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A review of possible therapeutic agents for COVID-19 pandemic

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ABSTRACT

The epidemic of Coronavirus disease 2019 (COVID-19) caused by novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome, coronavirus 2) infection has been considered by the World Health Organization (WHO) as a public health emergency of global interest. The efforts nowadays of different countries focus on the fast isolation and fast diagnosis of patients as well as to find possible therapeutic agent or vaccine. Several sites, articles, reports, reviews, and web pages discussing COVID-19 virus and possible treatments were investigated, the data were collected between November-2020 and May-2021. Approximately 170 articles and reports were opened and read, but nearly 80 of them were used for this review. Several drugs showed hopeful potential results such as colchicine, dexamethasone, kaletra (Lopinavir/ritonavir), cefuroxime, favipiravir, and inhaled furosemide, but until now there is no WHO approved antiviral drug against COVID-19, although remdesivir is approved by Food and drug administration (FDA) as antiviral for COVID-19, but WHO doesn't recommend it's use. The protocol followed by WHO until now is a symptomatic treatment, e.g., antipyretics, antitussive, adequate nutrition, and rehydration, antibiotics if suffering from secondary infection, antithrombotic prophylaxis for hospitalized COVID-19 patients, and corticosteroids in exacerbation cases. Fortunately, there are several vaccines that reached an advanced phase in research trials, and the world is hopeful for mass vaccination in early to mid-2021. Currently, there is no WHO-approved treatment for COVID-19, but there are many other promising drugs/agents under investigation. Supportive care and protocols were followed to manage the current crisis situation. However, many vaccines are approved for the prevention of COVID-19 available now such as Vaxzevria **(**Astrazeneca vaccine), tozinameran (Pfizer/BioNTech vaccine), Moderna: mRNA-1273 vaccine and Janssen COVID-19 vaccine while others are still in clinical trials.

Keywords: COVID-19, SARS, PubMed, treatment.

INTRODUCTION

The first case of the communicable disease, called coronavirus disease 2019 (COVID-19), appeared in December 2019 in Wuhan, China, caused by SARS-CoV-2 (severe acute respiratory syndrome, coronavirus 2). It then diffused enormously and becomes an ongoing pandemic. Until 24 November 2020, over 58,700,000 cases and over1.3 million deaths have been reported. COVID-19 was announced as a public health emergency of international concern on 30 January, 2020, and as a pandemic on 11 March, 2020 [1].

SARS-CoV-2 is linked to the known SARS-CoV and belongs to the betacoronavirus genus, however, it possesses a zoological origin. It can affect the upper and lower respiratory tract, with the virus attacking the host cell through attached ACE-2 (angiotensin-converting enzyme -2) via special virus surface glycoproteins (spikes) [2]. The virus is found in considerable numbers in alveolar cells, so the lungs are the most vulnerable organs, so there are a few scientists suggesting that decreasing ACE-2 activity can be protective [3].

Respiratory failure might develop as the alveolar disease progresses. Because of the considerable expression of ACE-2 in the glandular cells of the gastric, rectal, and duodenal epithelium, the virus also affects gastrointestinal (GI) organs. Acute myocardial injury and cardiovascular chronic damage have been observed [4].

Those patients that require ICU (intensive care unit) or have a high incidence of

thrombosis, show a poor diagnosis. One of the common reasons for death is kidney complications; in about 30% of patients in China and New York hospitals, patients suffered from kidney injury (although some of them did not have previous kidney problems), and acute respiratory distress syndrome [5].

The virus spreads easily through the air between physically close people, via small droplets produced from patient's breath, sneezes, coughs, or talking, and can also be also transmitted via contaminated surfaces. Patients can infect others two days prior to the onset of symptoms. Infection persists for around for 7–12 days in moderate cases, and up to 14 days in more severe cases. Reverse transcription polymerase chain reaction (rRt-PCR) from a nasopharyngeal swab is used in diagnosis as a standard method, while a CT scan chest image can be helpful in the diagnosis of individuals with suspicion of infection, however, it is not recommended for routine screening.

According to symptom profiles, COVID-19 has variable and nonspecific symptoms, but the most common are fever and cough (dry or productive), with other less common symptoms of fatigue, shortness of breath, and muscle, back and joint pain. About 40% of patients suffer from temporary loss of smell and taste senses, while some patients suffer from gastrointestinal symptoms such as diarrhoea, nausea, sore throat, loss of appetite, headache, and vertigo. The incubation period for COVID-19 is 4 to 5 days; although some patients do not experience any symptoms, they can still spread the disease [6].

To minimize infection, transmission, frequent hand washing, social distancing, covering coughs, and keeping unwashed hands away from the face and face mask are recommended.

Until now, there is no specific proven treatment for COVID-19, but there are several ongoing studies. Management involves treating symptoms, isolation, and supportive care with antivirals, antibiotics, corticosteroids, supplements, alone or in combination [7].

In this review article, we will be concerned about COVID-19 drugs management drug, and assessing them through evaluation of their possible mechanisms, safety profile, and availability with cost considerations by searching PubMed, Google Scholar and grey literature search, articles and reviews discussing COVID-19 virus possible treatment.

Possible therapeutic agents

Antibiotics

Azithromycin

Azithromycin (Figure 1) is a macrolide antibiotic. It binds to the 50S subunit of the bacterial ribosome and inhibits bacterial protein synthesis and quorum sensing, decreasing biofilms formation through suppressing protein production. It effectively accumulates in cells (especially phagocytes) and is transported to infection sites in high concentrations. It is used in chronic inflammation, such as diffusive panbronchiolitis, posttransplant bronchiolitis, and rosacea. It also used in respiratory, dermal, urogenital, and other bacterial infections. It has an immunomodulatory property also, so it is used in cystic fibrosis, COPD (Chronic obstructive pulmonary disease) exacerbations, and non-eosinophilic asthma [8].

Azithromycin is usually well tolerated; the most common side effects are GI discomfort, headache and dizziness, and transient changes in transaminases in 1.5% of patients. Hearing loss or damage has also been reported, especially in patients with COPD, and in some patients, it appears to be irreversible; there were about 20 case reports that have been published about hearing loss associated with short-term use of azithromycin. QT prolongation and torsades de pointes, which can result in death may occur; an alert was given by the FDA to recognise the possibility of a fatal heart rhythm due to azithromycin [9]. Azithromycin does not significantly interfere with CYP 450 3A4.

Azithromycin shows good activity against influenza virus and zica virus, but it does not work against COVID-19, so they have tried to mix it with hydroxychloroquine in trials. This resulted in 95% of patients recovered after 8 days, but they do not know why this occurs with this medication. How-

ever, the latest (HFHS) trial in Southeast Michigan involved patients admitted to the health system from 10 March, 2020 to 12 May, 2020 with COVID-19. The study was carried out on 2541 patients 18 years of age or older. They were divided into groups according to the treatment they had received: hydroxychloroquine alone, combination therapy of hydroxychloroquine and azithromycin, and the azithromycin alone group. They concluded that combination therapies of hydroxychloroquine and azithromycin were linked to COVID-19 mortality reduction.

An online survey discovered that azithromycin was the second most prescribed medication for COVID-19, and it confirmed that the president of the USA took azithromycin combined with other medicines [10].

Doxycycline

Doxycycline (Figure 1) is a tetra-cycle derivative antibiotic, which binds to the 30S subunit of bacterial ribosomes and inhibits bacterial protein synthesis. Protein synthesis is also inhibited by binding to the 70S subunits of mitochondrial ribosomes. It is a bacteriostatic agent.

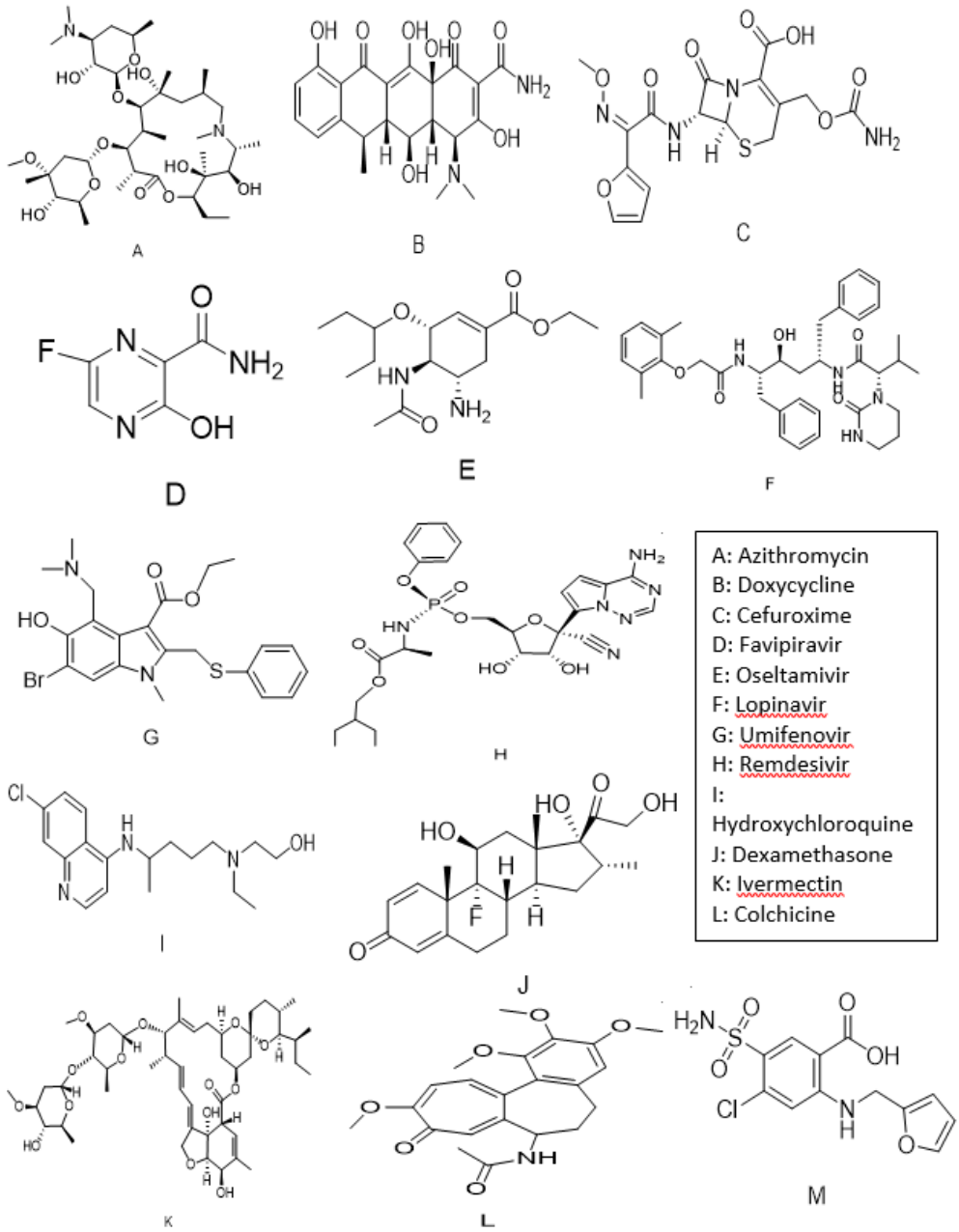

Figure (1): Chemical structures of some drugs' candidates for COVID19.

It enters into the inner cytoplasmic membrane through the bacterial cell membrane and is a pH-dependent active transport system. It inhibits inflammatory-cell-generated proteolytic enzymes. It has a good activity against a wide variety of Gram +ve, Gram –ve, and atypical bacteria. It also has activity in certain protozoa such as malaria. Doxycycline is used for respiratory tract infections, sexually transmitted infections and prophylaxis from malaria and some arthropod-borne rickettsia infections. According to the safety profile, doxycycline has major GI and dermatologic side effects. It is contraindicated in pregnancy and in children due to discolouration of developing teeth and it has effects on bone. It interacts with antacids, iron, oral contraceptives, and methotrexate. Long term use of these antibiotics affects the growth of the male reproductive tract, but it has not been fully clarified [11].

In a prospective study done on 100 COVID-19 patients to evaluate the combination therapy between Ivermectin and Doxycycline as a potential therapy for COVID-19. The results show that patients between 4 and 18 days of the beginning of treatment were negative for corona virus and their clinical condition improved. In a mild to moderate cases of COVID-19, the combination between doxycycline and ivermectin is very effective in viral clearance [12]. Multicenter study is needed to evaluate this therapy to be included in the global guideline.

Cefuroxime

Cefuroxime (Figure 1) is a second-generation cephalosporin. It is a cell wall inhibitor and interferes with its synthesis, inhibiting peptidoglycan cross-linking. Cefuroxime is a bactericidal drug. It also plays a role in the activation of autolysis of bacterial cell wall.

Common side effects associated with this drug are maculopapular rash, pruritis, urticaria, anaphylaxis, eosinophilia, thrombocytopenia, neutropenia, leucopenia, diarrhoea and interstitial nephritis [13].

It is used for soft tissue infections, respiratory tract infections and genitourinary tract infections. Use in CNS (Central nervous system) is under investigation. It has an excellent penetration into bone and joints, but clinical data are insufficient to recommend its use in these infections [14].

Cefuroxime is a potential inhibitor for three important proteins in SARS-CoV-2 (protease, RNA dependent polymerase, and ACE2 Spike complex) cefuroxime is ranked as a top potential protein inhibitor drug for COVID-19 [15]. There are many ongoing studies on cefuroxime.

Antivirals

Favipiravir

Favipiravir (Figure 1) is a prodrug of a purine nucleotide, which inhibits an important enzyme in replication and transcription of the viral genome RNA polymerase. It is used routinely for influenza, Ebola, and Lassa virus treatment, and in trials for COVID-19 treatment.

The Japanese Ministry of Health approved favipiravir as a resistant influenza drug, with no clear adverse effects in 2014. However, it has many side effects, for example, weight loss, vomiting, reduced the production of red blood cells, increased liver function, increased vacuolisation in hepatocytes, and it is teratogenic [16].

Few clinical experiences have shown positive results about using favipiravir for COVID-19. One of the clinical experiences was a random, prospective study for 120 patients with moderate to severe COVID-19 taking favipiravir compared with 120 patients who took arbidol, resulting in an observed difference in clinical recovery at day 7 of treatment within moderate infection (55.9% arbidol and 71.4% favipiravir, $P = 0.019$), however, there was no noticeable differences within severe or moderate to severe cases.

The second one was a study of 80 patients participating in clinical tests in China, including 35 patients who took favipiravir and 45 patients who did not. It showed that favipiravir treatment shortened the time of curing compared with control group patients. However, another multicentred randomised clinical study at Wuhan University hinted that favipiravir treatment was not better.

Nevertheless, medical treatment teams have recommended treatment with favipiravir and included it within COVID-19 diagnosis and treatment plan [17].

Tamiflu (Oseltamivir)

Oseltamivir (Figure 1) is approved for the treatment of influenza A and B, and similarly, zanamivir (Relenza®) is also FDA approved only for influenza A and B treatment. Both drugs are similar in structure and are comparably potent in inhibiting neuraminidase enzymes (which stimulate the viruses' release from infected cells and enhances the respiratory tract's viral movement and effects the replication of the virus). The neuraminidase enzyme, expressed on the viral surface, is inhibited by oseltamivir. Virion remains bound to the membrane of infected cells in the presence of a neuraminidase inhibitors and are also ensnared in respiratory secretion [18].

Oseltamivir is suitable for adult and paediatric patients that have acute, uncomplicated influenza A or B, including neonates 14 days, and older, neonates younger can also receive the drug, but the safety and efficacy have not been identified in this population. There is some evidence in hospitalised patients that oseltamivir may be effective up to 4 to 5 days after the onset of symptoms, and therefore, guidelines support ordering the drug in patients with serious or progressive influenza or in high-risk patients with complicated illness, irrespective of the onset of symptoms [19].

Vomiting, diarrhoea, dizziness, headache, nose bleeding, redness of the eyes or pain, problems with sleep or coughing or other breathing issues, and extreme mental mood changes can rarely be triggered by Tamiflu, this may be more likely in infants [20].

Research in Wuhan reported that after receiving oseltamivir antiviral treatment in COVID-19 patients, there were no positive results were observed. The efficacy of the drug in SARS-CoV-2 infection is still were tested in further trials. Oseltamivir is also used with other drugs such as chloroquine and favipiravir in clinical trials [21].

Another Study looked at 13 COVID-19 suspected medical groups and their cohabitation families' hypoxia-free who had arrived in a clinic from March to May, 2020. Antibacterial and antiviral therapy (mainly oseltamivir) was given jointly to all patients, and the results showed that oseltamivir administration partially decreased temperature within 24 hours. Clinical data was compared between patients that received it in the early treatment period (within 24 hours), and others who received it in the late treatment period (after 24 hours); the result showed that the fever period in the early treatment group was shorter than the late treatment group. Our findings indicate that the early administration of oseltamivir in combination with antibacterials can decrease the temperature in free hypoxia COVID-19 patients [22].

Ritonavir/Lopinavir (kaletra)

Lopinavir is a novel protease inhibitor (PI) formed from ritonavir (Figure 1). Co-administration with low-dose ritonavir greatly increases the pharmacokinetic properties and, thus, the anti-HIV-1 protease activity of lopinavir. Co-formulated lopinavir/ritonavir has been developed as a part of combination therapy with other antiretroviral agents for ease of administration and to ensure that both medicines are taken together [23].

It is used in HIV disease by inhibiting the HIV protease enzyme via the formation of an inhibiter enzyme complex, so that some immature, non-infectious viruses will be produced. It also seems that it is the mechanism in fighting SARS-CoV-19 is the same in SARS-CoV and MERS-CoV.

The 3-Chymotrypsin like protease (3CLpro) enzyme plays a big role in viral RNA processing, since lopinavir is a protease inhibitor. Thus, the activity of 3-CLpro can be inhibited, affecting the process of viral replication and released from the host cell. In patients undergoing lopinavir/ritonavir-based regimens, diarrhoea, nausea, and asthenia are commonly recorded adverse effects, with increased total cholesterol, triglyceride and hepatic enzyme levels also recorded [24].

Recent evidence indicates that lopinavir has in vitro anti-SARS-CoV-2 antiviral activ-

ity, although there is no C2-symmetric pocket in the coronavirus proteases, like 3-CLpro [25].

In a study following 127 COVID-19 patients in Hong Kong, 86 patients in the combination group received ritonavir, lopinavir, ribavirin, and interferon-b, while the others in the control group received lopinavir and ritonavir only. The results showed that the combination group had a shorter time of viral shedding and hospital stay than the control group. Another significant trial finding was that patients on lopinavir/ritonavir had a shorter time of 6 days in the ICU compared to 11 days in others. This is useful, however, as in the current pandemic there is a shortage of ICU beds. In conclusion, there is a significant shorter hospital stay for patients taking lopinavir/ritonavir in combination or alone [26].

Umifenovir

Umifenovir (Figure 1; also called arbidol) is an indole carboxylic acid derivative, which is considered a broad-spectrum antiviral which acts by inhibiting viral fusion with the host's cell membrane, so that it prevents viral entry. It is licensed to be used in influenza A a and B treatment and prophylaxis in China and Russia. It also shows a good activity against SARS-CoV hepatitis B [27]. Later on, it demonstrated its antiviral activity in Ebola, human herpes virus 8, and hepatitis C viruses [28].

The use of Umifenovir in COVID-19 remains unclear. A retrospective study was done on 81 non-intensive care unit covid-19 confirmed patients, with 45 patients receiving oral umifenovir (0.2 g three times a day), and others were not. After 1 week, the same negative rate of COVID-19 in pharyngeal swab was shown, thus, in other words, umifenovir treatment did not alter the duration of infection and hospital stay in non-ICU patients [29]. However, other systematic reviews and meta-analyses studies with 1052 patients found that umifenovir on day 7 was not associated with higher negative rates (rate of positive to negative conversion), but on day 14 it was associated with higher negative rates [30].

Studies have shown that arbidol and lopinavir\ritonavir combination therapy was associated with noticeable elevated negative conversion rates, and chest CT scans showed improvements compared with lopinavir\ritonavir monotherapy [31].

All clinical studies available on umifenovir have several limitations in study design and sample size. It seems that umifenovir monotherapy is not effective, but combinations of umifenovir with other antivirals might be beneficial in viral clearance and chest CT. improvement.

Remdesivir

Remdesivir (Figure 1) is an analogue of adenosine nucleotide. It is a prodrug broad-spectrum antiviral against RNA viruses, inhibiting important viral enzymes called RNA polymerase, and it has activity against several coronaviruses such as MERS virus (Middle East Respiratory Syndrome) [32, 33]. It also has good antiviral activity against Ebola virus [34, 35].

Remdesivir is one of the most COVID-19 promising drugs, and there are many case reports and clinical trials that have shown its effectiveness. Remdesivir was used in the first COVID-19 infected case treatment in the US. Firstly, he had received parenteral vancomycin and cefepime, but on day 7 of hospitalisation (day 11 of illness), he developed severe pneumonia, and so physicians decided to start antiviral therapy (remdesivir) and discontinued the previous drugs. Treatment with IV remdesivir was started on day 7. On day 8, the patient's clinical condition was improved [36].

A cohort study was done on 53 patients receiving remdesivir (64% of them needed invasive ventilation). After follow-up from taking the first dose of remdesivir, 68% of patients showed an improvement in the clinical condition, whereas 15% showed a worsened condition. Seven of the 53 patients died after the completion of remdesivir treatment [37].

A randomised, placebo-controlled, double-blind study was done on 236 patients (158 taking remdesivir and 79 taking placebo) within 10 days of symptom onset. The results showed that remdesivir was not asso-

ciated with noticeable clinical improvement or reduction in mortality, although it numerically reduced the time needed for clinical improvement (the median was about 21 days with remdesivir, versus 23 days with placebo) [38].

Another double-blind, randomised, placebo-controlled trial of IV remdesivir was done on 1059 patients (538 taking remdesivir and 521 taking placebo). The results showed a significant shortened recovery time in those who took remdesivir (the median of recovery time was 11 days with remdesivir versus 15 days with placebo), and it also showed a noticeable reduction in the mortality rate (7.1% with remdesivir, and 11.9% with placebo) [39]. The researchers stated that larger studies were needed to confirm the results.

Remdesivir is given by IV administration because it has a poor oral absorption and is taken by 200 mg IV loading dose on day 1, then 100 mg daily maintenance dose for 5 to 9 days [40]. Some studies recommend combining nebuliser inhalation of remdesivir and IV administration to increase the distribution of remdesivir to the lungs [41].

Remdesivir has a low affinity for human enzymes (human RNA polymerase II and human mitochondrial RNA polymerase), so it has an acceptable safety profile in humans. The most common adverse effects are increased hepatic enzymes, increased blood glucose, anaemia, and renal impairment [39].

On October 15, WHO solidarity trial published, its results of a RCT study that involve more than seven thousands COVID-19 patients that Remdesivir has no significant impact on mortality rate reduction, clinical improvement or the need for mechanical ventilation[42]. However, on October 22, FDA approved Remdesivir use in COVID-19 and became the first drug approved by the US FDA. [43], however on 20th of November, WHO recommends against the use of it in COVID-19 patients regardless of disease severity, as there is no evidence to improve survival.[42]

Hydroxychloroquine

Hydroxychloroquine (Figure 1) is a 4-aminoquinoline. It has anti-malarial, anti-autophagy, anti-inflammatory, and immunosuppressive activity, but the exact mode of action is unknown. It may inhibit the immune function through changing the presentation of antigens and the production of cytokines. Hydroxychloroquine raises the pH of lysosomes, which impairs the degradation of autophagic proteins, hydroxychloroquine-mediated ineffective autophagosomes, accumulation might end in the death of cells that relay on autophagy to survive.

Additionally, this drug is extremely active against erythrocytic strains such as malaria, P. vivax, and different strains of P. falciparum, but it is not effective against the gametocytes of P. falciparum. It accumulates within the malarial parasitic lysosomes and raises the pH of the vacuole, which affects its ability to proteolyse hemoglobin to inhibit the growth and development of the parasite. It may also affect the action of parasitic heme polymerase leading to the accumulation of toxic beta hematin. Hydroxychloroquine accumulates in human organelles and increases their pH, which interferes with the processing of antigens and prevents the dimerisation of the alpha and beta MHC II chains [44].

The most common use of hydroxychloroquine is as an anti-rheumatologic agent in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), because it acts as an immunosuppressant that inhibits the rheumatoid factor and acute phase proteins assembly. Additionally, hydroxychloroquine accumulates in WBC, stabilises the lysosomal membrane, and inhibits collagenase and protease enzymes.

The most common side effects of hydroxychloroquine are nausea, diarrhoea, rash, skin pigment and hair alterations, and muscle weakness. Therapy with hydroxychloroquine is not associated with liver function abnormalities, but it may be a very rare reason for acute liver injury. Hydroxychloroquine in rare cases can cause anaemia and visual changes or loss of vision, so it is recommended to do an eye examination within the first year of use, and then repeat it every one to five years as per current guidelines. Reports of heart rhythm abnormalities are also reported, particularly along with other medications [45].

On 28 March, 2020, the FDA permitted the distribution and utilisation of hydroxychloroquine for hospitalized COVID-19 patients, because the initial in vitro studies showed that hydroxychloroquine may have utility in fighting coronavirus, because it has antiviral activity due to endosomal pH elevation that inhibits viral particles fusion, and entry into host cells. In addition, it also inhibits the terminal glycosylation of ACE-2 (the receptor that SARS-CoV and SARS-CoV-2 use to enter target cells), and it also has anti-inflammatory and anti-thrombotic activity [46].

On 21 March, 2020, president trump claimed that hydroxychloroquine can prevent and treat COVID-19. After one week from this declaration, prescriptions of hydroxychloroquine were increased up to 200% compared to previous years. The majority of excess prescriptions were written between 14 March and 4 April, because news spread about deficiency and shortage of this drug without any evidence to support its use. Research now shows that hydroxychloroquine is not effective in the prevention or treatment of COVID-19, but the damage has already occurred, and thousands of USA citizens have unnecessarily taken this medication, which may have serious side effects. In addition, people who really need hydroxychloroquine found themselves unable to get the drugs that they needed [47].

On 17 June, 2020, the WHO declared that hydroxychloroquine utilisation in the treatment of COVID-19 was being stopped because the available data showed that hydroxychloroquine does not reduce the mortality rate reduction among COVID-19 patients. [48]

Dexamethasone

Dexamethasone (Figure 1) is one of the most common long-acting glucocorticoids, just like a natural hormone produced by the adrenal gland (36–55 h). It stimulates hepatic glucose production by enhancing gluconeogenesis, and as a result, it raises glucose plasma levels and body energy, so increasing body resistance to stress. It also decreases eosinophils, basophils, monocytes, and lymphocytes, but increases haemoglobin, erythrocytes, and platelets, but the most important therapeutic properties of glucocorticoid are its anti-inflammatory and immunosuppressive actions by blocking the power of macrophages and inhibiting the energy of leukocytes to retort to antigens and mitogens, and reduce the production of cytokines. In addition, it can block the phospholipase A2 enzyme, which blocks arachidonic acid liberation, leading to anti-inflammatory and suppression expression of inflammatory mediators. At high levels, it provides negative feedback to reduce ACTH production, so suppressing the synthesis of glucocorticoids and thyroid-stimulating hormone. It is thirty times more potent than cortisol [49].

Dexamethasone has many uses: it is employed as a test for Cushing's syndrome, relieves inflammation in different organs in our body, decreases fluid accumulation of water (oedema), is related to cancer in the brain or spine, decreases inflammation in the eye, can prevent or treat hypersensitivity reactions, is a treatment of kinds of autoimmune diseases, e.g., rheumatoid arthritis; conditions in the skin, lung conditions (asthmatic patients), and is used as a therapy for spreading tumours such as lymphoma, multiple myeloma and leukaemia. In addition, it can be used for patients who are having chemotherapy to reduce and treat side effects including nausea and vomiting. In cancer patients, we can use it as an appetite stimulant, especially for patients with very severe appetite problems, and it can be used in cases of adrenal insufficiency as a replacement therapy, to accelerate foetal lung maturation, and immunosuppressant in transplantation procedures [50].

There are various adverse effects of long-term therapy. In osteoporosis, it can repress the absorption of Ca+2 intestinally and reduce the formation of bone. It can interfere with hormone production (e.g., sex hormones), create aa Cushing like syndrome (distribution of fat become's different with a moon face, hair growth and increased need of food), cataracts and glaucoma can also occur, plus hyperglycemia, so that DM patients should monitor their blood glucose level. In addition, long-term use can decrease WBC and increase the risk for infection, cause hypokalemia, emotional disturbances (euphoria, depression), peripheral oedema, increase the risk of hypertension and increase appe-

tite. Topical therapy can cause atrophy in the skin, purple stria, and bruising [51].

This drug must be tapered slowly, because sudden discontinuation can cause serious results if the patient has the suppression of HPA axis, so it can cause acute adrenal insufficiency which can be fatal. Coronavirus stimulates inflammation as a normal response of the body to defend against the the virus, but in some cases, the immune system goes into overdrive because the immune system attacks own cells. Dexamethasone lowers and calms this effect, so it is only used for those that are receiving oxygen or on mechanical ventilation. Hospitalized patients with COVID-19 in the United Kingdom have been tested in the national clinical trial RECOVERY (Randomized Evaluation of COVID-19 therapy) trial, which was established as a randomized clinical trial to test a possible therapy for COVID-19 patients. Among them was dexamethasone, given to about 11,500 patients in hospitals in the UK; 2104 patients received 6 mg dexamethasone per day (by IV injection or by mouth) for ten days and were compared with 4321 patients who took ordinary care alone. The 28-day death rate was elevated in people who needed oxygen (41%), among patients who received usual care alone, intermediate in patients who needed oxygen (25%), and the percentage among people who did not require any respiratory intervention was the lowest (13%).

Dexamethasone treatment showed a reduction in mortality in about one-third of people with COVID-19 on ventilators, and about one-fifth of patients who needed oxygen only. In other words, it saved one life in every eight patients on ventilators, and one life in every twenty-five patients on oxygen.

It was administered as oral (liquid or tablet) or by intravenous route. It can be taken as 6 mg once daily for ten days, but they gave prednisolone (a milder corticosteroid) for pregnancy or breastfeeding women. A Professor of Emerging Infectious Diseases said, "Dexamethasone is the first drug to be shown to improve survival in COVID-19, so dexamethasone should now become the standard of care in these patients. Dexamethasone is inexpensive and easily available."

On 22 July, 2020, the Ministry of Health of Japan approved the employment of the dexamethasone glucocorticoid drug as a novel treatment of coronavirus patients [52].

Ivermectin

Ivermectin (Figure 1) was discovered in the 1970s as an anthelmintic agent. It stimulates GABA gate and Cl channels resulting in organism paralysis, and it is an immunomodulator of host response, to activated neutrophils, C- reactive protein, and IL-6 (interleukin-6) [53]; then it was used as an antiviral against certain flavivirus, e.g., dengue fever, Japanese encephalitis, tick-borne encephalitis virus, and chikungunya virus [54].

Ivermectin is marketed in doses of 200 mcg/kg for strongyloidesstercoralis (an intestinal parasite capable of causing severe systemic disease), and for onchocerciasis, or liver blindness, and against lymphatic filariasis, and scabies as single doses of up to 400 mcg/kg, 200–300 mcg/kg doses within a month are recommended for the treatment of severe crusted scabies. Although it is not marketed for these indications, ivermectin has partial efficacy against other common intestinal parasites in humans such as Ascarislumbricoide and Trichuristrichura. It is also used out of labels against ectoparasites like head lice, and Tungapenetrans among many other internal or external parasites [55].

At currently approved doses, ivermectin is very safe, because most adverse reactions are mild and associated with parasite death rather than with the drug itself, e.g., nausea, skin rash, dizziness, suppressing immunity, abdominal cramps, fever, heart rate elevation and unstable BP. Ivermectin targets are only present in invertebrates. Mammals only having a similar channel that could cross-react with ivermectin (GABA-gated chlorine channel), but it is only expressed in the central nervous system, which is protected by the blood-brain barrier. There is no evidence that indicates its employment in children or pregnancy. It is safely administered at 600 mcg/kg daily for three days [56].

In April 2020, studies on ivermectin demonstrated that ivermectin in combination with the antibiotic doxycycline, and zinc supplement is effective in COVID-19 treat-

ment. However, at the current time, we still do not have definitive clinical trials to demonstrate this. Regarding observational studies and physician thought, there were 16 current clinical trials about ivermectin. These studies are unlikely to be beneficial due to the small sample size, poor study design, and combining ivermectin with other drugs.

In vitro studies on monkey cells show that ivermectin can block SARS-CoV-2 replication within 2 to 3 days of exposure to ivermectin, through preventing the movement of viral proteins in and out of the nucleus of the host cells, which is crucial for viral replication [57]. The problem is with the potential overdose of ivermectin (more than the recommended dose is required), which can increase the potential of side effects and it may cross the blood-brain barrier, causing visual impairment, hamper the CNS (that may affect heart rate, respiration and consciousness) [58].

Finally, the results of clinical trials are needed to decide if ivermectin is effective against COVID-19 or not. In Peru and Bolivia, the Ministries of Health have authorised this drug for this indication.

Anticoagulants

COVID-19 can be associated with several haematological disorders that can lead to coagulopathy. Several patients with COVID-19 have existent coagulopathy similar to other systemic coagulopathies in critical infections, such as disseminated intravascular coagulation (DIC) or thrombotic microangiopathy. The percentage of thrombotic disorders in patients with COVID-19 infection who enter in ICU is 31%, which is clearly high [59].

To clarify how coagulopathy occurs in COVID-19, there are many mechanisms that could be involved. One of these theories is about the endothelial cells that play a serious role in hemostasis regulation, fibrinolysis, and the integrity of the vessel wall. An injury to the endothelial cell will activate multiple proinflammatory cytokines such as IL-1, IL-6, and TNF-alpha (Tumour Necrosis Factor alpha). The rise in the activity of inflammation can contribute to microvascular thrombosis [60].

The most common finding in patients with COVID-19 and coagulopathy is an elevation in D-dimer levels, but decreased platelet count (present in 70–95% of patients with intense COVID-19), and prolongation of prothrombin time. Mean fibrinogen levels are higher than normal borders. However, an abrupt decline in the blood level of fibrinogen was detected shortly before death in many patients. Plasma levels of antithrombin are higher in COVID-19 survivors than in nonsurvivors (91% of normal survivors vs 84% in nonsurvivors) [61].

A retrospective study was done including 183 patients with novel coronavirus pneumonia (NCP) reported that the overall mortality was 11.5%. There were 71.4% of nonsurvivors and 0.6% survivors who met the criteria of DIC during their hospital stay, this can lead us to conclude that the abnormal coagulation is linked with bad prognosis because it is common in deaths with NCP [62].

This has led to the introduction of anticoagulant therapy. 449 Patients with COVID-19 were introduced to a study where they gave heparin to 99 patients (mainly LMW heparin) for 7 days at least. There was no variation in mortality between patients who took heparin and who did not take heparin within 28-day (30.3% vs 29.7%). However, the 28-day death rate among patients who took heparin was less than in patients who did not take it in patients with sepsis-induced coagulopathy (SIC) score ≥4 (40.0% vs 64.2%), or D-dimer >6 times of the upper border of normal (32.8% vs 52.4%). Anticoagulant treatment seems to be linked to better prognosis in severe COVID19 patients [63].

Any hospitalised patients who do not have any proof of active bleeding should receive anticoagulants as a prophylactic measure, as COVID-19 infection is associated with thrombosis. The anticoagulation of choice is LMWH (such as enoxaparin 0.5 mg/kg), unfractionated heparin, or subcutaneous fondaprinux. If pharmacological anticoagulants are contraindicated, mechanical thromboprophylaxis like intermittent pneumatic devices (IPD) should be used [60].

COVID-19 related morbidity and mortality may contribute to thrombotic events, and the use of anticoagulants is linked to a

better prognosis. However, the individualised risk-benefit ratio of the use of anticoagulants must be determined.

Colchicine

Colchicine (Figure 1) is a molecule composed of tricyclic alkaloids extracted from a plant known as Colchicum autumnale (autumn crocus), which is commonly used to treat various types of diseases and some syndromes like familial Mediterranean fever (FMF; known as auto inflammatory disease caused by mutations in the Mediterranean fever gene, the characteristics of this disease are fever, abdominal lining inflammation, pain in lung line joint, swelling and ankle rash). Colcicine is also used to prevent gout attacks (a disease caused by the accumulation of uric acid in blood, where uric acid makes very hard crystals in joints cause that cause sudden and very severe pain in joints in adults) [64].

It also used for Behcets disease (an uncommon syndrome that causes blood vessel inflammation throughout the body), coronary artery disease, pericarditis (inflammation and soreness of the pericardium, the fibrous sac surrounding the cardiac muscle), and other inflammatory and fibrotic conditions.

The pharmacotherapeutic mechanism of action for this drug is from its ability to relate to the molecular biology known as tubulin. It can prevent the polymerization of the polymers of tubulin that form part of the cytoskeleton microtubules, which are important to maintain the shape of the cell [65, 66]. Colchicine can block cell division during metaphase when it binds to tubulin, and form colchicine complexes with the protein forming a complex bounding to the ends of microtubules to stop the prolongation of the microtubule polymer, affecting the immune system [67].

Its main technique is the suppression of chemotaxis of neutrophils and the release of a glycopeptide crystal-derived chemotactic factor (CCF) from neutrophil lysosomes after phagocytosis. Monosodium urate crystals (MSU) cause stimulation of a chemotactic factor called S100A8-9, which is believed to be a similar factor to CCF and is supposed to amplify neutrophil recruitment.

Elevated levels of proinflammatory neutrophilia and cytokines are one of the signs that can be detected in COVID-19 patients with severe acute respiratory syndrome. In this situation, there is no medication, but supportive, additional therapy and nursing care try to decrease the inflammation. Colchicine works on leukocytes, and so is utilised as a support therapy.

One double-blind, controlled trial on colchicine used in COVID-19 treatment (which had a positive outcome) was done on 38 moderate to severe COVID-19 patients from 11 April to 6 July, 2020, with the first group taking 0.5 mg colchicine twice daily, the second group not. The first endpoints for this trial were the need for supplemental oxygen, time of hospitalisation, requirement for the intense nursing unit, and mortality rate; as secondary endpoints, they measured serum C-reactive protein, serum lactate dehydrogenase, and the relationship of lymphocytes to neutrophils in peripheral blood samples from zero day to day 7.

The results showed that the median time needed for additional supplemental oxygen was 3.0 (1.5 to 6.5) days for the first group, versus 7.0 (3.0 to 8.5) days for the second group (the percentage of patients needing oxygen supplement on day 2 was 53% versus 83%, but on day 7 the values were 39% versus 61% in the control, and colchicine groups, respectively), and the first group showed a noticeable reduction in C-reactive protein levels. The use of colchicine did not affect the cardiac muscle, however, the main adverse effect with its use was diarrhoea [67].

In summary, colchicine was found to decrease hospitalisation and oxygen supplement need, and thus, it is considered a beneficial and not expensive option for COVID-19 treatment.

Inhaled Furosemide

Inhaled Furosemide (Figure 1) is classified as a loop diuretic, which is a weak organic acid, with a relatively short half-life and low volume distribution, leading to a low distribution. However, the drug's clearance mostly happens in the kidneys (85%), and around half of the drug is metabolised to glu-

curonic acid, with the rest secreted unchanged in the urine.

To achieve its diuretic effect, furosemide can be given orally, intravenously, or inhaled. The mechanism of the drug is to block the reabsorption of sodium, potassium, and chloride in both the proximal distal tubules and in the loop of Henle. It takes effect after 60 to 90 minutes and promotes the excretion of potassium, chloride, and sodium in the urine [68].

Furosemide has antiinnate immune system activity; this effect was noticed when they used the inhaled form of furosemide, but not orally, and caused exercise-induced bronchospasm in asthmatic patients. Since then, it has been approved as a possible treatment for patients suffering from shortness of breathing and symptomatic dyspnea. It mainly depends on supposing that the volume of affected edematous cells in the airway will be decreased by the diuretic effect of the drug, resulting in an improvement in the respiratory tract. However, some current studies show that its therapeutic effect comes from the decreased secretion of proinflammatory cytokines, particularly its effect on IL-6 and IL-8 and TNF-alpha.

This drug has an anti-inflammatory effect, has a good effect against dyspnea, and shows antiviral effects. It blocks the K+/Na+/Cl co-transporter in viruses, which increases the concentration of Na+ and K+, and as a result, increases the cell volume of the virus leading to membrane distribution and death.

Hypokalemia, i.e., electrolyte depletion, is a possible disadvantage of using furosemide in COVID-19 patients. Inhalation using a nebuliser mask will cause the evolution of aerosols and may elevate viral prevalence if done without physical distancing. Because coughing is a primary way for disease spreading, and since inhaled furosemide reduces coughing, it can reduce the spread of the disease.

Furosemide helps in the early and late stages of COVID-19, by blocking pulmonary failure progress in the early stages, and reducing ventilator support needed in later stages.

Even though cytokine storms are known to have a considerable role in very intense viral pneumonia, the detailed mechanism of hypercytokinemia in COVID-19 is not yet fully delineated.

Inhalation of furosemide has been used in the past for a variety of pulmonary disturbance and concerns as a safe way. Therefore, we suggest an evaluation of inhaled nebulised furosemide in COVID-19 patients because of its inflammatory effect [68]

After this, although the drug is found globally and it has anti-inflammatory, antiviral effects, it is still unapproved.

Interleukin-6 inhibitors (Tocilizumab)

Tocilizumab is a recombinant humanized monoclonal antibody that can inhibits the binding of IL-6 to both soluble and membrane IL-6 receptors. Early evaluations from China founded some improved outcomes in hospitalised COVID-19 patients with who received tocilizumab. These early reports were followed by a few observational works in critically ill COVID-19 patients with, that suggested a mortality benefit with this drug [69].

Convalescent plasma (CP)

Convalescent (or immune) plasma refers to plasma that is collected from people after recovery from infection and their development of antibodies. Passive administration of these antibodies during convalescent plasma transfusion offers a short-term method to supply immediate immunity for an infected person. Convalescent plasma from recovered people is more promising when it is administered as a prophylaxis or when it is given shortly after the appearance of symptoms (within two weeks) [70].

Convalescent plasma is obtained by using apheresis (continuous blood centrifugation to permit a selective collection of plasma). During apheresis, they obtain neutralising antibodies (Nabs), clotting factors, anti-inflammatory cytokines, defensins, natural antibodies, and other proteins. The major goal is to neutralise pathogens to allow its eradication. [71].

Passive immunisation has been successfully used in the treatment of infectious dis-

eases in previous years. It was used in Spanish influenza (it is the first viral infection where convalescent plasma was found to be effective during clinical studies) [72], Ebola virus [73] and influenza A (H1N1) [74] . Additionally, Convalescent plasma was used in other coronavirus' such as SARS-CoV [75], MERS outbreaks [75].

The donor is a person who has recovered from COVID-19. Recovery is defined as a normal body temperature for at least three days, no respiratory symptoms, and negative results for COVID-19 for two consecutive PCR tests at least three weeks after the appearance of symptoms. The donor has for be negative to anti-HBV, HCV, HIV and positive for anti SARS-CoV-2 [76].

Convalescent plasma is a good agent to be tested as a potential therapy to face this pandemic. Several studies (but unfortunately not clinical trials) have evaluated this option. From 23 Januaryto 19 February, 2020, ten patients in three hospitals participated in a pilot study. All of them were diagnosed to have severe COVID-19 and were admitted to the ICU to receive antiviral therapy; some of them were receiving antibiotics, antifungals, corticosteroids, and oxygen when necessary. A single dose of 200 ml of inactivated CP was administered over four hours to ten patients, and researchers studied the safety and clinical improvement after convalescent plasma transfusion. The result was that all symptoms in all patients disappeared or largely improved after one to three days upon convalescent plasma transfusion [77].

Another study of a case series of five critically ill patients who had COVID-19 and ARDS with severe pneumonia and continuously elevated viral load, despite taking antiviral treatment. All patients received convalescent plasma and within three days of transfusion, the body temperature of four of five patients became normal, viral load decreased and became negative within 12 days after transfusion; ARDS improved in 4 patients after 12 days. The limitation of this study was the small sample size and concomitant treatment with other drugs (such as remdesivir, corticosteroids, etc.), however, it suggested that convalescent plasma transfusion is safe, and decreased viral load and improved the clinical condition [78]. The dose of convalescent plasma was 3.125 ml/kg (for a typical adult patient of 80 kg they need 250 ml of plasma for three days) [70].

According to the safety profile of CP transfusion, a study done on 5000 hospitalized patients with life-threatening COVID-19 found the incidence of all dangerous adverse reactions (such as severe allergic reactions, lung injury, circulatory overload) in the first 4 hours was less than 1%, and the mortality rate was not excessive [79]. These indicate that CP is safe for hospitalized COVID-19 patients.

Human plasma obtained from recovered patients of COVID-19 is a safe and possibly effective treatment for SARS-CoV-2. However, it is important to perform randomized clinical trials to assure its efficacy.

Herbal and food supplements

Artemisia annua

Artemisia annua belongs to the Asteraceae family and is used as an anti-malarial, due to its active compound, artemisinin [80]. It also contains many essential oils which have anti-inflammatory [81], antitumor [82], antibacterial and antioxidant properties [83].

Semi-synthetic derivatives of artemisinin, such as di-hydro artemisinin, β-artemether, and artesunate have been developed with more potency, stability, and water solubility, because artemisinin has poor water solubility and bioavailability [84].

Currently, studies show that it has antiviral activity against SARA-CoV-2, by inhibiting chymotrypsin-like protease (CLPro) (an enzyme produced by the virus during infection). It also supports adaptive immunity and modulates the inflammatory response by regulating proinflammatory cytokines such as PG-E2, IL-6, IL-10, and TNF-alpha, and may also be used in fever treatment [85].

Artemisia annua is a possible candidate to use in COVID-19, but more studies are required to prove its safety and efficacy.

Vitamin D

Vitamin D is a fat-soluble supplement with substantial benefits for the immune system. It regulates the production of a protein that selectively kills infectious agents, enhances pathogen-fighting by white blood

cells (WBC), and decreases inflammation. There are many people with low concentrations of vitamin D, which affects the immune function negatively, so increasing the risk of respiratory infections including COVID-19, and worsening the COVID-19 patient status.

We advise all older adults, hospital inpatients, nursing home residents, and other vulnerable groups to take vitamin D supplement with 20–50 μg/d to enhance their resistance to COVID-19 [86].

Vitamin C

The key factor of fatality in COVID-19 disease is acute respiratory distress syndrome (ARDS), because of a significant increase in free radicals and cytokines leading to cellular injury, organ failure and death; therefore, the early using of big dose vitamin C as an antioxidant may be efficient in these patients.

The latest clinical trials reaching high doses of vitamin C were found to protect against viral infection. It has a tolerated safety profile in high doses of oral administration, and even intravenously, so it should be included in COVID-19 treatment and protection.

Vitamin C and other antioxidants are currently using to alleviate COVID-19 associated with ARDS, because of the development of effective vaccines and long-term treatment.

There is a significant need for clinical studies to develop protocols for bedside use [87].

Zinc

Zinc has antiviral activity by viral replication suppression and by immune response support. It is considered an inexpensive and effective adjunct therapy for some viral species that can trigger respiratory tract infection.

It is available as a tablet, lozenges, etc., alone or in combination with other supplements, for example, vitamin C. Maintaining sufficient zinc blood levels is important to protect from microorganisms, including COVID-19, so consuming about 50 mg of zinc per day will provide an additional shield against COVID-19.

To prove the beneficial role of zinc in COVID-19 disease, more clinical validations are required [88].

1. Combination Therapy that Eliminates COVID-19 Virus

Among the choices for accelerating and progressing the treatment of COVID-19, a combination therapy was the best. This strategy is attractive for a number of reasons. Firstly, combining two or more drugs with related or complementary therapeutic effects provides a multipronged effect, addressing the mutable pathways of the virus. Secondly, the combination may give a synergistic effect, and as a result may be better outcomes. Thirdly, this plan is time-saving, rather than taking a step-by--by-step treatment approach (monotherapy), and this strategy begins with testing all relevant therapeutic options (Table 1).

Table (1): Drug combination list and the classification of each drug use.

Drug combination	Classification of drugs	
	Drug Name	Approved use
Hydroxychloroquine and azithromycin	Hydroxychloroquine	Antimalarial
	Azithromycin	Antibiotics
Lopinavir, ritonavir and ribavirin	Lopinavir, ritonavir and ribavirin	Antiviral
Ivermectin and Doxycycline	Ivermectin	Anthelmintic
	Doxycycline	Antibiotics
Remdesivir with baricitinib, or with leronlimab	Remdesivir with baricitinib, or with leronlimab	Antiviral
Triple combination antiviral therapy (lopinavir, ritonavir, and ribavirin) with interferon beta-1b	lopinavir, ritonavir, and ribavirin	Antiviral
Inhalable Gapme and anti-viral drug	Gapme	Antiviral

Drug combination	Classification of drugs	
	Drug Name	Approved use
Nitazoxanide and azithromycin	Nitazoxanide	antiprotozoal
	azithromycin	antibiotics
Ivermectin and Doxycycline with Zinc and Vitamin D3	Ivermectin	Anthelmintic
	Doxycycline	antibiotics
	Zinc and Vitamin D3	dietary supplement
Colchicine and Hydroxychloroquine and Ivermectin	Colchicine	anti-gout
	Hydroxychloroquine	Antimalarial
	Ivermectin	Anthelmintic
Colchicine with chloroquine or hydroxychloroquine and azithromycin	Colchicine	anti-gout
	chloroquine	Antimalarial
	azithromycin	antibiotics
Ivermectin and Nitazoxanide	Ivermectin	Anthelmintic
	Nitazoxanide	antiprotozoal
Colchicine along with Ivermectin	Colchicine	anti-gout
	Ivermectin	Anthelmintic

2. WHO approved the clinical management protocol?

Patients with mild COVID-19 were recommended only to receive symptomatic treatment such as antipyretics, e.g.: paracetamol (at present there is no evidence for adverse effects in patients who were taken non-steroidal anti-inflammatory drugs (NSAIDs) for fever) and anti tussive for cough, they should receive adequate nutrition and appropriate rehydration.

WHO does not recommend antibiotics therapy or prophylaxis for patients with mild COVID-19 disease unless they suffer from secondary infection.

Signs, symptoms, and complications should be provided to the patient's caregiver, in case he seeks urgent care. Thrombosis prophylaxis, such as low molecular weight heparin is recommended in hospitalized patients with COVID-19 by WHO.

WHO does not recommend routine systemic corticosteroids using, unless they indicated for other reasons including exacerbation cases, ARDS, and who needs oxygen or ventilator [89].

3. Vaccines

World Health Organization (WHO) estimated that there are more than hundred current vaccines are under development, some of these vaccines reach human trial phase [90]. Some examples on these vaccines: First of them is Pfizer/BioNTech vaccine, it's RNA vaccine, it's given by IM injection in two doses on day 0 and 21 [91]. Data from large studies showed that it's 95% effective in COVID-19 prevention, recommended for older than 12 years old [92]. This vaccine faces distribution challenges because it should be stored at -94 degree Celsius [93]. Other vaccine is AstraZeneca/Oxford it's a Non-Replicating viral vector (it consist of engineered virus that carry COVID 19 genes, it can't replicates because it does not have DNA), it's given by IM injection in two doses on day 0 and after 4 to 12 weeks, it recommended for older than 18 years old [91]. Phase III interm analysis indicates that its 76% effective in preventing COVID-19 [94]. It can have kept in refregirator (not freezing) so it is easier to distributed, but there have been cases reported venous clots, so in England it was recommended other vaccines for people older than 40 years old. Moderna vaccine its RNA vaccine (mRNA to generates viral spike proteins), it recommended for older than 18 years old , it's given by IM injection in two doses on day 0 and 28, [91]. It should kept at -20 degree Celsius which makes a challenge to transport it [95]. Moderna announced that their vaccine is 94% effective [96]. Regarding the last updated data of COVID-19 vaccines, forty vaccines are under clinical evaluation, the national regulatory authorities have granted emergency use authorizations for some COVID-19 vaccines, a few of them such as Oxford–

AstraZeneca, Pfizer-BioNTech, Sinopharm-BBIBP, Moderna, and Sinovac, have been approved for emergency use by at least one WHO-recognized stringent regulatory authority [97, 98].

Researchers found a study in Spain that show a mixing thereby with both the Astra-Zeneca and Pfizer, COVID-19 vaccines this combination make an effective immune response against the virus SARS-CoV-2. Experience of more than 600 people results from the advertise on 18 May in an online presentation are the first to presentation the benefits of mixing various coronavirus vaccines. A United Kingdom (UK) trial of an identical strategy reported safety data last week, and is predictable to deliver further findings on immune responses soon. A study in Britain called Com-COV, which mixed the same type of two vaccines, found that people in the mix-and-match groups had common vaccine-related side effects, such as fever, compared to people who received the two doses. From the same vaccine 1. In Spain's CombivacS trial, mild side effects were common, and similar to those of standard COVID-19 vaccine regimens. None of it was considered severe [99, 100].

CONCLUSION

The COVID-19 pandemic represents the greatest global public health crisis in the last ten decades, potentially since the influenza outbreak of 1918. Scientists worldwide are working hard to find an effective therapy, learning from previous outbreaks of SARS and MERS. There are several ongoing clinical trials on preexisting drugs to evaluate their efficacy and safety, many of these drugs have hopeful potential results such as colchicine, dexamethasone, kaletra (Lopinavir/ritonavir), cefuroxime, favipiravir and inhaled furosemide. However, until now there is no available approved drug to use in COVID-19 by WHO, although the FDA approved Remdesivir using in COVID-19 and became the first drug approved by the US.FDA, WHO recommends against the use of remdesivir in COVID-19. A supportive care and many protocols (symptomatic treatment, e.g., antipyretics, antitussive, adequate nutrition, rehydration, antibiotics suffer from secondary infection, antithrombotic prophylaxis for hospitalized COVID-19 patients and corticosteroids in exacerbation cases) were followed by governments and organizations. Many vaccines passed phase 3 in research trials, and the scientists hope that it will be ready for mass distribution in early to mid - 2021.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

FOUNDING

Not applicable.

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