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

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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.

Introduction

Human coronaviruses are a group of spherical or pleomorphic 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
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) (ECDC2020; 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 (Cal y 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,
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 second 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
| Drugs name          | Chemical structure | Biological activity/Therapeutic effect                                                                 | Mode of action                                                                                                           | References                                      |
|---------------------|--------------------|--------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| **Hydroxychloroquine** | ![Chemical structure](image) | 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**    | ![Chemical structure](image) | 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**      | ![Chemical structure](image) | 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) α/β1 heterodimer) through the rise in antiviral response, inhibits the nuclear import of viral and host protein | (Caly et al. 2020; Choudhary & Sharma 2020) |
| **Favipiravir**      | ![Chemical structure](image) | 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**      | ![Chemical structure](image) | It belongs to prodrug of an adenosine triphosphate (ATP) analog. Its activity against viruses such as Lassa fever, Nipah, Hendra, respiratory syncytiatal, 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**      | ![Chemical structure](image) | 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**     | ![Chemical structure](image) | 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**    | ![Chemical structure](image) | 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)
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

| Drugs name      | Chemical structure | Biological activity/Therapeutic effect                                                                 | Mode of action                                                                 |
|-----------------|--------------------|--------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Dexamethasone   | ![Chemical Structure](dexamethasone.png) | 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     | ![Chemical Structure](doxycycline.png) | 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       | ![Chemical Structure](ribavirin.png) | 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 | ![Chemical Structure](mycophenolic.png) | It is an antineoplastic antibiotic derived from *Penicillium* fungal species. It is an active metabolite of the prodru 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  | ![Chemical Structure](chlorpromazine.png) | 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     | ![Chemical Structure](chloroquine.png) | It is an aminooquinoline 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     | ![Chemical Structure](toremifene.png) | 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 | ![Chemical Structure](methylprednisolone.png) | 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) |
COVID-19 by the single dose of Ivermectin was found to reduce the viral load up to 5000 fold in vitro culture within 48h (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) α/β1 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 neuraminidase 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
teicoplanin has potential efficacy to inhibit the virus activity and reduces the load of SARS-CoV-2 (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 (thiazolidine)**

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 coronivirus 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
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 every 12 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

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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)                                                        |
| Synthetic drug       | Lipopolysaccharides (LPS)        | Activation of macrophage and B-lymphocytes                                             |
| 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 |
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

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