ and FV + AZ combinations. The mode of action of FV is different when compared with HCQ and AZ, which is a good sign where combination will prove to provide with good results (Jean et al., 2020). Furthermore, these combinations has already reached the phase III clinical trials. Administration of these two drugs are 800 mg HCQ on day 1, followed by 400 mg doses for 2–5 days with 3200 mg FV on day 1, followed by 1200 mg on 2–5 days. On the other hand, the current drug combination of FV and AZ dose used against COVID-19 infected patients are 500 mg AZ on day 1, followed by 250 mg doses for 2–5 days with 3200 mg FV on day 1, followed by 1200 mg on 2–5 days (NCT04411433).

Favipiravir (FV) plus tocilizumab (TZ) and remdesivir (RD) plus tocilizumab (TZ)

Another approach to create new drug combination for the treatment of COVID-19 infected patients is by using antiviral drug plus cytokine (IL-6) blocking agent such as TZ. TZ is currently used to treat cytokines release syndrome (CRS) and arthritis (Zhang, Li, et al., 2020). During SARS-CoV-2 infection, the researcher observed that many cytokines increases and one of them is interleukin-6. The mechanism of action of TZ is still not clear. However, this drug has been started using in clinical trials with combination of FV and RD and have reached phase III of clinical trials. Administration of these two drugs are 1600 mg of FV twice on day 1, followed by 600 mg doses twice for 2–7 days with 400 mg TZ on day 1 (NCT04310228). Moreover, drug combination with TZ + RD has also reached the clinical trial level (NCT04409262).

Umifenovir (UF) plus lopinavir (LP)/ritonavir (RT) plus hydroxychloroquine (HCQ) plus interferon-β 1a (IA)

Recently, antiviral drugs such as UF, LP/RT, HCQ (anti-malarial) and immunomodulator interferon-β 1a have been used as potential effective agents against COVID-19. Furthermore, these combinations have already reached phase IV clinical trials for the treatment of COVID-19 patients (NCT04350684). However, there is another drug combination IA + LP/RT + ribavirin, which was also used to treat COVID-19 patients and shown good results of viral load elimination from nasopharyngeal swabs in phase II clinical trials (Jalkanen et al., 2020).

Conclusion

Till date, there is no specific drug or vaccine has been developed against COVID-19 disease. It is important to develop a specific and novel inhibitor for blocking the viral entry and

its replication on the host cells, which will essentially control this pandemic disease. As we know that, there are many clinical trials related to new drugs, drug repositioning and vaccine development studies against novel coronavirus are on track. However, novel strategies like combinational therapeutic approaches with different drugs and immunomodulators will possibly show a better path in controlling COVID-19 infection. Furthermore, at this stage, computational approaches could help and lead us in developing or designing new therapeutic drugs at rapid level. On the other hand, successful vaccine development can only be achieved by using variety of therapeutic approaches and correctly shared information. This is significant and a must requirement to develop an important vaccine against COVID-19 and eradicate this pandemic from the world.

Disclosure statement

The authors have declared no conflict of interest.

ORCID

Arif Jamal Siddiqui http://orcid.org/0000-0002-6236-0920
Mitesh Patel http://orcid.org/0000-0002-9283-2124
Mohd Adnan http://orcid.org/0000-0002-7080-6822

References

Aanouz, I., Belhassan, A., El-Khatabi, K., Lakhlifi, T., El-Ldrissi, M., & Bouachrine, M. (2020). Moroccan Medicinal plants as inhibitors against SARS-CoV-2 main protease: Computational investigations. *Journal of Biomolecular Structure and Dynamics*, *6*, 1–9. https://doi.org/10.1080/07391102.2020.1758790

Acter, T., Uddin, N., Das, J., Akhter, A., Choudhury, T. R., & Kim, S. (2020). Evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as coronavirus disease 2019 (COVID-19) pandemic: A global health emergency. *The Science of the Total Environment*, *730*, 138996. https://doi.org/10.1016/j.scitotenv.2020.138996

Adeoye, A. O., Oso, B. J., Olaoye, I. F., Tijjani, H., & Adebayo, A. I. (2020). Repurposing of chloroquine and some clinically approved antiviral drugs as effective therapeutics to prevent cellular entry and replication of coronavirus. *Journal of Biomolecular Structure and Dynamics*, *15*, 1–11. https://doi.org/10.1080/07391102.2020.1765876

Agostini, M. L., Andres, E. L., Sims, A. C., Graham, R. L., Sheahan, T. P., Lu, X., Smith, E. C., Case, J. B., Feng, J. Y., Jordan, R., Ray, A. S., Cihlar, T., Siegel, D., Mackman, R. L., Clarke, M. O., Baric, R. S., & Denison, M. R. (2018). Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *mBio 9*, *9*(2), e00221. https://doi.org/10.1128/mBio.00221-18

Al-Kofahi, M., Jacobson, P., Boulware, D. R., Matas, A., Kandaswamy, R., Jaber, M. M., Rajasingham, R., Young, J. H., & Nicol, M. R. (2020). Finding the dose for hydroxychloroquine prophylaxis for COVID-19; the desperate search for effectiveness. *Clinical Pharmacology & Therapeutics*, 1–4. https://doi.org/10.1002/cpt.1874

Al Saleh, A. S., Sher, T., & Gertz, M. A. (2020). Multiple myeloma in the time of COVID-19. *Acta Haematology*, *17*, 1–7. https://doi.org/10.1159/000507690000507690

Ali, I., Alfarouk, K. O., Reshkin, S. J., & Ibrahim, M. E. (2017). Doxycycline as Potential Anti-cancer Agent. *Anti-Cancer Agents in Medicinal Chemistry*, *17*(12), 1617–1623. https://doi.org/10.2174/1871520617666170213111951

Andreani, J., Le Bideau, M., Duflot, I., Jardot, P., Rolland, C., Boxberger, M., Wurtz, N., Rolain, J. M., Colson, P., La Scola, B., & Raoult, D. (2020a). In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect. *Microbial Pathogenesis*, *104228*, S0882–S4010. https://doi.org/10.1016/j.micpath.2020.104228

Andreani, J., Le Bideau, M., Duflot, I., Jardot, P., Rolland, C., Boxberger, M., Wurtz, N., Rolain, J. M., Colson, P., La Scola, B., & Raoult, D. (2020b). In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect. *Microbial Pathogenesis*, *145*, 104228. https://doi.org/10.1016/j.micpath.2020.104228

Asai, A., Konno, M., Ozaki, M., Otsuka, C., Vecchione, A., Arai, T., Kitagawa, T., Ofusa, K., Yabumoto, M., Hirotsu, T., Taniguchi, M., Eguchi, H., Doki, Y., & Ishii, H. (2020). COVID-19 drug discovery using intensive approaches. *International Journal of Molecular Sciences*, *21*(8), 2839. https://doi.org/10.3390/ijms21082839

Augustin, M., Hallek, M., & Nitschmann, S. (2020). [Remdesivir for patients with severe COVID-19]. *Internist (Berl)*, *61*, 644–645. https://doi.org/10.1007/s00108-020-00800-5

Azad, C. S., Saxena, M., Siddiqui, A. J., Bhardwaj, J., Puri, S. K., Dutta, G. P., Anand, N., & Saxena, A. K. (2017). Synthesis of primaquine glyco-conjugates as potential tissue schizontocidal antimalarial agents. *Chemical Biology & Drug Design*, *90*(2), 254–261. https://doi.org/10.1111/cbdd.12944

Azeem, S., Ashraf, M., Rasheed, M. A., Anjum, A. A., & Hameed, R. (2015). Evaluation of cytotoxicity and antiviral activity of ivermectin against Newcastle disease virus. *Pakistan Journal of Pharmaceutical Sciences*, *28*(2), 597–602.

Aziz, M., Fatima, R., & Assaly, R. (2020). Elevated interleukin-6 and severe COVID-19: A meta-analysis. *Journal of Medical Virology*. https://doi.org/10.1002/jmv.25948

Babadaei, M. M. N., Hasan, A., Vahdani, Y., Bloukh, S. H., Sharifi, M., Kachooei, E., Haghighat, S., & Falahati, M. (2020). Development of remdesivir repositioning as a nucleotide analog against COVID-19 RNA dependent RNA polymerase. *Journal of Biomolecular Structure and Dynamics*, *20*, 1–9. https://doi.org/10.1080/07391102.2020.1767210

Bakheit, A. H., Al-Hadiya, B. M., & Abd-Elgalil, A. A. (2014). Azithromycin. *Profiles of Drug Substances, Excipients, and Related Methodology*, *39*, 1–40. https://doi.org/10.1016/B978-0-12-800173-8.00001-5

Baron, S. A., Devaux, C., Colson, P., Raoult, D., & Rolain, J. M. (2020). Teicoplanin: An alternative drug for the treatment of COVID-19? *International Journal of Antimicrobial Agents.*, *55*(105944). https://doi.org/10.1016/j.ijantimicag.2020.105944

Basit, A., Ali, T., & Rehman, S. U. (2020). Truncated human angiotensin converting enzyme 2; a potential inhibitor of SARS-CoV-2 spike glycoprotein and potent COVID-19 therapeutic agent. *Journal of Biomolecular Structure and Dynamics*, *20*, 1–10. https://doi.org/10.1080/07391102.2020.1768150

Beura, S., & Prabhakar, C. (2020). In-silico strategies for probing chloroquine based inhibitors against SARS-CoV-2. *Journal of Biomolecular Structure and Dynamics*, *8*, 1–25. https://doi.org/10.1080/07391102.2020.1772111

Bhardwaj, J., Siddiqui, A. J., Goyal, M., Prakash, K., Soni, A., & Puri, S. K. (2016). Repetitive live sporozoites inoculation under arteether chemoprophylaxis confers protection against subsequent sporozoite challenge in rodent malaria model. *Acta Tropica*, *158*, 130–138. https://doi.org/10.1016/j.actatropica.2016.02.016

Bhardwaj, J., Siddiqui, A. J., Goyal, M., Prakash, K., Soni, A., Puri, S. K., & Srivastava, M. (2015). Host immune response is severely compromised during lethal *Plasmodium vinckei* infection. *Parasitology Research*, *114*(9), 3445–3457. https://doi.org/10.1007/s00436-015-4570-4

Bienvenu, A.-L., Marty, A. M., Jones, M. K., & Picot, S. (2020). Systematic review of registered trials of hydroxychloroquine prophylaxis for COVID-19 health-care workers at the first third of 2020. *One Health (Amsterdam, Netherlands))*, *10*, 100141. https://doi.org/10.1016/j.onehlt.2020.100141

Boopathi, S., Poma, A. B., & Kolandaivel, P. (2020). Novel 2019 coronavirus structure, mechanism of action, antiviral drug promises and rule out against its treatment. *Journal of Biomolecular Structure and Dynamics*, *30*, 1–10. https://doi.org/10.1080/07391102.2020.1758788

Borba, M. G. S., Val, F. F. A., Sampaio, V. S., Alexandre, M. A. A., Melo, G. C., Brito, M., Mourao, M. P. G., Brito-Sousa, J. D., Baia-da-Silva, D., Guerra, M. V. F., Hajjar, L. A., Pinto, R. C., Balieiro, A. A. S., Pacheco, A. G. F., Santos, J. D. O., Jr., Naveca, F. G., Xavier, M. S., Siqueira, A. M., Schwarzbold, A., … Lacerda, M. V. G, CloroCovid-19 Team (2020).

Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection: A randomized clinical trial. *JAMA Network Open*, *3*(4), e208857. https://doi.org/10.1001/jamanetworkopen.2020.8857

Cai, Q., Yang, M., Liu, D., Chen, J., Shu, D., Xia, J., Liao, X., Gu, Y., Cai, Q., Yang, Y., Shen, C., Li, X., Peng, L., Huang, D., Zhang, J., Zhang, S., Wang, F., Liu, J., Chen, L., … Liu, L. (2020). Experimental treatment with favipiravir for COVID-19: An open-label control study. *Engineering*, https://doi.org/10.1016/j.eng.2020.03.007

Calderon, J. M., Zeron, H. M., & Padmanabhan, S. (2020). Treatment with hydroxychloroquine vs hydroxychloroquine + nitazoxanide in COVID-19 patients with risk factors for poor prognosis: A structured summary of a study protocol for a randomised controlled trial. *Trials*, *21*(1), 504. https://doi.org/10.1186/s13063-020-04448-2

Caly, L., Druce, J. D., Catton, M. G., Jans, D. A., & Wagstaff, K. M. (2020). The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Research*, *178*, 104787. https://doi.org/10.1016/j.antiviral.2020.104787

Cao, Y. C., Deng, Q. X., & Dai, S. X. (2020). Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. *Travel Medicine and Infectious Disease*, *35*, 101647. https://doi.org/10.1016/j.tmaid.2020.101647

Chaccour, C., Hammann, F., Ramon-Garcia, S., & Rabinovich, N. R. (2020). Ivermectin and novel coronavirus disease (COVID-19): Keeping rigor in times of Urgency. *American Journal of Tropical Medicine and Hygiene*, *102*, 1156–1157. https://doi.org/10.4269/ajtmh.20-0271

Chafekar, A., & Fielding, B. C. (2018). MERS-CoV: Understanding the latest human coronavirus threat. *Viruses*, *10*, E93. https://doi.org/10.3390/v10020093

Chan, J. F., Lau, S. K., To, K. K., Cheng, V. C., Woo, P. C., & Yuen, K. Y. (2015). Middle East respiratory syndrome coronavirus: Another zoonotic betacoronavirus causing SARS-like disease. *Clinical Microbiology Reviews*, *28*(2), 465–522. https://doi.org/10.1128/CMR.00102-14

Chen, Z., Hu, J., Zhang, Z., Jiang, S., Han, S., Yan, D., Zhuang, R., Hu, B., & Zhang, Z. (2020). Efficacy of hydroxychloroquine in patients with COVID-19: Results of a randomized clinical trial. *medRxiv*. https://doi.org/10.1101/2020.03.22.20040758

Choudhary, R., & Sharma, A. K. (2020). Potential use of hydroxychloroquine, ivermectin and azithromycin drugs in fighting COVID-19: Trends, scope and relevance. *New Microbes New Infections*, *35*, 100684. 100684. https://doi.org/10.1016/j.nmni.2020.100684

Conforti, C., Giuffrida, R., Zalaudek, I., & Di Meo, N. (2020). Doxycycline, a widely used antibiotic in dermatology with a possible anti-inflammatory action against IL-6 in COVID-19 outbreak. *Dermatology and Therapy*, e13437. https://doi.org/10.1111/dth.13437

Cong, Y., Hart, B. J., Gross, R., Zhou, H., Frieman, M., Bollinger, L., Wada, J., Hensley, L. E., Jahrling, P. B., Dyall, J., & Holbrook, M. R. (2018). MERS-CoV pathogenesis and antiviral efficacy of licensed drugs in human monocyte-derived antigen-presenting cells. *PLoS One*, *13*(3), e0194868. https://doi.org/10.1371/journal.pone.0194868

Coomes, E. A., & Haghbayan, H. (2020). Favipiravir, an antiviral for COVID-19? *The Journal of Antimicrobial Chemotherapy*, *75*(7), 2013–2014. https://doi.org/10.1093/jac/dkaa171

Costanzo, M., De Giglio, M. A. R., & Roviello, G. N. (2020). SARS-CoV-2: Recent reports on antiviral therapies based on lopinavir/ritonavir, darunavir/umifenovir, hydroxychloroquine, remdesivir, favipiravir and other drugs for the treatment of the new coronavirus. *Current Medicinal Chemistry*, *27*. https://doi.org/10.2174/0929867327666200416131117

de Wilde, A. H., Jochmans, D., Posthuma, C. C., Zevenhoven-Dobbe, J. C., van Nieuwkoop, S., Bestebroer, T. M., van den Hoogen, B. G., Neyts, J., & Snijder, E. J. (2014). Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. *Antimicrobial Agents and Chemotherapy*, *58*(8), 4875–4884. https://doi.org/10.1128/AAC.03011-14

de Wit, E., Feldmann, F., Cronin, J., Jordan, R., Okumura, A., Thomas, T., Scott, D., Cihlar, T., & Feldmann, H. (2020). Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(12), 6771–6776. https://doi.org/10.1073/pnas.1922083117

Delang, L., Abdelnabi, R., & Neyts, J. (2018). Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. *Antiviral Research*, *153*, 85–94. https://doi.org/10.1016/j.antiviral.2018.03.003

Dyall, J., Coleman, C. M., Hart, B. J., Venkataraman, T., Holbrook, M. R., Kindrachuk, J., Johnson, R. F., Olinger, G. G., Jr., Jahrling, P. B., Laidlaw, M., Johansen, L. M., Lear-Rooney, C. M., Glass, P. J., Hensley, L. E., & Frieman, M. B. (2014). Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. *Antimicrobial Agents and Chemotherapy*, *58*(8), 4885–4893. https://doi.org/10.1128/AAC.03036-14

Dyall, J., Gross, R., Kindrachuk, J., Johnson, R. F., Olinger, G. G., Jr., Hensley, L. E., Frieman, M. B., & Jahrling, P. B. (2017). Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome: Current therapeutic options and potential targets for novel therapies. *Drugs*, *77*(18), 1935–1966. https://doi.org/10.1007/s40265-017-0830-1

ECDC. (2020). European Centre for Disease Prevention and Control; https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases.

Elfiky, A. A. (2020). SARS-CoV-2 RNA dependent RNA polymerase (RdRp) targeting: An in silico perspective. *Journal of Biomolecular Structure and Dynamics*, *6*, 1–9. https://doi.org/10.1080/07391102.2020.1761882

Falzarano, D., de Wit, E., Rasmussen, A. L., Feldmann, F., Okumura, A., Scott, D. P., Brining, D., Bushmaker, T., Martellaro, C., Baseler, L., Benecke, A. G., Katze, M. G., Munster, V. J., & Feldmann, H. (2013). Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. *Nature Medicine*, *19*(10), 1313–1317. https://doi.org/10.1038/nm.3362

Ferner, R. E., & Aronson, J. K. (2020a). Chloroquine and hydroxychloroquine in covid-19. *BMJ (Clinical Research ed.).)*, *369*, m1432. https://doi.org/10.1136/bmj.m1432

Ferner, R. E., & Aronson, J. K. (2020b). Remdesivir in covid-19. *BMJ (Clinical Research ed.).)*, *369*, m1610. https://doi.org/10.1136/bmj.m1610

Furuta, Y., Komeno, T., & Nakamura, T. (2017). Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proceedings of the Japan Academy. Series B, Physical and Biological Sciences*, *93*(7), 449–463. https://doi.org/10.2183/pjab.93.027

Gautret, P., Lagier, J.-C., Parola, P., Hoang, V. T., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., Giordanengo, V., Vieira, V. E., Dupont, H. T., Honoré, S., Colson, P., Chabrière, E., La Scola, B., Rolain, J.-M., Brouqui, P., & Raoult, D. (2020a). Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents*, *56*(1), 105949. https://doi.org/10.1016/j.ijantimicag.2020.105949

Gautret, P., Lagier, J. C., Parola, P., Hoang, V. T., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., Giordanengo, V., Vieira, V. E., Dupont, H. T., Honore, S., Colson, P., Chabriere, E., La Scola, B., Rolain, J. M., Brouqui, P., & Raoult, D. (2020b). Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents*, *105949*(20), S0924–S8579. https://doi.org/10.1016/j.ijantimicag.2020.105949

Geleris, J., Sun, Y., Platt, J., Zucker, J., Baldwin, M., Hripcsak, G., Labella, A., Manson, D. K., Kubin, C., Barr, R. G., Sobieszczyk, M. E., & Schluger, N. W. (2020). Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *The New England Journal of Medicine*, *382*(25), 2411–2418. https://doi.org/10.1056/NEJMoa2012410

Gotz, V., Magar, L., Dornfeld, D., Giese, S., Pohlmann, A., Hoper, D., Kong, B. W., Jans, D. A., Beer, M., Haller, O., & Schwemmle, M. (2016). Corrigendum: Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. *Scientific Reports*, *6*, 25428. https://doi.org/10.1038/srep25428

Gravesen, C., & Judy, J. D. (2020). Effect of biosolids characteristics on retention and release behavior of azithromycin and ciprofloxacin. *Environmental Research*, *184*. https://doi.org/10.1016/j.envres.2020.109333

Grein, J., Ohmagari, N., Shin, D., Diaz, G., Asperges, E., Castagna, A., Feldt, T., Green, G., Green, M. L., Lescure, F. X., Nicastri, E., Oda, R., Yo, K., Quiros-Roldan, E., Studemeister, A., Redinski, J., Ahmed, S., Bernett, J.,

Chelliah, D., … Flanigan, T. (2020). Compassionate use of remdesivir for patients with severe covid-19. *The New England Journal of Medicine*, *382*(24), 2327–2336. https://doi.org/10.1056/NEJMoa2007016

Hart, B. J., Dyall, J., Postnikova, E., Zhou, H., Kindrachuk, J., Johnson, R. F., Olinger, G. G., Frieman, M. B., Holbrook, M. R., Jahrling, P. B., & Hensley, L. (2014). Interferon-β and mycophenolic acid are potent inhibitors of Middle East respiratory syndrome coronavirus in cell-based assays. *The Journal of General Virology*, *95*(Pt 3), 571–577. https://doi.org/10.1099/vir.0.061911-0

Hasan, A., Paray, B. A., Hussain, A., Qadir, F. A., Attar, F., Aziz, F. M., Sharifi, M., Derakhshankhah, H., Rasti, B., Mehrabi, M., Shahpasand, K., Saboury, A. A., & Falahati, M. (2020). A review on the cleavage priming of the spike protein on coronavirus by angiotensin-converting enzyme-2 and furin. *Journal of Biomolecular Structure and Dynamics*, *22*, 1–9. https://doi.org/10.1080/07391102.2020.1754293

He, T., Yang, W., Zhang, X., Li, P., Yang, D., Wu, Y., Fan, Y., Xiang, M., Huang, Q., Chen, J., Zhou, R., Lv, Q., & Chen, J. (2020). Comparative effectiveness of tamoxifen, toremifene, letrozole, anastrozole, and exemestane on lipid profiles in breast cancer patients: A network meta-analysis. *Medicine*, *99*(2), e18550. https://doi.org/10.1097/MD.0000000000018550

Hendaus, M. A. (2020). Remdesivir in the treatment of coronavirus disease 2019 (COVID-19): A simplified summary. *Journal of Biomolecular Structure and Dynamics*, *6*, 1–6. https://doi.org/10.1080/07391102.2020.1767691

Islam, R., Parves, M. R., Paul, A. S., Uddin, N., Rahman, M. S., Mamun, A. A., Hossain, M. N., Ali, M. A., & Halim, M. A. (2020). A molecular modeling approach to identify effective antiviral phytochemicals against the main protease of SARS-CoV-2. *Journal of Biomolecular Structure and Dynamics*, *12*, 1–12. https://doi.org/10.1080/07391102.2020.1761883

Jalkanen, J., Hollmén, M., & Jalkanen, S. (2020). Interferon beta-1a for COVID-19: Critical importance of the administration route. *Crit Care)*, *24*(1), 335. https://doi.org/10.1186/s13054-020-03048-5

Jean, S. S., Lee, P. I., & Hsueh, P. R. (2020). Treatment options for COVID-19: The reality and challenges. *Journal of Microbiology, Immunology, and Infection = Wei mian yu gan ran za zhi*, *53*(3), 436–443. https://doi.org/10.1016/j.jmii.2020.03.034

Ap, K., S K, T. S., Vs, A., & Tc, V. (2020). Design of multi-epitope vaccine candidate against SARS-CoV-2: A In-Silico study. *Journal of Biomolecular Structure and Dynamics*, *1*, 1–10. https://doi.org/10.1080/07391102.2020.1770127

Kelleni, M. T. (2020). Nitazoxanide/azithromycin combination for COVID-19: A suggested new protocol for early management. *Pharmacological Research*, *157*(104874), S1043–S6618. https://doi.org/10.1016/j.phrs2020.104874

Khan, R. J., Jha, R. K., Amera, G. M., Jain, M., Singh, E., Pathak, A., Singh, R. P., Muthukumaran, J., & Singh, A. K. (2020). Targeting SARS-CoV-2: A systematic drug repurposing approach to identify promising inhibitors against 3C-like proteinase and 2′-O-ribose methyltransferase. *Journal of Biomolecular Structure and Dynamics*, *20*, 1–14. https://doi.org/10.1080/07391102.2020.1753577

Lian, N., Xie, H., Lin, S., Huang, J., Zhao, J., & Lin, Q. (2020). Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: A retrospective study. *Clinical Microbiology and Infection*, *26*(20), 917-921. https://doi.org/10.1016/j.cmi.2020.04.026

Lin, M. H., Moses, D. C., Hsieh, C. H., Cheng, S. C., Chen, Y. H., Sun, C. Y., & Chou, C. Y. (2018). Disulfiram can inhibit MERS and SARS coronavirus papain-like proteases via different modes. *Antiviral Research*, *150*, 155–163. https://doi.org/10.1016/j.antiviral.2017.12.015

Liu, J., Cao, R., Xu, M., Wang, X., Zhang, H., Hu, H., Li, Y., Hu, Z., Zhong, W., & Wang, M. (2020). Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discovery*, *6*, 16. https://doi.org/10.1038/s41421-020-0156-0

Lobo-Galo, N., Terrazas-López, M., Martínez-Martínez, A., & Ág, D.-S. (2020). FDA-approved thiol-reacting drugs that potentially bind into the SARS-CoV-2 main protease, essential for viral replication. *Journal of Biomolecular Structure and Dynamics*, *14*, 1–9. https://doi.org/10.1080/07391102.2020.1764393

Lu, C. C., Chen, M. Y., Lee, W. S., & Chang, Y. L. (2020). Potential therapeutic agents against COVID-19: What we know so far. *Journal of the Chinese Medical Association: Jcma*, *83*(6), 534–536. https://doi.org/10.1097/JCMA.0000000000000318

Lu, G., Wang, Q., & Gao, G. F. (2015). Bat-to-human: Spike features determining 'host jump' of coronaviruses SARS-CoV, MERS-CoV, and beyond. *Trends in Microbiology*, *23*(8), 468–478. https://doi.org/10.1016/j.tim.2015.06.003

Magagnoli, J., Narendran, S., Pereira, F., Cummings, T., Hardin, J. W., Sutton, S. S., & Ambati, J. (2020). Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. *medRxiv*, *2020*(04), 16. https://doi.org/10.1101/2020.04.16.20065920

Mahanta, S., Chowdhury, P., Gogoi, N., Goswami, N., Borah, D., Kumar, R., Chetia, D., Borah, P., Buragohain, A. K., & Gogoi, B. (2020). Potential anti-viral activity of approved repurposed drug against main protease of SARS-CoV-2: an in silico based approach. *Journal of Biomolecular Structure and Dynamics*, *25*, 1–10. https://doi.org/10.1080/07391102.2020.1768902

Malek, A. E., Granwehr, B. P., & Kontoyiannis, D. P. (2020). Doxycycline as a potential partner of COVID-19 therapies. *IDCases*, *21*, e00864. https://doi.org/10.1016/j.idcr.2020.e00864

Mandal, H. (2020). Mobilizing the research ecosystem for scientific advances towards positive impact in the context of the COVID-19 Pandemic. *Turkish Journal of Medical Sciences*, *50*(SI-1), 485–488. https://doi.org/10.3906/sag-2004-180

Mastrangelo, E., Pezzullo, M., De Burghgraeve, T., Kaptein, S., Pastorino, B., Dallmeier, K., de Lamballerie, X., Neyts, J., Hanson, A. M., Frick, D. N., Bolognesi, M., & Milani, M. (2012). Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: New prospects for an old drug. *The Journal of Antimicrobial Chemotherapy*, *67*(8), 1884–1894. https://doi.org/10.1093/jac/dks147

Muralidharan, N., Sakthivel, R., Velmurugan, D., & Gromiha, M. M. (2020). Computational studies of drug repurposing and synergism of lopinavir, oseltamivir and ritonavir binding with SARS-CoV-2 protease against COVID-19. *Journal of Biomolecular Structure and Dynamics*, *16*, 1–6. https://doi.org/10.1080/07391102.2020.1752802

Murthy, P. K. (2019). Strategies to control human lymphatic filarial infection: Tweaking Host's immune system. *Current Topics in Medicinal Chemistry*, *19*(14), 1226–1240. https://doi.org/10.2174/1568026619666190618110613

Pandey, A., Nikam, A. N., Shreya, A. B., Mutalik, S. P., Gopalan, D., Kulkarni, S., Padya, B. S., Fernandes, G., Mutalik, S., & Prassl, R. (2020). Potential therapeutic targets for combating SARS-CoV-2: Drug repurposing, clinical trials and recent advancements. *Life Sciences*, *256*(117883), S0024–S3205. https://doi.org/10.1016/j.lfs.2020.117883

Pepperrell, T., Pilkington, V., Owen, A., Wang, J., & Hill, A. M. (2020). Review of safety and minimum pricing of nitazoxanide for potential treatment of COVID-19. *Journal of Virus Eradication*, *6*(2), 52–60.

Pshenichnaya, N. Y., Bulgakova, V. A., Lvov, N. I., Poromov, A. A., Selkova, E. P., Grekova, A. I., Shestakova, I. V., Maleev, V. V., & Leneva, I. A. (2019). Clinical efficacy of umifenovir in influenza and ARVI (study ARBITR). *Terapevticheskii Arkhiv*, *91*(3), 56–63. https://doi.org/10.26442/00403660.2019.03.000127

Rabaan, A. A., Al-Ahmed, S. H., Haque, S., Sah, R., Tiwari, R., Malik, Y. S., Dhama, K., Yatoo, M. I., Bonilla-Aldana, D. K., & Rodriguez-Morales, A. J. (2020). SARS-CoV-2, SARS-CoV, and MERS-COV: A comparative overview. *Le Infezioni in Medicina*, *28*(2), 174–184.

Rajoli, R. K., Pertinez, H., Arshad, U., Box, H., Tatham, L., Curley, P., Neary, M., Sharp, J., Liptrott, N. J., Valentijn, A., David, C., Rannard, S. P., Aljayyoussi, G., Pennington, S. H., Hill, A., Boffito, M., Ward, S. A., Khoo, S. H., Bray, P. G., … Owen, A. (2020). Dose prediction for repurposing nitazoxanide in SARS-CoV-2 treatment or chemoprophylaxis. *medRxiv*, https://doi.org/10.1101/2020.05.01.20087130

Roesch, C., Mairet-Khedim, M., Kim, S., Lek, D., Popovici, J., & Witkowski, B. (2020). Impact of the first-line treatment shift from dihydroartemisinin/piperaquine to artesunate/mefloquine on *Plasmodium vivax* drug susceptibility in Cambodia. *Journal of Antimicrobial Chemotherapy*, *75*, 1766–1771. https://doi.org/10.1093/jac/dkaa0925811382

Russell, B., Moss, C., George, G., Santaolalla, A., Cope, A., Papa, S., & Van Hemelrijck, M. (2020). Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current

evidence. *Ecancermedicalscience*, *14*(1022), 1022. https://doi.org/10.3332/ecancer.2020.1022

Shea, K. W., & Cunha, B. A. (1995). Teicoplanin. *Medical Clinics of North America*, *79*(4), 833–844. https://doi.org/10.1016/s0025-7125(16)30042-6

Sheahan, T. P., Sims, A. C., Graham, R. L., Menachery, V. D., Gralinski, L. E., Case, J. B., Leist, S. R., Pyrc, K., Feng, J. Y., Trantcheva, I., Bannister, R., Park, Y., Babusis, D., Clarke, M. O., Mackman, R. L., Spahn, J. E., Palmiotti, C. A., Siegel, D., Ray, A. S., Cihlar, T., … Baric, R. S. (2017). Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Science Translational Medicine*, *9*(396), eaal3653. https://doi.org/10.1126/scitranslmed.aal3653

Siddiqui, A. J., Bhardwaj, J., Goyal, M., Prakash, K., Adnan, M., Alreshidi, M. M., Patel, M., Soni, A., & Redman, W. (2020). Immune responses in liver and spleen against *Plasmodium yoelii* pre-erythrocytic stages in Swiss mice model. *Journal of Advanced Research*, *24*, 29–41. https://doi.org/10.1016/j.jare.2020.02.016

Siddiqui, A. J., Bhardwaj, J., Goyal, M., Prakash, K., Soni, A., Tiwari, V., & Puri, S. K. (2015). Assessment of real-time method to detect liver parasite burden under different experimental conditions in mice infected with *Plasmodium yoelii* sporozoites. *Microbial Pathogenesis*, *89*, 35–42. https://doi.org/10.1016/j.micpath.2015.08.015

Siddiqui, J. A., Adnan, M., Jahan, S., Redman, W., Saeed, M., & Patel, M. (2020). Neurological disorder and psychosocial aspects of cerebral malaria: What is new on its pathogenesis and complications? A mini-review. *Folia Parasitologica*, *67*, 1–10. https://doi.org/10.14411/fp.2020.015

Sims, A. C., Burkett, S. E., Yount, B., & Pickles, R. J. (2008). SARS-CoV replication and pathogenesis in an in vitro model of the human conducting airway epithelium. *Virus Research*, *133*(1), 33–44. https://doi.org/10.1016/j.virusres

Simsek Yavuz, S., & Unal, S. (2020). Antiviral treatment of COVID-19. *Turkish Journal of Medical Sciences*, *50*, 611–619. https://doi.org/10.3906/sag-2004-145

Sinha, N., & Balayla, G. (2020). Hydroxychloroquine and covid-19. *Postgraduate Medical Journal*, 1–6. https://doi.org/10.1136/postgradmedj-2020-137785

Soni, A., Goyal, M., Prakash, K., Bhardwaj, J., Siddiqui, A. J., & Puri, S. K. (2015). Cloning, expression and functional characterization of heme detoxification protein (HDP) from the rodent malaria parasite *Plasmodium vinckei*. *Gene*, *566*(1), 109–119. https://doi.org/10.1016/j.gene.2015.04.037

Szolnoky, G. (2020). Further aspects of doxycycline therapy in COVID-19. *Dermatology and Therapy*, e13810. https://doi.org/10.1111/dth.13810

Tchesnokov, E. P., Feng, J. Y., Porter, D. P., & Gotte, M. (2019). Mechanism of inhibition of ebola virus RNA-dependent RNA polymerase by remdesivir. *Viruses*, *11*(4), 326. https://doi.org/10.3390/v11040326

Thanh Le, T., Andreadakis, Z., Kumar, A., Gomez Roman, R., Tollefsen, S., Saville, M., & Mayhew, S. (2020). The COVID-19 vaccine development landscape. *Nature Reviews Drug Discovery*, *19*(5), 305–306. https://doi.org/10.1038/d41573-020-00073-5

Theoharides, T. C., & Conti, P. (2020). Dexamethasone for COVID-19? Not so fast. *J Biol Regul Homeost Agents*, *34*. https://doi.org/10.23812/20-EDITORIAL_1-5

Wang, Y., Jiang, W., He, Q., Wang, C., Wang, B., Zhou, P., Dong, N., & Tong, Q. (2020). A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. *Signal Transduction and Targeted Therapy*, *5*(1), 57. https://doi.org/10.1038/s41392-020-0158-2

WHO. (2020). World Health Organization. Coronavirus disease 2019 (COVID-19) Situation report https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200429-sitrep-100-covid-19.pdf?sfvrsn=bbfbf3d1_2.

WorldOmeter. (2020). Coronavirus WorldOmeter; https://www.worldometers.info/coronavirus/.

Wu, R., Wang, L., Kuo, H. D., Shannar, A., Peter, R., Chou, P. J., Li, S., Hudlikar, R., Liu, X., Liu, Z., Poiani, G. J., Amorosa, L., Brunetti, L., & Kong, A. N. (2020). An update on current therapeutic drugs treating COVID-19. *Current Pharmacology Reports*, *6*(3), 56–15. https://doi.org/10.1007/s40495-020-00216-7

Yaqinuddin, A., & Kashir, J. (2020). Innate immunity in COVID-19 patients mediated by NKG2A receptors, and potential treatment using Monalizumab, Cholroquine, and antiviral agents. *Medical Hypotheses*, *140*, 109777. https://doi.org/10.1016/j.mehy.2020.109777

Zhang, J., Ma, X., Yu, F., Liu, J., Zou, F., Pan, T., & Zhang, H. (2020). Teicoplanin potently blocks the cell entry of 2019-nCoV. *bioRxiv*. https://doi.org/10.1101/2020.02.05.935387

Zhang, S., Li, L., Shen, A., Chen, Y., & Qi, Z. (2020). Rational use of tocilizumab in the treatment of novel coronavirus pneumonia. *Clin Drug Investig*, *40*(6), 511–518. https://doi.org/10.1007/s40261-020-00917-3

Zhou, Y., Hou, Y., Shen, J., Huang, Y., Martin, W., & Cheng, F. (2020). Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discovery*, *6*, 14–10. https://doi.org/10.1038/s41421-020-0153-3

Zhu, L., Xu, X., Ma, K., Yang, J., Guan, H., Chen, S., Chen, Z., & Chen, G. (2020). Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. *American Journal of Transplantation*, *20*(7), 1859–1863. https://doi.org/10.1111/ajt.15869

Zumla, A., Chan, J. F., Azhar, E. I., Hui, D. S., & Yuen, K. Y. (2016). Coronaviruses - drug discovery and therapeutic options. *Nature Reviews. Drug Discovery*, *15*(5), 327–347. https://doi.org/10.1038/nrd.2015.37