Potential pharmacological Therapeutics options for COVID-19: Review

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Abstract
Unusual pneumonia result from unknown pathogen was emerged in December 2019 in a seafood market of Wuhan city in China. The pathogen was soon identified as a novel coronavirus (2019-nCoV), which is closely related to sever acute respiratory syndrome CoV (SARS-CoV) which has taken the world to the edge of health emergency. On 11th March 2020, COVID-19 was declared a pandemic by the World Health Organization. SARS-CoV-2 belongs to the family of Coronaviridae. Corona virus has been reported to cause similar morbific impacts on the lower respiratory system. Transmits occurs when people breathe in air contaminated by droplets and small airborne particles. Transmission can also occur if sprayed with contaminated fluids, in the eyes, nose or mouth. People remain contagious for up to 20 days, and can spread the virus even if they do not develop any symptoms. Although this disease primarily targets lungs, damages in other organs, such as heart, kidney, liver, and testis, may occur.

Key words: Acute Respiratory Disease, corona virus infection, SARS-CoV-2, corticosteroids, antimalarial drugs, viral diseases, remdesivir, auranofin.

Introduction
The outbreak emerged in a seafood market that sold wild animals in Wuhan city, suggested that some animals could be a disease reservoirs, and this disease caused by zoonotic transmission (1). However, scientists’ confirmed that droplet and human- to -human direct contact is a primary means of transmission (2). This is the reason of rapid spreading of cases in China outside Wuhan (3). On January 30, 2020 the world health organization (WHO) announced that the COVID-19 outbreak is a global health emergency (4).

A novel coronavirus (2019-nCoV) belongs to Beta-coronavirus, which previous viral diseases as SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV) also belongs to. In fact angiotensin- converting enzyme 2 (ACE2) is mostly expressed in nasal mucosa, bronchus and lung. This explained the reason to consider epithelial cells of the lungs as the primary target of the SARS-CoV-2. Other organs that susceptible to SARS-CoV-2 are bladder, stomach, ileum, heart and kidney were ACE2 also expressed (5). The first step of viral infection is the virus binding to a receptor expressed by human cells. After virus
binding to the receptor it fused with the cell membrane. Accordingly, many researchers investigated that human to human transmissions of the virus occurs through binding between the receptor-binding domain (RBD) located within virus spikes and ACE2, the cellular receptor (6). China scientists found that SARS-CoV-2 (Figure 1) is similar to SARS-CoV, regarding the requirements of the (ACE2) receptor (7), to enter host cells (8), passing via the nasal and larynx mucous membranes. Then through the respiratory passage the virus enters the lungs. Thus fever and cough are the most prevalent and early symptoms of COVID-19 contagion (9).

However, pneumonia is a typical characteristic feature of the COVID-19 patient (10, 11). The chest X-ray and computer tomography (CT) imaging in a study showed that 75% of 99 patients demonstrated bilateral pneumonia and the remaining 25% unilateral pneumonia. Overall, 14% of the patients showed ground-glass opacity along with multiple mottling (12).

The main symptoms include: fever and cough, fatigue, chest pain, dyspnea (shortness of breath), headache, sore throat and anorexia (12). Other manifestation of COVID-19 is gastrointestinal symptoms like nausea, abdominal pain, and diarrhea (6). However, patients infected by COVID-19 may be asymptomatic, mild, or severe illness (13). Severe cases included severe pneumonia, acute respiratory disease illness, respiratory and multi-organ failure as well as septic shock. Death was recorded in elderly people who may have comorbidities conditions like hypertension, diabetes, cardiovascular disease, chronic respiratory disease and cancer (14). The patients with severe acute respiratory illness urgently need vital organ support (13).

The rapid identification of effective interventions against SARS-CoV-2 is a major challenge. The purpose the presence of antiviral drugs is a potentially essential near-term strategy to tackle COVID-19 (15). Currently there are no specific antiviral drugs agents SARS-CoV-2, thus treatment is basically depend upon symptomatic handling in addition to oxygen therapy of urgent cases (16). However, many treatments choices have been suggested and applied to control COVID-19 depending on previous experiences with other viral infectious diseases like Ebola, malaria and cholera (17). In fact there is no confirmed vaccine or antiviral drug accessible to be used against COVID-19. A few broad-spectrum antiviral drugs have been determined against this disease in clinical trials that achieved clinical recovery (18). Many therapies like lopinavir- ritonavir, ribavirin and corticosteroids previously used to treat patients infected with SARS or MERS (19) are effective in related viral infections, although efficacy of these drugs remains controversial.
Fig. 1: Illustrate the structure of human coronavirus. Spike (S), envelop (E), membrane (M) and nucleocapsid (N) proteins are the structural proteins [www.google.com].

1- Treatment of COVID-19 with Remdesivir

Remdesivir is a phosphoramidate prodrug of an adenine derivative. Remdesivir has broad-spectrum action against RNA viruses like MERS and SARS in cell cultures. It also tested in a clinical trial for Ebola (20). Warren and his work team 2016 (21) mentioned that remdesivir as an adenosine analogue, incorporates into nascent viral RNA chains and causes premature termination of it. Study of Zhou and his colleagues 2020 (22) reported that remdesivir functioned at a stage post virus entry which is correspond with its assumed antiviral mechanism as a nucleotide analogue. Remdesivir also inhibits the virus infection effectively in a human cell line, human liver cancer and Huh-7 cells, which is sensitive to SARS-CoV-2.

Recently small molecules of remdesivir and chloroquine are used to effectively inhibit the replication of SARS-CoV-2 in vitro (20). The enzymes catalytic domains like RdRp are extremely conserved in SARS-CoV-2 and SARS based on the comparison of genome sequences of SARS-CoV-2 with SARS sequence. Venkataraman et al., 2018 (23) cited that “the enzymes protein sequence of drug binding pocket is significantly conserved”. Consequently a highly promising drug targets when the scientists develop a therapeutic approach for COVID-19 are spike protein and these enzymes (24).

In fact RdRp, also known as nsp12, is a primary enzyme of the coronaviral replication/transcription machinery complex. RdRp catalyzes the synthesis of coronavirus RNA. Using cryo-EM, a specific research recently investigated the SARS-CoV-2 structure full-length nsp12 in complex with co-factors nsp7 and nsp8. Except for the conserved features of the polymerase component of the viral polymerase family and key domains for the coronavirus replication found in RdRp SARS-CoV-2 nsp12 has new characteristic (B-hairpin domain) at
the N-terminal (25), which gave new understanding into the key enzyme of the coronaviral replication/transcription complex and put a sturdy base for the designing of new antiviral drugs targeting RdRp of SARS-CoV-2. A randomized control trial of Phase III trials of remdesivir have been initiated, and tested on 761 patients in Wuhan, in China (15) and a United States patients with COVID-19 has been recovered after receiving intravenous remdesivir (26).

2-Treatment of COVID-19 with favipiravir

On February 15, 2020 favipiravir (Trade name: Avigan) a nucleotide analogue has been approved for COVID-19 treatment in China. In 2002, Fujifilm Toyama Chemical Company developed favipiravir (27, 28). In 2014 pyrazinecarboxamide was created and favipiravir (C5H4FN3O2) is a derivative of this structure. This therapy was investigated to be well tolerated in patients with influenza virus and in healthy volunteers. Then favipiravir was confirmed in Japan for treatment of influenza viral infections in the event of an outbreak of this disease. But this drug was contraindicated for use in pregnancy due to its embryo-toxic and teratogenic effects observed in animals. However, lack of generation of resistance to favipiravir among influenza viruses is an important characteristic of this drug (29).

In fact favipiravir has a broad spectrum of activity against a wide range of RNA viruses involving norovirus (30), Ebola virus (31), Zika virus (32), Respiratory Syncytial Virus and Rhino but it has no effect against DNA viruses such as Herpes (33). This drug efficaciously inhibits the RNA-dependent RNA polymerase of RNA viruses like influenza, chikungunya, norovirus, yellow fever, as well as enterovirus (34). Resemble to remdesivir, favipiravir suppress viral RNA synthesis via chain termination (35, 36). Studies done by Smee et al., 2009 (31) and Arias et al., 2014 (37), investigated that favipiravir is metabolized into ribofuranosyl 5’-triphosphate (RTP) and integrate in the nascent RNA strand. However, the incorporation of favipiravir-RTP double molecules could completely block the further extension of RNA strand while a single molecule incorporation of favipiravir-RTP could terminates partially the elongation of RNA strand. This mechanism effectively suppresses the function of the viral RNA-dependent RNA polymerase, as well as reducing the viral titre in vitro (38) (Figure 2).

Furthermore study of Smee et al., 2009 (31) indicating that favipiravir could suppresses virus replication in vivo and allows the patient infected with COVID-19 to raise a virus-specific adaptive immune response to manage the infection. Recently several studies on potential therapeutic drugs in treating patients with COVID-19 has been done including lopinavir/ ritonavir, chloroquine, hydroxychloroquine, favipiravir, ribavirin, sarilumab, interferon and tocilizumab (39).

In a nonrandomised clinical trial Cai, 2020 (40) tested the effects of favipiravir vs lopinavir/ ritonavir for the treatment of CDVID-19. Thirty five patients were treated with favipiravir at dose 1600mg twice daily at day 1; and 600mg twice daily for 2-14 days while forty five patients were treated with Lopinovir / ritonavir at dose 400mg/100mg twice daily for 2-14 days and followed up to two weeks after treatment. These researchers revealed that
favipiravir has higher rates improvement in chest imaging and independently associated with faster viral clearance. Furthermore adverse effects from favipiravir were rare and tolerable. However, patients with CDVID-19 are being approved in randomized trials for assessment the efficacy of favipiravir plus interferon-α and favipiravir plus baloxavir marboxil (19).

A different randomized clinical trial was conducted; a total of 240 patients from February 20, 2020 to March 12, 2020. Patients treated with favipiravir at doses of 1600-2400 mg in comparisons with patients received other antiviral therapies as oseltamivir, hydroxyl-chloroquine and kaletra. The finding showed that the patients treated with favipiravir revealed more recovery rate and more efficiently regarding decreasing the symptoms of cough and fever as main symptoms of COVID-19 in mild and moderate state patients through this initial stage of illness in which SARS-CoV-2 multiplies and binds to ACE2 receptor on host cells (41). Some studies collected data on the effectiveness and safety of favipiravir in diminution the viral load and lower mortality rate among patients compared to control group. These findings were confirming by FPV trials in Guinea (42, 43).

Chang and his colligates 2020 (44) performed a randomised clinical trial of favipiravir; one hundred and sixteen patients, using two doses 1600mg and 600mg twice daily on first day and twice daily for (7-10 days) respectively vs umifenovir (one hundred and twenty patients) for patients infected with Covid-19 in Wuhan city. They reported that in patients suffered from moderate COVID-19 untreated with antiviral, favipiravir revealed a high efficacy in the clinical recovery rate at day seven and more effectively relief fever and cough. At day 7 the clinical recovery rate was 71.4% in the favipiravir treated patients while in the group treated with umifenovir it was 55.8%. The age of patients were 18 years or older. Favipiravir has been studied for its potential effects in the treatment of patients with COVID-19 because of lack of therapeutic options and clinical severity of this disease.

However, data collected from a study of Dany and his colleagues 2020 (45) concluded that using favipiravir give a promising results as a therapy for COVID-19. But new researches need mainly randomized clinical trials, to improve the potential use of favipiravir to treat patients with coronaviruses. Findings has been also obtained by Kun and Mahmoud. 2020 (46) for structural analysis of favipiravir efficacy against COVID-19 confirmed that favipiravir could be revealed activity against COVID-19 but with low binding strength, thus further investigations to examine several sides of pharmacotherapy application of favipiravir are still required. Currently further evaluate the safety and effectiveness of favipiravir for the treatment of patients with COVID-19 were sustained in Thailand and China as monotherapy or combination drug.
3- Treatment of COVID-19 using disulfiram, ritonavir and lopinavir.

Disulfiram a protease inhibitors has been reported to treat alcohol dependence. This drug investigated to be active against MERS and SARS by suppressing the papain-like protease of these diseases in cell cultures. Zumla and his work team 2016 (19) reported that the clinical trials have been initiated to evaluate HIV protease inhibitors like lopinavir and ritonavir in patients with SARS-CoV-2. Lopinavir and ritonavir were initially supposed to inhibit the 3-chymotrypsin-like protease of SARS and MERS, and manifest to be linked with enhance clinical research results of patients infected with SARS. Meanwhile it is controversial if lopinavir and ritonavir efficiently suppress the 3-chymotrypsin-like and papain-like proteases of SARS-CoV-2 (15).

Que and his colleagues 2003 (47) observed that combination of lopinavir/ ritonavir with antivirals or alone result in good advantages as therapies of MERS and SARS involved minimise occurrence of acute respiratory disease syndrome (ARDS) or even reducing mortality rate. Currently systematic assessment approved that lopinavir/ ritonavir’s are effective as anti-coronavirus and it was particularly manifested in its early application, for decreasing mortality rate and decreased consumption of glucocorticoid. Meanwhile if the disease didn’t treat earlier, there can be no essential effect of lopinavir/ ritonavir (48).

Despite the convenient response detected when lopinavir- ritonavir used in SARS treatment (49), recent trials against SARS-CoV-2 seems to be not effective (50). Thus studies stills demand to further search the scientific effects and necessity of its early use in COVID-19 aggravate pneumonia. In fact efficacy of the combination use of these drugs as antivirals remains debatable (51, 52). However, most in vitro studies indicated the potential
valuable effects, despite the fact that the data are too preliminary to be used as reasoning for clinical use (53).

4-Treatment of COVID-19 with antimalarial drugs

Food and Disease Administration (FDA) confirmed chloroquine (CQ) therapy which has been used for the prevention and treatment of malaria infection as the most candidates and promising drug to treat COVID-19. In fact CQ has received a great attention for its prospect affectivity against COVID-19 as antiviral drugs (25).

Chloroquine was synthesized as substitute for natural quinine in 1934 for its efficacy against malaria. CQ is a 9-aminoquinoline (54, 55). This drug mostly used to treat a wide range of bacterial, fungal (56, 57) and autoimmune diseases. CQ also has antiviral activity against RNA viruses such as Ebola virus, poliovirus, HIV, influenza viruses and hepatitis viruses (60, 61). In addition to its widely used to treat some human diseases like amoebiasis (58, 59).

The use of CQ as an antiviral drug is not uncommon (62). Vincent and his work team 2005 (63) in their work, tested this drug in vitro against SARS virus and supposed that CQ revealed a sturdy antiviral activity regarding SARS virus, partly because of its effect in arising the endosomal pH and its capability to glycosylated the viral entry receptor, ACE2 (59). While Porotto et al., 2009 (64) reported that CQ has ability to suppressed in vitro Nipah and Hendra virus infections.

Because of its weak base characteristic, CQ could stacks in low-pH organelles, like Golgi vesicles, endosomes and lysosomes and interferes with their acidification impeding viral replication and the low-pH-dependent steps of protein degradation, involving fusion and uncoating (57). However, CQ can change the glycosylation of the cellular receptors of viruses, which in turn may affect viral binding (65).

The mechanism of action of CQ is its ability to block virus infection through rising the endosomal pH essential for the virus fusion with the cell, and interfering with cellular receptors glycosylation of SARS-CoV (63). CQ has an immune- modulating activity, which may synergistically promote its antiviral effect in vivo. After oral administration CQ is widely distributed in the whole body, involving the human lungs (66).

CQ may be more effective as a prophylactic treatment due to its activity during the early stages of a viral cycle, by establishes residence in the patient via replication of SARS-CoV-2 throughout the incubation period which diagnostic to be mild condition of the disease (6). Furthermore chloroquine has been used for more than 70 years due its safety and cheap. Therefore, it is potentially clinically usable against the SARS-CoV-2 (66).

Many clinical trials confirmed that the most potential antiviral activities with low cytotoxicity are CQ and remdesivir. The effective concentration (EC50) for CQ was 0.77μM
while remdesivir were 1.13\(\mu\)M. CQ functions at viral entry and post-entry stages of the SARS-CoV-2 infection \textit{in vitro} E6 cells whilst remdesivir functions at post-entry stage only \cite{58,59}. Wang and his colleagues 2020 \cite{20} recently confirmed that CQ and remdesivir has powerful efficiency in prohibition the replication of a clinical isolated of SARS-CoV-2.

Qin \textit{et al.}, 2020 \cite{67} in their work reported in a clinical trial from 100 patients that chloroquine phosphate was excellent for suppressing the aggravation of pneumonia, boost a virus negative conversion, enhancement the lung imaging findings, and shorter the course of the disease, since these symptoms occurs throughout the severe stage of COVID-19.

Moreover Gao and his work team 2020 \cite{25} reported that the findings of CQ treated patients (no. 100) revealed a reduction in fever, boost computerized tomography scan of lung, and limiting the convalescent time. A clinical trial from France also used CQ in some of infected patients with COVID-19 claimed to have positive clinical outcomes \cite{68}. Manli and his team work 2020 \cite{66} and Wang \textit{et al.}, 2020 \cite{20} also observed that remdesivir and CQ are highly effective in the control of SARS-CoV-2 infection \textit{in vitro}, promising the potentially effective use of these two drugs as combination for treatment and management of COVID 19 in future. Thus an antimalarial drug, CQ believed to be one of the drug candidates that show to have good supporting effects on SARS-CoV-2 at the cellular level \cite{68}.

However, despite a systematic review of the effect of CQ on COVID-19 infection has been investigated \cite{69}, these treatments have resulted in controversy since it is not based on data from a direct conventional clinical trials albeit, a list of registered clinical trials have been reported by Zhang and his colleagues 2020 \cite{70} suggesting that this drug should be tested through appropriately conducted clinical trials in patients with the COVID-19 \cite{66}. However, the toxicity of CQ is well acknowledged, but it is often ignored \cite{71}.

In fact the interest in the use of antimalarial drugs came from the beneficial effect of hydroxychloroquine in the treatment of HIV patients \cite{72}. Hydroxychloroquine is a relatively safe drug being used by a majority of patients with early rheumatoid arthritis \cite{71}. Thus many researchers cited that focus of the studies should be on hydroxychloroquine instead of more toxic chloroquine. More recently Gautret \textit{et al.}, 2020 \cite{73} cited that “the decline in the viral load in patients with COVID-19 treated with hydroxychloroquine combined with azithromycin was reinforced in all cases in their study, especially in cases accompanying upper or lower respiratory tract infections in comparison with asymptomatic patients”. In fact azithromycin has been given to suppress bacterial infection. Azithromycin has been improved to have anti-viral effects \cite{74}. Furthermore the mechanism for this synergistic effect of this combination in declining the viral load has not been detected yet.

5 - Treatment of COVID-19 with convalescent plasma (CP) therapy

For more than one century, many drugs have been used to the inhibition and treatment of many infectious diseases, one such medicament is a traditional immunotherapy as convalescent plasma (CP). However, CP therapy was applied to treat MERS- 2009, H1N1 and SARS pandemic with safety and efficiency \cite{44,75 and 76}. It is also used in the
inhibition and treatment of Spanish flu and Ebola virus disease (77). Since SARS, MERS, and SARS-CoV-2 share the same virological and clinical characteristics (78). CP therapy considered as a promising treatment for COVID-19 (12). However, CP can be obtained from the sera of recovered COVID-19 patients or could obtain using engineered technology (77, 12). Marano et al., 2016 (79) also reported that the CP patients recovered completely from COVID-19 developed a humoral immunity against the virus comprise a considerable quantity of neutralizing antibodies that able to neutralizing SARS-CoV-2 and eliminating the virus from pulmonary tissues and blood circulation.

However, S protein has two subunits, the S1 subunit with a receptor binding domain that linked with the host cell receptor (ACE2), and the S2 subunit which has essential role in organizing the fusion between host cell membranes and the invaded virus. The S protein plays significant role in the stimulation of neutralizing antibodies (Nab) result in T cell responses (80). So the principle is using antibodies in order to neutralize the invading virus from entering the host cells. Thus it could be administered safely to patients in need (77, 12 and 81). This produce an instantaneous immunity to high risk patients or susceptible patients and it is effectiveness when used immediately at the early stage of the disease or as prophylactic drug (6).

Kai and his team work 2020 (82) in their study work given 200-mL CP transfusion as one dose. These researchers investigated that this drug was well tolerated, and finding shows that the clinical symptoms was significantly enhanced with the rising of oxyhemoglobin saturation within three days, associated with rapid neutralization of viremia. Furthermore all investigated patients including in this study revealed serum SARS-CoV-2 RNA negativity after treated with CP transfusion with elevation of lymphocyte counts and oxygen saturation, in addition to enhances of liver function as well as CRP. These findings indicated that the immune system response was increased by CP therapy that consists of antibodies. Thus used CP therapy is safe, and considered as promising drug for patients with severe COVID-19.

Patients recovered from COVID-19, with neutralizing antibody titter above 1:640 considered as suitable donors. However, clinical trials show that the neutralizing antibody titters of patients raised to 1:640 within two days (76). Eickmann et al., 2018 (83) applied methylene blue photochemistry to maintain the activity of neutralizing antibodies in addition to inactivate the potential residual virus.

Another strategy to achieve passive immunity is by administering engineered Nabs (81). Very recently the scientists developed an engineered human monoclonal antibody (mAb) with the prospect to prevent SARS-CoV-2 from infected the host cells. The monoclonal antibody binds to the virus spike receptor. In fact the mAb did not compete with the host receptor (ACE2) binding and is suggesting neutralizing the virus through a receptor independent mode (84). This strategy confirms on engineering antibodies specific to the virus of COVID-19 to avoid infection, to be applied in diagnostic systems or decline viral load.
6-Treatment of COVID-19 with corticosteroids

Systemic corticosteroid was given to control the inflammatory response resulted from SARS-CoV-2 (9). While Russell et al., 2020 (85) cited that “the clinical use of corticosteroids for COVID-19 treatment was not recommended, unless prescribes for another reason”.

Methylprednisolone is a corticosteroid medication used to decrease inflammation (86). It is administered as convenient for patients with severe infection. Consistently achieving good results with the severity of the disease could be done by giving methylprednisolone at doses range from 40 to 80 mg per day, but dose should not be more than 2 mg/kg each day (87). Appropriate using of glucocorticoids can deeply enhances the symptoms of patients suffering from SARS and accelerates the lung lesions absorption but it didn’t diminish the duration of hospital stay (88).

Previous studies done by Cron et al., 2019, Riegler et al., 2019, Gerlach 2016 and Liu et al., 2016 (89, 90, 91, 92) improved that the corticosteroids, intravenous immunoglobulin (IVIg), monoclonal antibody depend on prevented of interleukin 1 (IL-1) receptor antagonist protein (Anakinra), interleukin 6 (IL-6) (tocilizumab), as well as JAK inhibition are the some strategies that confirmed the efficacy of dampening excessive immune activation in a different diseases. Hence, these will continue to be used in the conventional therapy in the management of cytokine release syndrome and other symptoms of patients with COVID-19.

Additionally, in later stages of COVID-19, excessive response, and dysregulated immune response was also confirmed like functionally exhausted cytotoxic T lymphocytes and natural killer cells because of a rise expression of an inhibitory receptor (NKG2A) that give rise to decreased anti-viral response (93). Meanwhile André et al., 2018; Creelan and Antonia 2019 (94, 95) cited that “utilizing monoclonal antibodies could blocked these receptors to obtained curative advantages, thus scientists could harness the immune response to manage infection by depending on such selective modulation of activator and inhibitory receptors on anti-viral responsive lymphocytes at various stages”. However, the use of corticosteroids for severe acute respiratory disease syndrome (ARDS) is contentious. Therefore, it is sensible that systemic usage of glucocorticoids to be cautious (96).

7-Treatment of COVID-19 with intravenous immunoglobulin (IVIg) and low molecular weight heparin (LMWH) anticoagulant therapy

Liu et al., 2016 (92) recommend that when T and B lymphocytes in circulated peripheral blood are reduced remarkably, inflammatory cytokines like IL-6 are extremely elevated, coagulation parameters like D-Dimer unusually rise and chest computerized tomography (CT) showed lung lesions expansion, IVIg should be administrated as early as possible. Hence patient with severe COVID-19 infection receiving high doses IVIg (0.3- 0.5 g / kg
weight) per day for 5 days, this could halt the storm of inflammatory factors at early stage of the disease and improving immune function. More clinical data of COVID-19 patients required to improve the findings of this randomized clinical trial.

Ling et al., 2020 (97) reported that in the early stage of COVID-19, the low molecular weight (LMWH) heparin anticoagulant drug is especially recommended. However, a common reason of disseminated intravascular coagulation is infection. These researchers confirmed depending on clinical trials that patients with COVID-19 suffer from severe type may develop disseminated intravascular coagulation (DIC) in addition to ischemic changes in the fingers and toes (Figure 3). However, for COVID-19 patients when the D-Dimer value is four times higher than the normal upper limit, anticoagulation drug is recommended with exception for patients with anticoagulant contraindications. For LMWH, the dose recommended is 100U/ kg weight per twelve hour subcutaneously for at least 3- 5 days. Doctors with responsibility for patients should closely observe the measurements of laboratory examination of patients to notice the side effects after anticoagulant therapy administration.

Fig. 3: COVID-19 patient with severe type showed the ischemic changes in the toes (Ling et al., 2020) (97).

8-Treatment of COVID-19 with auranofin

Food and Drug Administration (FDA) reported that since 1985 a gold-containing triethyl phosphine, auranofin is confirmed as therapy for rheumatoid arthritis (98). Auranofin has been approved for its prospect therapeutic application in many diseases such as HIV/AIDS, neurodegenerative disorders, bacterial and parasitic infections (99). May and her colleagues 2018 (100) cited that “auranofin recently is uses for phase II cancer therapy in clinical trials. Auranofin mechanism includes the suppression of redox enzymes like thioredoxin reductase, endoplasmic reticulum (ER) stress induction and unfolded protein response (UPR) activation”. Furthermore, auranofin could decrease cytokines production since it has an anti-inflammatory effects and it could activates cell-mediated immunity (101).
It has been investigated that endoplasmic reticulum stress induction and activation of the UPR considerably participate in viral replication and pathogenesis of COVID-19 (102). SARS-COV infection increasing expression of the ER protein folding chaperons (GRP78 and GRP94) in addition to other ER stress related genes to preserve protein folding (103). SARS-COV spike protein expressing as well as other viral proteins which revealed increased activation of UPR (104). SARS-CoV-2, the virus that causes COVID-19, has similar characteristics and closely related to SARS-CoV (96). Hence suppression of redox enzymes like thioredoxin reductase and motivate of ER stress by auranofin could extremely affect the synthesis of SARS-CoV-2 protein (105).

Moreover severe cases of COVID-19 infection that causes a lung destructive resulted from cytokines storm which accompanied with many organs dysfunctions, is a major cause of high mortality rate (106, 107). Food and Drug Administration (FDA) reported that auranofin mechanism of action is via suppressing SARS-CoV-2 replication in host cells at low micro molar concentration, resulted in a 95% decreasing in viral RNA at forty eight hours after the onset of infection. Auranofin also has a potential reduction in the expression of SARS-CoV-2 cytokines storm induction in human cells. Suggesting that auranofin is beneficial therapy to control the SARS-CoV-2 infection and related lung damage due to it's anti-viral, anti-inflammatory and anti-reactive oxygen species (ROS), thus considered safe for human use (108).
Table 1: Shows the potential pharmacological therapeutics in COVID-19 (Jiansheng et al., 2020) (109).

<table>
<thead>
<tr>
<th>Therapeutic Targets</th>
<th>Functions</th>
<th>Potential Drug candidates</th>
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<tbody>
<tr>
<td>RNA-dependent RNA polymerase, RdRp</td>
<td>An RNA-dependent RNA polymerase for replicating coronavirus genome</td>
<td>Remdesivir, Ribavirin and Favipiravir can inhibit viral RdRp</td>
</tr>
<tr>
<td>Papain-like protease, PLpro</td>
<td>A protease for the conversion of viral polyprotein into functional enzyme</td>
<td>Lopinavir, protease inhibitors that may inhibit the viral protease 3CLpro or PIpro. Darunavir inhibits the proteolysis activity of 3-chymotrypsin-like protease</td>
</tr>
<tr>
<td>Main protease 3CL protease, 3CLpro</td>
<td>A protease for the conversion of viral polyprotein into functional protein</td>
<td>Lopinavir, protease inhibitors that may inhibit the viral protease 3CLpro or PIpro.</td>
</tr>
<tr>
<td>S protein and TMPRSS2</td>
<td>A viral surface protein for binding to host cell receptor ACE2, TMPRSS2, a host cell, produced protease that primes S protein to facilitate its binding to ACE2</td>
<td>Arbidol can prevent S protein-ACE2 interaction and inhibit membrane fusion of the viral envelope by preventing the binding of viral envelope protein to host cells and preventing viral entry to the target cell. Camostat mesylate inhibits TMPRSS2 and viral cell entry.</td>
</tr>
<tr>
<td>ACE2</td>
<td>A viral receptor protein on the host cells which binds to viral S protein</td>
<td>Chloroquine and hydroxychloroquine can inhibit viral entry and endocytosis by increasing endosomal pH, interfere with ACE2 glycosylation as well as host immunomodulatory effects.</td>
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In this stage of lack of effective drugs, the only way to slow the prevalence of the SARS-CoV-2 is the traffic control bundle and application of infection control interventions to effectively control human to human contact and transmission and prevent spreading of this disease. The infection control interventions involved early recognition of cases and their
contacts, convenient hand washing, avoiding and stay away from people with respiratory symptoms, and boost infection prevention, in addition to control practices in the healthcare setting (110).

**Conclusion:**

The present review emphasizes that there is no effective therapy against corona virus. Therefore, identifying specific antiviral agents to combat the disease is urgently needed.

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