Review

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Drugs intervention study in COVID-19 management

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Abstract: By 9 February 2021, the Coronavirus has killed 2,336,650 people worldwide and it has been predicted that this number continues to increase in year 2021. The study aimed to identify therapeutic approaches and drugs that can potentially be used as interventions in Coronavirus 2019 (COVID-19) management. A systematic scoping review was conducted. Articles reporting clinical evidence of therapeutic management of COVID-19 were selected from three different research databases (Google Scholar, PubMed, and Science Direct). From the database search, 31 articles were selected based on the study inclusion and exclusion criteria. This review paper showed that remdesivir and ivermectin significantly reduced viral ribonucleic acid (RNA) activity. On the other hand, convalescent plasma (CP) significantly improved COVID-19 clinical symptoms. Additionally, the use of corticosteroid increased survival rates in COVID-19 patients with acute respiratory distress syndrome (ARDS). Findings also indicated that both hydroxychloroquine and favipiravir were effective against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, lopinavir-ritonavir combination was not effective against COVID-19. Finally, ribavirin, galidesivir, and sofosbuvir showed potential therapeutic benefit in treating COVID-19, but there is a lack of clinical evidence on their effectiveness against SARS-CoV-2. Remdesivir, ivermectin, favipiravir, hydroxychloroquine, dexamethasone, methylprednisolone, and CP are the therapeutic agents that can potentially be used in COVID-19 management.

Keywords: antiviral; clinical trial; COVID-19; drug intervention; SARS-CoV-2.

Introduction

In early December 2019, the world was shocked by Coronavirus Disease 2019 (COVID-19) outbreak which originated in Wuhan city, China [1]. The disease has caused a global pandemic as it spreads across countries [2]. At first, it was not known which strain of coronaviruses (CoVs) has caused the COVID-19 pandemic. It was later discovered by health workers that the COVID-19 was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 originated from CoVs that belong to the family Coronaviridae, which is a sub-family of Coronavirinae [3]. CoVs are characterised as enveloped viruses with a single-strand and positive-sense ribonucleic acid (RNA) genome. The size of the CoVs is approximately 26–32 kilobases. All CoVs share similarities in term of its organisation and genome expression. The organisation of CoVs has been associated with the presence of 16 non-structural proteins and four structural proteins such as spike (S), envelope (E), membrane (M), and nucleocapsid (N) [4].

In 2017, six different types of CoVs have been shown to cause infection in humans. Two of these are alpha CoVs: HCoV-229E and HCoV-NL63. The remaining four types are beta CoVs: HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1. SARS-CoV-2 that was discovered in late 2019, is a member of the order Nidovirales. Specifically, it belongs to family Coronaviridae and sub-family Orthocoronavirinae, which is divided into four genera: (i) alphacoronavirus; (ii) betacoronavirus; (iii) gammacoronavirus; and (iv) deltacoronavirus [5]. The alphacoronavirus and betacoronavirus originated from bats, while the gammacoronavirus and deltacoronavirus originated from birds and swine gene pools [6].

The appearance of novel CoVs is possible due to the ability of CoVs to sustain in their natural host, which cause them to favour the probability of genetic recombination. For this reason, CoVs resulted in the occurrence of high frequency and reactive mutations. This would eventually increase the risk of infection in multiple host species. This condition may be due to alteration of RNA-dependent RNA polymerase (RdRp) and higher rates of homologous RNA

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recombination that resulted from high genetic diversity [7]. In addition, the SARS-CoV-2 genome sequences obtained from the patients showed more than 70% similarity with SARS-CoV [8]. Thus, it is important to identify the SARS-CoV identical origin and the evolution of pathogen in the development of new therapeutic drugs, improvement of disease surveillance, and epidemics prevention.

Furthermore, signs and symptoms of SARS-CoV-2 may appear between two and 14 days after viral infection. The most common symptoms are fever, dry cough, tiredness, dyspnoea, expectoration, and headache [9]. Other minor signs and symptoms are loss of taste or smell, diarrhoea, haemoptysis, and shortness of breath [10]. In addition to these, COVID-19 causes lungs disorder that is diagnosed clinically using computed-tomography (CT) scan. In the CT scan image, the disorder is characterised by the appearance of multiple, dense ground-glass opaque lesions, with irregular consolidated shadows in lung lobes [11]. At present, there are no standard treatments or vaccines that can be used to prevent and cure the infection. However, there have been several ongoing randomised clinical trials on potential drugs to treat COVID-19 effectively.

Therefore, this systematic scoping review aimed to (i) examine features of the SARS-CoV-2, (ii) determine the pathogenesis of COVID-19, and (iii) identify potential therapeutic approaches and drugs intervention in COVID-19 management.

Methods

The review was conducted to answer a research question on what is current drug in clinical trial that can be used in COVID-19 treatment? The data was obtained from three databases; Scopus, Pubmed and Sciencedirect from year 2019 until 2020. The keywords used were “COVID-19 treatment” or “COVID-19 management” or “COVID-19 drugs” or “hydroxychloroquine” or “antiviral agents” or “remdesivir” or “lopinavir” or “ritonavir” or “ribavirin” or “galidesivir” or “Sofosbuvir” or “favipiravir” or “ivermectin” or “corticosteroids” or “dexamethasone” or “methylprednisolone” or “convalescent plasma”. The inclusion and exclusion criteria are presented in Table 1.

Pathogenesis of COVID-19

The receptor of SARS-CoV-2 has been recognised as the human angiotensin-converting enzyme 2 (hACE2) [12]. The distribution of angiotensin-converting enzyme 2 (ACE2) is mainly located in the lungs, kidneys, heart, liver, intestine, testes, and brain [13]. In the normal human lung, ACE2 is expressed as type I and II alveolar epithelial cells. Between these two types of cells, the type II alveolar cells have most ACE2 expression, which increases the cells potential to serve as primary sites for viral invasion [14]. ACE2 is also

Table 1: Study exclusion and inclusion criteria.

No.	Category	Exclusion criteria	Inclusion criteria
1.	Language of publication	Language other than English	English
2.	Year of publication	Before 2019	2019–2020
3.	Publication type	Abstracts, reports, commentaries, editorial, book chapters, review, protocol study & pilot study.	Full text randomized clinical trials (RCTs) and observational studies (prospective and retrospective study) discussing drugs intervention in COVID-19 management.
4.	Outcome measure	RCTs and observational studies with only laboratory and experimental outcomes on animals or cell cultures.	Full text RCTs and Observational studies measuring rationale drugs used and patients' outcomes clinically. The outcomes can be positive or negative.
5.	Methodology	<ul style="list-style-type: none"> – Studies that investigated effect of anti-viral drugs only on MERS. – Studies that investigated effect of anti-viral drugs only on SARS. – Studies that investigated only on adverse effects of drugs used in COVID-19 instead of its effect in killing SARS-CoV-2. – Studies that demonstrated the uses of potential drugs in COVID-19 treatment on patients with morbidity other than coronavirus infection. 	<ul style="list-style-type: none"> – Studies included, must reported the potential therapies against COVID-19. – Studies included, must demonstrate the use of drugs such as anti-viral, anti-malarial, convalescent plasma as well as corticosteroids on patients with SARS-CoV-2 infection.

known as a potent negative regulator in the renin-angiotensin system, which is crucial in conserving and maintaining homeostasis of the human body [13]. The primary role of ACE2 is to degrade angiotensin (Ang) II into Ang (1–7). Initially, the binding of Ang II to Ang II Type 1 receptor stimulates the production of pro-inflammatory agents, induce vasoconstriction, and causes fibrosis. In contrast, binding of Ang (1–7) to mitochondrial assembly receptor causes vasodilation, promote the release of anti-inflammatory agents, and anti-fibrotic substances [14]. Additionally, ACE2 plays an essential role in controlling amino acid absorption in the kidney and modulating the expression of amino acid transporters [13].

Apart from that, SARS-CoV-2 and the original SARS-CoV are almost similar in structure. Specifically, the spike proteins of SARS-CoV-2 and SARS-CoV are approximately 75% similar in amino acid sequences. Thus, it can be said that the spike proteins in both SARS-CoV-2 and SARS-CoV have a high degree of homology [15]. Based on a previous study on biochemical interaction and crystal structure analysis, SARS-CoV spike protein has a strong binding affinity to human ACE2 [16]. The S protein binds to the ACE2 receptor that is located on the surface of the host cell and allows the insertion of RNA into the host cell cytoplasm. This interaction also requires S protein priming that occurs when SARS-CoV-2 binds to the cellular transmembrane protease serine 2 (TMPRSS2) before entering the host cell [17]. As a result, the binding of SARS-CoV-2 to ACE2 receptor causes the virus to enter the host cell mainly through endocytosis and initiates a dysregulated immune response, resulting in an acute lung injury [12]. A result from a clinical test revealed a significant reduction of regulatory T cells and an increment of pro-inflammatory cytokines production [18]. The pro-inflammatory cytokines included tumour necrosis factor- α (TNF- α), interleukin-1 (IL-1), interleukin-6 (IL-6), D-Dimer, erythrocyte sedimentation rate (ESR), and C-reactive peptide (CRP) [18]. Thus, if the condition is left untreated, these hyper pro-inflammatory responses may lead to the development of severe respiratory diseases such as pneumonia, leading to sepsis and multi-organ dysfunctions [19].

Potential therapeutic approaches to encounter ACE2 mediated COVID-19

There are several potential therapeutic approaches to treat COVID-19. As mentioned above, binding of SARS-CoV-2 to ACE2 receptor induce viral invasion and consequently leads to viral replication. The S protein of SARS-CoV-2 has been

considered as the primary target for designing CoV potential therapies in overcoming ACE2 mediated COVID-19 [20]. The first potential approach was to use spike protein-based vaccine. The vaccine works by stimulating neutralising antibodies responsible for immune system protection. The activation ACE2 receptor before S protein binding promotes viral replication and duplication. Thus, the S protein vaccine may be used to eradicate the virus [3].

The second potential therapeutic approach was by using type II transmembrane serine protease (TMPRSS2) inhibitors. Examples of TMPRSS2 inhibitors are bromhexine, aprotinin, camostat, nafamostat. A study has shown that SARS-CoV-2 utilises SARS-CoV-receptor, ACE2, cellular protease, and TMPRSS2 to enter the targeted host cells, which consequently leads to host cell division [21]. Thus, TMPRSS2 inhibitor is crucial in suppressing SARS-CoV-2 activity by restricting viral entry [21].

The third potential therapeutic approach was by using ACE2 inhibitor that may work against SARS-CoV-2 by suppressing stimulation of the ACE2 receptor. A study has confirmed on the interaction sites between ACE2 and SARS-CoV based on the mutual interaction of SARS-CoV-2 towards ACE2 receptor at the atomic level [3]. The binding of SARS-CoV-2 spike protein towards the ACE2 receptor would allow viral entry and replication. This binding eventually leads to suppression of tissue protection mechanism and increases the risk of developing a severe lung injury. Therefore, research should focus on these interaction sites as they may be used to block any potential interaction with antibodies or small molecules.

Discussion

The clinical evidence of reviewed drugs that used in COVID-19 treatment is summarized in Table 2. The selection of the following drugs was up to date of the manuscript completed, based on the chosen criteria that they must show potential therapies against viral and had been tested to COVID-19. It was found that the drugs such as anti-viral, anti-malarial, convalescent plasma as well as corticosteroids had been tested on patients with SARS-CoV-2 infection. The clinical trial of those drug was conducted mainly during the high peak case of the COVID-19. They may not relevant after a series of studies regarding their efficacy and toxicity.

Chloroquine and hydroxychloroquine

Chloroquine, or also known as N4-(7-Chloro-4-quinolinyl)-N1, N1-diethyl-1, 4-pentanediamine, has been used in the

Table 2: Clinical evidence of drugs used in COVID-19 treatment.

Drugs	Classification of drug	Potential efficacy	Preclinical or clinical evidence	Status of clinical trial
Hydroxychloroquine (HCQ)	Anti-malarial, anti-SARS-CoV [22]	– Immunomodulatory effect and anti-inflammatory in patients with viral infections [23].	– RTCT on 62 patients with HCQ treatment vs. control group. There is an increment in resorption of pneumonia in HCQ arm (80.6 vs. 54.8%) [24]. – An <i>in vitro</i> test was reported that HCQ able to against SARS-CoV-2 in infected VERO E6 cells [22].	Clinical trial ID: NCT04328961, NCT04303507, NCT04318444, NCT04318015, NCT04330144
Remdesivir	Nucleotide analogue inhibitor of RNA-dependent RNA polymerase (RdRps) [25]	– Antiviral effect against SARS-CoV-2 via RdRp [26]. – Anti SARS-CoV-2 activity in during cell cultures [27]. – Animal studies were reported that there is a reduction of viral load present in lung tissue of infected mice, improvement of lung function, as well as diminish pathological destruction to lung tissue after administering remdesivir [28]. – It can effectively suppress viral activity in mice which has been infected with MERS-CoV better than the group who got treatment for infection with Lopinavir/Ritonavir combined with interferon- β as well as compared with the control group [27].	– An <i>in vitro</i> test was reported potent antiviral effect caused by Remdesivir with low concentration of the drug [27].	Clinical trial – Phase 2 Randomized, placebo-controlled trial with ID: NCT04280705 Clinical trial– Phase 3 Randomized, open-label trial with ID: NCT04293899
Favipiravir	Nucleotide analogue inhibitor of RdRps [29]	National Medical Products Administration of China has approved favipiravir as the earliest drug that can provide beneficial therapy in COVID-19 treatment [29]. It was approved as therapeutic agent that can be used in influenza treatment in earlier year of 2020 in China [30].	An <i>in vitro</i> test which using Vero E6 cells was reported potential reduction of SARS-CoV-2 performance in the infected cells at high concentration of the drug [30].	Clinical trial ID: NCT04336904
Galidesivir	Nucleotide analogue inhibitor of RdRps [29]	Galidesivir was emphasized as one of the good suited inhibitors that has been screened through <i>in silico</i> analysis. Due to potential inhibition effect, this drug can be used for preclinical trials of COVID-19 [29]. – Galidesivir and its drug-like compounds CID123624208 and CID11687749 have shown an effective binding interaction to the priming site of viral RdRp, which consequently may lead to failure of viral replication [29].	No clinical data available	–

Table 2: (continued)

Drugs	Classification of drug	Potential efficacy	Preclinical or clinical evidence	Status of clinical trial
Ribavirin	Synthetic guanosine nucleoside inhibitor of RdRps. It acts as a broad-spectrum anti-viral agent [31]	<ul style="list-style-type: none"> – Its attachment to SARS-CoV-2 RdRp which consequently may lead to viral eradication [26]. – Ribavirin was delivered among 138 patients who infected with SARS-CoV. As a result, the treatment was associated with declination of antiviral activity [32]. – There is a retrospective cohort study involves 44 MERS patient. As a result, combination treatment between interferon-alfa2a and ribavirin was associated with improvement survival events at 14 days [33]. 	No clinical data available	–
Lopinavir–ritonavir	Antiretroviral protease inhibitor, with ritonavir as a booster [34]	<ul style="list-style-type: none"> – Treatment of lopinavir–ritonavir combined with ribavirin associated with positive outcomes in term of clinical status among 44 patients who have been infected with SARS-CoV as compared to control ribavirin-treated patients [35]. 	<ul style="list-style-type: none"> – A randomized, controlled, open-label trial involving about 199 COVID-19 adult patients who have been hospitalized and progress to respiratory disorder. As a result, no benefit on combination between lopinavir and ritonavir treatment was observed once administering to the patients [36]. 	Clinical trials ID: NCT04307693, NCT04255017
Dexamethasone	Synthetic corticosteroids [37]	<ul style="list-style-type: none"> – A study was reported that dexamethasone reduces risk of death cases among the most severely ill patients who have needed mechanical ventilation as well as critically ill patients who have needed oxygen support. Thus, some researchers at the University of Oxford successfully identified the first drug proven as lifesaving drugs in COVID-19 treatment [37]. 	<ul style="list-style-type: none"> – An observational study demonstrated that dexamethasone was marked with beneficial outcomes among COVID-19 patients who develop with the onset of hypoxemia after more than seven days administering the drug [38]. – Another observational study shows corticosteroid therapy lengthen survival days in COVID-19 patients who suffering with acute respiratory distress syndrome (ARDS). In this case, lower dose of dexamethasone has been used in the treatment that possess high risk of ARDS development among patients who suffered with moderate to severe pneumonia [38]. – Next, a study was reported that the use of dexamethasone as therapeutic agents among 277 patients with ARDS have produce a result of accelerated liberation from ventilation and consequently lead to increment of survival cases [39]. 	–

Table 2: (continued)

Drugs	Classification of drug	Potential efficacy	Preclinical or clinical evidence	Status of clinical trial
Sofosbuvir	Anti-hepatitis C virus (HCV) [40]	<ul style="list-style-type: none"> – Sofosbuvir is clinically approved drug against HCV with diverse genotypes since it promotes antiviral effects [40]. – It was demonstrated that sofosbuvir possesses significant potency in binding to the SARS-CoV-2 RdRp, and consequently inhibit the viral replication [26]. 	No clinical data available	–
Ivermectin	Broad spectrum anti-parasitic agent [41]	<ul style="list-style-type: none"> – It exerts a broad antiviral outcome in both RNA as well as DNA viruses [41]. – It has been hypothesized that combination treatment between hydroxychloroquine and ivermectin may share similar inhibitory effect on SARS-CoV-2 activity. The effects resulting from blockage of the entry of SARS-CoV-2 into the host cells which has been conducted by hydroxychloroquine whereas ivermectin promote viral eradication [41]. 	<ul style="list-style-type: none"> – An <i>in vivo</i> study was reported that some infected cells by SARS-CoV-2 have undergone treatment with ivermectin few hours after infection. Then, some cell pellets were collected in order to evaluate real-time reverse transcription polymerase chain reaction (RT-PCR) [42]. As a result, more than 5,000 reduction in viral RNA was observed in both supernatant and cell pellets from samples treated with ivermectin. – Apart from that, there are no harmful effects as well toxicity events were observed throughout duration of ivermectin used in treatment. Thus, the results demonstrate that ivermectin has antiviral action against the SARS-CoV-2 and hypothesize the effect is through mechanism of blocking importin-α/β1 family proteins (IMPα/β1) which induced nuclear importation of viral proteins [42]. 	–
Convalescent plasma (CP)	Passive antibody therapy [43]	<ul style="list-style-type: none"> – Some studies show CP therapy was successfully reported the uses of CP in the treatment of SARS, MERS and 2009 influenza A virus (H1N1) pandemic resulting a satisfactory performance [43]. – As the virology and clinical characteristics of CP shared similarity among SARS and MERS, thus CP therapy might become a potential therapy for COVID-19 pandemic [44]. 	<ul style="list-style-type: none"> – COVID-19 patient who already got antiviral treatment mainly lopinavir/ritonavir combined with interferon can receive CP. The clinical use of CP may cause good performance on clinical status such as reduction of high body temperature, improvements in Sequential Organ Failure Assessment scores as well as PAO2/FIO2 ratio among patients approximately after one week administering [45]. 	–

Table 2: (continued)

Drugs	Classification of drug	Potential efficacy	Preclinical or clinical evidence	Status of clinical trial
Methylprednisolone	Systemic synthetic corticosteroid [47]	<ul style="list-style-type: none"> It possesses significant anti-inflammatory and anti-fibrotic properties. A study has reported that low doses of corticosteroids may prevent cytokine threat event and promote alleviation of pulmonary as well as systemic inflammation in pneumonia condition [47]. 	<ul style="list-style-type: none"> There is a study associate with the use of one dose of 200 mL of CP which have been given to severe COVID-19 patients together with maximal supportive therapy as well as administration of anti-viral agents [46]. As a result, there was an improvement on the clinical symptoms such as increment of oxyhaemoglobin saturation within three days and no presence of severe adverse effect was observed. A retrospective, observational, single-centre study associated with 201 patients who suffered with ARDS due to COVID-19 were received methylprednisolone as a treatment to overcome it. As a result, the use of corticosteroid significantly reduce the risk of death among patients [48]. Another retrospective, observational, single-centre study was reported that methylprednisolone have been used as therapeutic agents among 46 COVID-19 patients who suffered with pneumonia and later progressed to acute respiratory failure. As a result, there is an improvement in clinical symptoms and shorten course of disease in patients who received the drug as compared with the patients who did not get methylprednisolone treatment. From the study, about 13 deaths occurred in three patients during hospitalization and two of these patients received methylprednisolone [49]. 	

treatment of malaria and amoebiasis [22]. Hydroxychloroquine sulphate is a derivative of chloroquine which was first synthesised in 1946 by adding a hydroxyl group into chloroquine. When tested in animals, it was reported that hydroxychloroquine was less toxic than chloroquine [22]. Chloroquine may inhibit the biosynthesis of sialic acid by blocking the

activity of quinone reductase 2, which is a structural neighbour of UDP-N-acetyl-glucosamine 2-epimerases. The presence of sialic acid moieties is essential for the interaction between SARS-CoV and ACE2 receptor as well as orthomyxoviruses [50]. Thus, the inhibition of sialic acid formation prevents SARS-CoV from attaching to the ACE2 receptor.

Apart from that, chloroquine shows antiviral activity through its specific interaction with sugar-modifying enzymes or glycosyltransferase [50]. This interaction leads to glycosylation inhibition, resulting in the suppression of SARS-CoV replication [50]. Additionally, chloroquine performs an immunomodulatory activity that could lead to an anti-inflammatory response in infected patients [22]. Thus, the rationale of using chloroquine or hydroxychloroquine in management of COVID-19 was based on its potential antiviral activity. However, hydroxychloroquine may cause several adverse effects, such as diarrhoea and prolonging the duration between the Q wave and T wave (QT interval) [34]. The Food and Drug Administration (FDA) has highlighted that one of the risks associated with the use of hydroxychloroquine or chloroquine is increased heart rhythm [51]. Therefore, the FDA has cautioned the use of these substances as therapeutic agents in COVID-19 treatment during a clinical trial or for public use [51].

Remdesivir

Remdesivir is a nucleotide analogue inhibitor of RdRp [25]. Remdesivir provides promising outcome as a potential COVID-19 treatment in the United States [52]. It exerted antiviral activity against several RNA viruses, including SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) [25]. The primary therapeutic mechanism of Remdesivir is initiated by the triphosphate form of the inhibitor (RDV-TP) that competes with its natural counterpart adenosine triphosphate (ATP). This initiation stops chain termination process and eventually delays the RNA transcription [53].

In an *in vitro* test, remdesivir demonstrated antiviral activity against SARS-CoV, MERS-CoV, and Ebolavirus [27]. Since then, remdesivir has proven to be the best drug for COVID-19 treatment [27]. In an *in vivo* test, on the other hand, it was found that remdesivir significantly decreased the viral concentration in lung tissue of mice that have been infected with MERS-CoV [28]. The reduction in viral concentration consequently leads to amelioration of lung function [28]. The use of remdesivir has also been associated with elevation of hepatic enzymes among 23% of 61 patients [54]. Collectively, these findings implied that remdesivir might be considered an effective antiviral agent for treating COVID-19 [55]. Therefore, the use of remdesivir has been approved in COVID-19 management due to its binding potential towards SARS-CoV-2 and RdRp [26].

Favipiravir–galidesivir

Favipiravir and galidesivir are the others type of RdRp inhibitors [29]. The rationale of using Favipiravir as an antiviral agent is due to its ability in suppressing the replication of flavi-, alpha-, filo-, bunya-, arena-, noro-, and other RNA viruses [56]. Also, due to its widespread antiviral activity, favipiravir could potentially treat emerging RNA viruses [34]. Moreover, studies have provided evidence of its ability to inhibit viral invasion in the treatment of influenza in China [30] and Japan [56].

Additionally, since favipiravir is nucleoside analogue, it requires intracellular phosphoribosylation, which allows it to undergo a conversion process from its initial form into an active phosphoribosyl form (favipiravir-RTP) in cells. In its active form, favipiravir is identified as a substrate by viral RNA polymerase. Thus, favipiravir increases potency to inhibit RdRp activity and consequently lead to the suppression of viral replication [57]. However, the use of Favipiravir in several patients was associated with an increased level of uric acid, gastrointestinal (GI) disorders, psychiatric symptoms, and enhanced liver function test [58].

Lopinavir–ritonavir

Lopinavir is a protease inhibitor used in the treatment of human immunodeficiency viruses (HIV) [36]. It is used with ritonavir that acts as a booster [36]. The combination of Lopinavir and Ritonavir is known as antiretrovirals. Lopinavir is a peptidomimetic molecule that has hydroxyethylene frames [59]. These frames imitate the peptide linkage that could be identified by the HIV-1 protease enzyme [59]. The combination of lopinavir and ritonavir improves the mean plasma concentration of lopinavir [34]. The rationale of using lopinavir–ritonavir as an antiviral agent was due to its antiviral activity, as demonstrated in an *in vitro* test against SARS-CoV and MERS-CoV. The result of the *in vitro* test showed that Lopinavir could block the cytopathic effect of the SARS-CoV [60]. Thus, lopinavir–ritonavir has demonstrated favourable clinical responses in SARS patients due to its therapeutic efficacy. It is also worth noting that lopinavir–ritonavir may cause several adverse effects, including diarrhoea, GI disorders, headache, and skin rash [61]. However, lopinavir–ritonavir is no longer used as the primary antiviral agent against COVID-19 [23]. This was because there have not been many published studies to support the effectiveness of its *in vitro* activity against SARS-CoV-2 [23].

Ribavirin

Ribavirin is a synthetic guanosine nucleoside, and it is known as a broad-spectrum antiviral agent to eradicate viral infection [30]. Ribavirin has been approved as a drug that has good potential in binding towards its SARS-CoV-2 and RdRp [26]. This binding process consequently leads to viral eradication [26]. Ribavirin may be used in combination with lopinavir–ritonavir, interferon- α (IFN- α), or interferon-alpha-2a (IFN- α -2a) [34]. However, combining ribavirin with IFN- α -2a causes unfavourable adverse effects, including anaemia, flu-like symptoms, and GI disorders [34]. Therefore, these adverse effects should be taken into consideration when using ribavirin with IFN- α -2a in clinical trials. The rationale of using ribavirin as an antiviral agent was because its effectiveness has been proven through randomised clinical trials among patients infected with SARS-CoV and MERS-CoV. Specifically, the result of the clinical trials showed reduced viral activity and increased survival rate in patients treated with ribavirin [33].

Dexamethasone

Dexamethasone is a synthetic adrenal corticosteroid that has good potential effects on innate (i.e., non-specific) and adaptive (i.e., specific) immune responses [37]. The adaptive immune response is initiated in the early symptomatic phase of acute respiratory distress syndrome (ARDS) that is caused by COVID-19 [38]. It can also be initiated by the presence of SARS-CoV-2 [38]. Several characteristics have been identified in patients with SARS-CoV-2. These characteristics included elevation of inflammatory markers such as CRP, lactate dehydrogenase (LDH), and IL-6. The presence of CRP indicates acute inflammation, tissue damage, and infections [38].

As mentioned previously, SARS-CoV-2 binds to ACE2 receptors that are located primarily located on type II pneumocytes. As a result of this binding, the cells stimulate the production of inflammatory signals that recruit macrophages and promote a “cytokine storm” event. The event is characterised by vasodilation, increased capillary permeability, and leucocyte migration [37]. Additionally, the signals induce the production of reactive oxygen species (ROS) along with loss of surfactant. This then leads to the destruction of pneumocytes and causes alveoli injuries. Consequently, patients may suffer from severe inflammatory response syndrome and develop SARS [39]. Concerning this, it has been shown that dexamethasone can suppress vasodilation, reduces capillaries permeability,

and restricts leucocyte migration to the inflammation sites [39]. Therefore, dexamethasone can potentially be used in the treatment of COVID-19 due to its antiviral effects mentioned above.

Sofosbuvir

Sofosbuvir is used in treating hepatitis that is caused by the hepatotropic virus [26]. Sofosbuvir undergo phosphorylation process within the hepatic cellular area. This process converts Sofosbuvir in its initial form into an active form (i.e., nucleoside triphosphate). In its active form, Sofosbuvir stops replication of reactive nitrogen species (RNS) in the nascent viral genome by competing with the viral nucleotides [40]. Additionally, sofosbuvir has different stability of nucleoside analogue triphosphates as compared to other agents. Mainly, the triphosphate exhibits extremely high intracellular stability, indicating the effectiveness of an active anti-hepatitis C virus drug to block the activity of non-structural protein 5B (NS5B)-polymerase [40].

Ivermectin

Ivermectin is known as a broad-spectrum anti-parasitic agent [41]. The potential therapeutic mechanism of ivermectin is mediated by its binding interaction to the target sites such as importin α/β (IMP α/β)-mediated nuclear transport of HIV-1 integrase, NS5 polymerase, NS3 helicase, nuclear import of UL42, and nuclear localisation signal mediated nuclear import of Cap [41]. SARS-CoV-2 is the primary agent that causes COVID-19, and it is characterised as a single-stranded positive-sense RNA virus [8]. Previous studies on SARS-CoV proteins have revealed its potential antiviral activity on IMP α/β 1 site during infection [42]. The signal-dependent nucleocytoplasmic suppressed the SARS-CoV nucleocapsid protein that may affect the division of the host cell [42]. Thus, these reports suggested that ivermectin ability to inhibit viral invasion may be the key to encountering COVID-19 outbreaks.

Methylprednisolone

Methylprednisolone is a systemic synthetic corticosteroid [47]. Severe COVID-19 pneumonia is due to the inflammation caused by SARS-CoV-2 invasion. The inflamed tissue activates immune cells (e.g., monocyte, macrophage, and lymphocytes) and consequently lead to the massive production of pro-inflammatory and anti-inflammatory cytokines (e.g.,

TNF, interleukin-1 β [IL-1 β], and IL-6) [62]. A large amount of these pro-inflammatory agents may obstruct deep airway and alveolar. Therefore, depletion of pro-inflammatory production and control of cytokine storm play is crucial in preventing the occurrence of inflammatory reaction. Thus, Methylprednisolone has the potential to treat COVID-19 due to its anti-inflammatory effects to reduce systemic inflammation [49]. When used appropriately, corticosteroids can significantly enhance the clinical status of SARS patients such as slowing down disease progression, ameliorating lung lesions, and shortening the duration of hospitalisation [49]. Collectively, findings from these observational studies demonstrated that methylprednisolone might serve as a potential therapeutic agent in treating COVID-19 patients with pneumonia and ARDS.

Convalescent plasma

Convalescent plasma (CP) is known as a passive antibody that has been used as a therapeutic agent in the treatment of COVID-19 [43]. This agent is obtained through apheresis, which is a medical procedure that involves taking blood samples in patients infected with COVID-19. The extracted blood samples contain pathogens that cause the infection and antibodies that have produced in response to the pathogens. About this, it has been shown that CP has the potential to eradicate the pathogens [45]. Therefore, administering CP to patients infected with COVID-10 may produce beneficial outcome such as immunomodulation (i.e., alteration of the immune response to consolidate severe inflammation caused by the infection) [63].

In some cases of SARS-CoV-2 infection, the immune system becomes over-activated in response to systemic hyper-inflammation or inflammation storm. These inflammations are caused by cytokines such as TNF α , IL-1 β , IL-2, IL-6, IL-8, IL-17, and chemokine ligand-2 (CCL2). Additionally, the inflammation may result in a sustain pulmonary destruction that eventually leads to fibrosis and depletion of pulmonary function [62]. Throughout the use of CP in the COVID-19 treatments, several reports proved that the administration of CP is safe and does not cause significant adverse effects [46]. Thus, CP may play an essential role as a therapeutic agent in the treatment of COVID-19 due to its high tolerance and effectiveness in eradicating viruses.

Conclusions

SARS-CoV-2 is a virus that causes COVID-19 pandemic. This disease is currently treated through preventive measures

and supportive care. To date, there are no specific therapeutic agents, including vaccines, antimalarials, and antivirals that have been developed to either prevent or cure this disease. However, there are several ongoing clinical trials to identify potential drugs to treat COVID-19 effectively. In summary, this systematic scoping review highlighted that the following drugs could potentially be used in COVID-19 treatment: (i) antivirals (e.g., remdesivir, ivermectin, and favipiravir), (ii) antimalarials (e.g., hydroxychloroquine), (iii) corticosteroids (e.g., dexamethasone and methylprednisolone), and (iv) CP. It is also important to note that some of these drugs have been clinically tested. However, lopinavir–ritonavir did not show any therapeutic benefit. Lastly, due to unfavourable side effects, more clinical evidence is needed to support the effectiveness of galidesivir, sofosbuvir, and ribavirin against COVID-19.

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