



Research Article

# COVID-19: How Effective Are the Repurposed Drugs and Novel Agents in Treating the Infection?

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## Abstract

Coronavirus disease 2019 (COVID-19) induced by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has impacted the lives and wellbeing of many people. This globally widespread disease poses a significant public health concern that urges to discover an effective treatment. This review paper discusses the effectiveness of repurposed drugs used to treat COVID-19 and potential novel therapies for COVID-19. Among the various repurposed drugs, remdesivir is the only agent approved by the Food and Drug Administration (FDA) to treat COVID-19. On the other hand, several drugs have been listed in the Emergency Use Authorization (EUA) by the FDA to treat COVID-19, including casirivimab and imdevimab, baricitinib (in combination with remdesivir), bamlanivimab, tocilizumab, and IL-6 inhibitors. In addition, *in vitro* and clinical studies have suggested cepharanthine, sotrovimab, and XAV-19 as potential treatments to manage COVID-19. Due to inadequate understanding of COVID-19 and the rapid mutation of SARS-CoV-2, COVID-19 remains a threat to global public health, with vaccination considered the most effective method to decrease COVID-19 transmission currently. Nevertheless, with the intense efforts of clinical researchers globally, more promising treatments for COVID-19 will be established in the future.

**Keywords:** COVID-19, SARS-CoV-2, treatment, drug repurposing, antiviral agents

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Received 5 March 2022

Accepted 14 July 2022

Published 31 December 2022

Production and Hosting by Knowledge E

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Editor-in-Chief:

Prof. Mohammad A. M. Ibnouf

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## 1. Introduction

The emergence of the latest coronavirus disease 2019 (COVID-19) in December 2019 has sparked a global public health crisis. This widespread disease, induced by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), impacted the lives and wellbeing of many people, leading to proclamation as a pandemic by the World Health Organization (WHO) on March 11, 2020 [1]. COVID-19 has been identified as the world's worst and most lethal infectious illness after the Spanish flu outbreak in 1918, with more than 276 million confirmed cases and 5.38 million mortalities reported to date [2]. The SARS-CoV-2, believed to originate from bats, triggers multiple critical pneumonia-like symptoms that rapidly worsen and can ultimately lead to fatality in patients [3]. In some cases, prolonged COVID-19 symptoms also termed as long COVID, and permanent complications are reported among COVID-19 patients [4].

Coronaviruses are characterized as a family of enveloped, single-stranded ribonucleic acid (RNA) viruses, predominantly attacking the respiratory system. As viruses constantly change through mutation, multiple variants of coronaviruses have emerged globally. There are various documented variants of concern, notably Alpha, Beta, Gamma, Delta, and Omicron [5]. Alpha and Beta variants are of particular concern due to their ability to spread from animals to humans, threatening human health [6]. The Delta variant is recognized as more infectious and deadly than other variants reported earlier. It is approximately twice as contagious and more likely to cause severe illness in unvaccinated individuals than previous variants [7]. The Omicron variant was first reported in November 2021, and its exact transmissibility and virulence are still under investigation [8]. Several examples of previous widely known coronaviruses include the severe acute respiratory syndrome coronavirus type 1 (SARS-CoV-1), the SARS-CoV-2 and the Middle East Respiratory Syndrome coronavirus (MERS-CoV). In the past, several studies on SARS-CoV-1 and MERS-CoV have been initiated during the disease outbreak due to their high mortality rates. However, research interest in these viruses has declined given the current low disease threat. The rapid mutation of SARS-CoV-2 with accelerated disease transmission has caused the COVID-19 pandemic to be poorly combated.

During its peak in the fall of 2020, approximately 960,000–2.4 million hospitalizations were reported due to COVID-19 in the United States, with 79% of intensive care hospital beds occupancy [9]. This was followed by India, which was hit with the second wave of the deadly disease in May 2021, with an average of 378,000 cases reported daily. This eventually led to the collapse of the Indian healthcare system due to insufficient healthcare workers, hospital beds, and medical supplies [10]. In Malaysia, a spike of

more than 20,000 daily cases was reported in August 2021 [11]. This evidently showed that COVID-19 poses a significant public health concern that urges for effective treatment. Drug repurposing offers an opportunity to reduce the timeline and cost of drug development and discovery. Several drugs have been repurposed for treating COVID-19, yet their effectiveness and mechanisms remain unclear. Some of the repurposed drugs widely used currently are those that have been shown to be less effective. This highlights the need of centralizing data in one place, and the CORONA project is an initiative to create a central database for all COVID-19 treatments [12]. However, it is also crucial for the data to be analyzed. Hence, this narrative review discusses the known and postulated mechanisms of repurposed drugs used to treat COVID-19 and potential novel therapies for the disease.

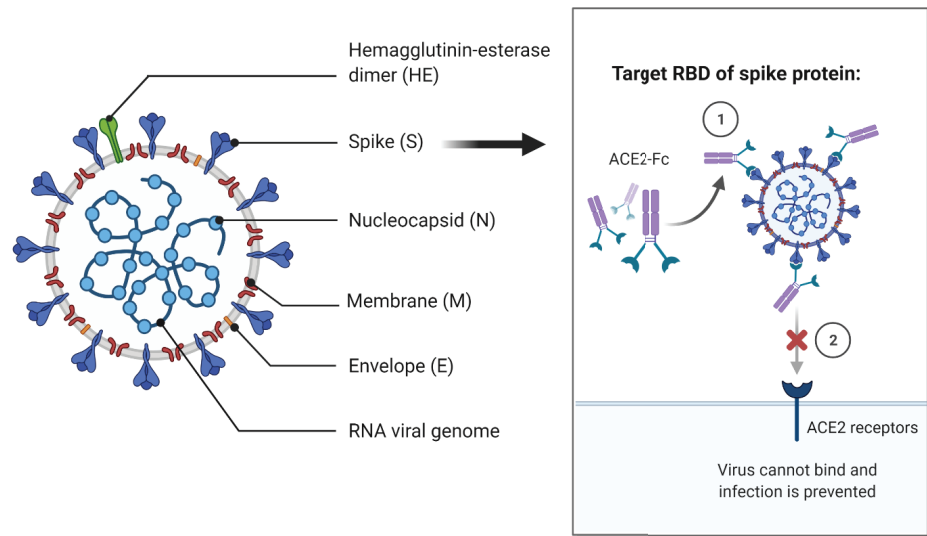
## 1.1. Structure of coronavirus

The SARS-CoV-2 genome consists of approximately 30,000 nucleotides, which encode four major types of structural proteins: spike (S), nucleocapsid (N), envelope (E), membrane (M) proteins; and several nonstructural proteins (NSPs) (Figure 1) [13]. It consists of a capsid that contains nucleocapsids bound to the single-positive RNA strand. Nucleocapsids are essential for the replication and transcription of the viral genome in host cells. The N-terminal of the nucleocapsid binds to the genomic and sub-genomic RNA from mouse hepatitis virus, which subsequently leads to viral replication and transcription. Hence, researchers have been trying to develop an effective drug to halt subsequent viral replication and transcription by preventing the binding of the N-terminal to the RNA strands [13].

The M proteins are the most abundant structural proteins presented on the surface of the viral particle. These proteins are responsible for binding to N proteins and serve as the central organizer for virion assembly [14]. On the other hand, the E proteins are the smallest structural proteins on the viral particle, which serve as small integral membrane polypeptides and act as viroporins. These viroporins play a role in the production and maturation of viruses by causing ion imbalances, and activating the host cell's immune system and releasing inflammatory cytokines. Severe SARS-CoV-2 infected patients were found to have a high concentration of proinflammatory cytokines, also known as "cytokine storm," which inhibit viroporin activity and reduce the inflammatory cytokine burst [15].

Among the major structural proteins, S proteins are the most essential because they are responsible for the infection in human host cells. These proteins are involved in

## Human Coronavirus Structure



**Figure 1:** Structure components of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). Spike proteins are the potential targets for therapeutic treatment of COVID-19 as they facilitate entry of virion into the host cells. The receptor-binding domain (RBD) in this virus is demonstrated to be strongly bound to angiotensin-converting enzyme 2 (ACE-2) receptors. Created with BioRender.com.

interaction and binding to angiotensin-converting enzyme 2 (ACE-2) receptors and fusion of both viral and host cell membranes. The S protein has become a target in therapeutic development due to its role in mediating viral entry into human host cells. By developing therapeutics that can block the attachment of S proteins to the AA sequence in the binding site of ACE-2 receptors, will block the entry of the virus into the human host cell [13]. Lastly, the surface of SARS-CoV-2 also consists of hemagglutinin-esterase dimer (HE). The HE plays a role in viral entry and infection of a host cell, yet it is not involved in the replication of viral genome.

### 1.2. Mutations leading to increased virulence

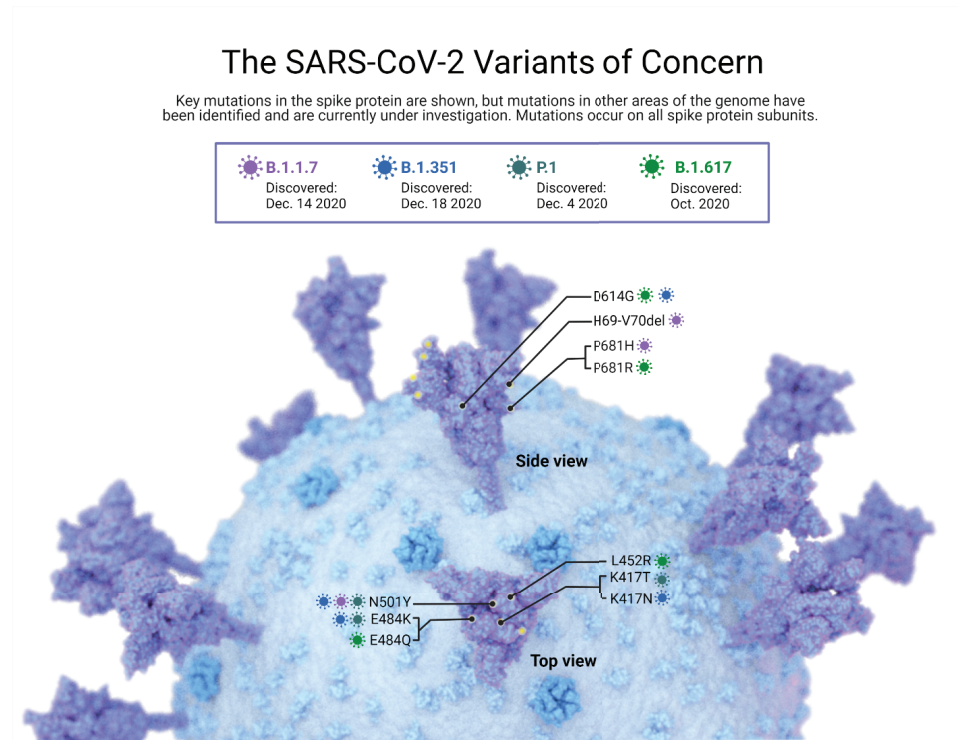
Mutation of the virus occurs each time it replicates. The more the virus spreads, the more likely it is to replicate and mutate. The location at which the mutation occurs in the viral genome may affect the virus's ability to cause infection. It is well-known that SARS-CoV-2 is an RNA virus that is prone to mutation. Generally, the RNA virus lacks internal proofreading and error-correcting mechanisms commonly found in DNA. However, an error-correcting protein was found and detected in SARS-CoV-2, which is believed to increase its replication error rate [16].

Mutations occur at different segments of the viral NSPs exclusively at NSP2 and NSP3, and in the S protein and RNA-dependent RNA polymerase (RdRp). As mentioned above, the S protein is the primary determinant of virulence, advancement, and transmission of a virus. This protein uses ACE-2 as the primary cell receptor, usually located on the epithelial cells of organs such as the heart, lungs, gastrointestinal tract, and kidneys. When the virus attaches to the ACE-2 receptor, the transmission of the signal via the ACE-2 is disturbed, which subsequently contributes to the malfunction of the lungs, kidneys, and heart, leading to severe myocardial infarction [16].

SARS-CoV-2 has evolved into various variants, which may have characteristics distinct from those of its ancestral strain [17]. The Centers for Disease Control and Prevention (CDC), WHO, and various national authorities are currently monitoring mutations of SARS-CoV-2 through periodic genomic sequencing [5, 18]. Mutant strain surveillance is essential for quickly identifying the types of variants and their concerning characteristics. According to CDC, emerging variants are presented with enhanced transmissibility, virulence, evasion of detection, and reduced susceptibility to therapeutics [19]. Due to the continued emergence of new variants, a classification system was established to differentiate the variants into variants of concern (VOC) and variants of interest (VOI). The VOIs are variants possessing a particular gene for mutations and are associated with changes in transmission, diagnostic impact, therapeutics, and virulence. Whereas, VOCs are variants that fulfill the criteria of VOI and have shown evidence of enhanced transmissibility and virulence, and decreased effectiveness to available therapeutics and diagnostic tests. Figure 2 depicts the mutations of S protein subunits that characterize the VOC B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta), and P.1 (Gamma). Information on the mutation and virulence of each variant is summarized in Table 1.

### 1.3. Clinically used drugs repurposed to treat Covid-19

Drug repurposing appears to be one of the important options in the context of this emerging disease associated with high morbidity and mortality. Those repurposed drugs were selected as candidates to combat COVID-19 due to their excellent therapeutic effects against human coronaviruses such as MERS-CoV and SARS-CoV-1. Clinical trials to evaluate the effectiveness of repurposed drugs in managing COVID-19 patients were quickly conducted following the outbreak (Table 2). Some drugs showed positive outcomes; however, in many cases, the investigated repurposed drugs showed disappointing results. More efforts are needed to identify the most effective and promising repurposed drugs for the treatment of COVID-19. This section discusses the



**Figure 2:** Mutations of S protein subunits that characterize the variants of concerns: B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617 (Delta) variants. The N501Y and E484K are common mutations of S protein possessed by SARS-CoV-2 variants. Created with BioRender.com.

latest update of repurposed drugs for COVID-19. The major pharmacological parameters and mechanism of actions of those drugs are summarized and illustrated in Table 3 and Figure 3, respectively.

#### 1.4. Remdesivir

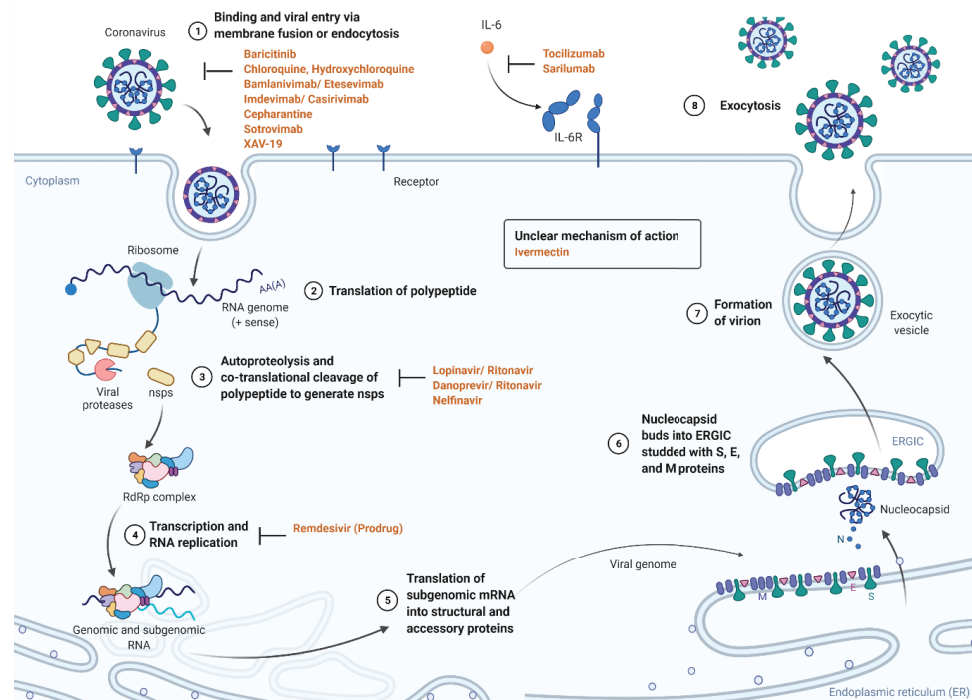
Remdesivir is a broad-spectrum antiviral agent that is effective against coronaviruses (SARS-CoV, MERS-Co-V, SARS-CoV-2), filoviruses (Ebola and Marburg) and paramyxoviruses (measles, and mumps virus). It is a phosphoramidate prodrug of nucleoside monophosphate analog that acts as a virus RNA-dependent RNA polymerase (RdRp) inhibitor, which interferes in viral replication [20]. Host cells metabolize remdesivir into pharmacologically active adenosine triphosphate analog, which in turn compete with adenosine triphosphate (ATP) by integrating into a new RNA strand through the RdRp complex. This results in the termination of viral RNA synthesis and limits viral replication [20]. Remdesivir has been shown to be effective against SARS-CoV-2 in primary cultured human airway epithelial cells by inhibiting its replication in a dose-dependent manner [21]. A randomized controlled clinical trial found that patients treated with a 10-day

TABLE 1: Characteristics of variants of concern.

Variant	First identified (Date reported)	Mutations	Virulence
B.1.1.7 (Alpha)	UK (Sept 2020)	17 genetic mutations and 8 (N501Y, A570D, P681H, T716I, S982A, D1118H, $\Delta$ 69-70 deletion, and $\Delta$ 144 deletion) are in S protein [92]	Approximately 50% enhanced transmissibility [19]; Death risk ratio of 1.65 compared to non-VOC [93]; No impact in neutralization [94]
B.1.351 (Beta)	South Africa (Oct 2020)	9 genetic mutations (L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, and A701V) in the S protein, including 3 mutations (K417N, E484K, and N501Y) are in the RBD [17]	Approximately 50% enhanced transmissibility [19]; Moderate resistance to neutralization by Pfizer-BTN162b2, Novanax, and Johnson & Johnson vaccines [95, 96]
P.1 (Gamma)	Brazil (Dec 2020)	10 genetic mutations (L18F, T20N, P26S, D138Y, R190S, H655Y, T1027I V1176, K417T, E484K, and N501Y) in the S protein, including 3 mutations (L18F, K417N, E484K) are in the RBD [17]	Enhanced transmissibility [19]; Decreased susceptibility toward combination of bamlanivimab and etesevimab monoclonal antibody treatment [19]; Decreased neutralization by plasma sera and vaccination sera [97]
B.1.617.2 (Delta)	India (Oct 2020)	Multiple mutations with 2 major mutations in the spike protein (K417N and D614G) and variation at position 478 [96]	60% more transmissible than Alpha variant [98]; Potential decrease in neutralization by several EUA monoclonal antibody treatments, and post-vaccination sera [99]
B.1.1.529 Omicron	South Africa (Nov 2021)	The spike protein is characterized by at least 30 amino acid substitutions, three small deletions, and one small insertion. 15 of the 30 amino acid substitutions are in RBD (G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H). A number of changes and deletions in other genomic regions [8]	Unknown on transmissibility (may be more transmissible than Delta) [8]; Disease severity and impact on vaccine-induced immunity or immunity from previous infection remain uncertain [8]

RBD: Receptor-binding domain; VOC: Variant of concern; EUA: Emergency Use Authorization.

remdesivir therapy had a 4-day shorter recovery time than placebo-treated patients [22]. It also decreased the mortality in patients who received supplemental oxygen on the 29th day of treatment (4% in the remdesivir-treated group vs. 13% in the placebo group) [22]. In terms of disease severity, remdesivir prevented oxygen-supplemented patients from developing severe respiratory diseases and reduced respiratory support requirements [22]. Due to the outstanding efficacy of remdesivir, it is so far the only FDA-approved agent for the treatment of patients with severe suspected or laboratory-confirmed COVID-19 infection [23]. However, in March 2020, WHO started a large,



**Figure 3:** Mechanisms of clinically repurposed drugs and potential therapeutic agents against SARS-CoV-2. Created with BioRender.com.

randomized trial involving hospitalized COVID-19 patients from multiple countries known as Solidarity trial to evaluate the efficacy of four drugs and remdesivir being one of them [24]. The interim findings reported that the rate ratio of death with remdesivir as compared to control was 0.91 (95% CI, 0.79 to 1.05,  $p=0.20$ ) which did not support the assumption that remdesivir may reduce the rate of mortality [24]. The final report of this trial was later released which mainly focused on the results of remdesivir [25]. The final report contained that overall, 14.5% of patients assigned to remdesivir died compared to those from control group 15.6% (RR=0.91, 95% CI: 0.82–1.02,  $p=0.12$ ) whereas among the non-ventilated patients, 11.9% assigned to remdesivir died compared to 13.5% from the control group (RR 0.86, 95% CI: 0.76–0.98,  $p=0.02$ ). Analysis on the ventilated patients revealed that 42.1% patients from remdesivir group died as compared to 38.6% from control group (RR=1.13, 95% CI: 0.89–1.42,  $p=0.32$ ). A total of 14.1% nonventilated patients in remdesivir progressed to ventilation as compared to 15.7% from control group (RR=0.88, 95% CI: 0.77–1.00,  $p=0.04$ ) and together 19.6% assigned to remdesivir died or progressed to ventilation as compared to 22.5% assigned to control (RR= 0.84, 95% CI: 0.75–0.93,  $p=0.001$ ). Therefore, it has been concluded that no significant effect of remdesivir on ventilated patients was observed, while there was a minor influence on death or progression to ventilation (or both) among hospitalized patients [25].



TABLE 2: Clinical trials of repurposed drugs for the treatment of COVID-19.

Drug or drug combination	Clinical trial status	Study site	Patient number and characteristics	Outcome	Statistical analysis	Ref.
Remdesivir*	Completed phase 3 (NCT04280705)	60 trial sites: United States (45), Denmark (8), United Kingdom (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1), and Singapore (1)	1062 hospitalized adult with COVID-19 and had evidence of lower respiratory tract infection	<p>Primary outcome:</p> <ul style="list-style-type: none"> <li>Significant shorter recovery time as compared to placebo (10 days vs 15 days)</li> </ul> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> <li>Significant clinical improvement at day 15 as compared to placebo</li> <li>Kaplan–Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29</li> </ul>	<p><math>P &lt; 0.001</math></p> <p>OR: 1.5; 95% CI: 1.2–1.9 HR: 0.73; 95% CI: 0.52–1.03</p>	[22]
	Completed phase 3 (NCT04315948)	454 hospitals in 35 countries	14221 hospitalized adult patients with diagnosis of COVID-19	<ul style="list-style-type: none"> <li>Overall, no significant effect in reducing mortality rate (14.5% vs 15.6%)</li> <li>Minimal effect on progression to ventilation and death among non-ventilated patients (19.6% vs 22.5%)</li> </ul>	<p>RR: 0.91; 95% CI: 0.82–1.02 <math>P = 0.12</math> RR: 0.84; 95% CI: 0.75–0.93 <math>P = 0.001</math></p>	[25]
Baricitinib plus ritonavir- lopinavir	Completed (NCT04358614)	Hospitals in Prato and Alessandria (Italy)	24 hospitalized patients aged between 18–85 years with mild to moderate COVID-19 disease	<ul style="list-style-type: none"> <li>Fever, SpO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub>, CRP, and MEWS significantly improved in the baricitinib-treated group compared with controls (ritonavir- lopinavir treated)</li> <li>No ICU admission was requested as compared to control group (33%).</li> <li>Higher discharged rate at week 2 (58% vs 8% in controls)</li> </ul>	<p><math>P = 0.000</math>; 0.000; 0.017; 0.023; 0.016, respectively</p> <p><math>P = 0.093</math></p> <p><math>P = 0.027</math></p>	[26]
Baricitinib plus remdesivir	Completed (NCT04401579)	67 trial sites: United States (55), Singapore (4), South Korea (2), Mexico (2), Japan (1), Spain (1), the United Kingdom (1), and Denmark (1)	1033 hospitalized adults with COVID-19	<p>Primary outcome:</p> <ul style="list-style-type: none"> <li>Significant shorter recovery time as compared to controls (7 days vs 8 days).</li> </ul> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> <li>A total of 30% higher odds of clinical improvement on day 15 than controls</li> <li>Shorter recovery time among those receiving high-flow oxygen or noninvasive ventilation compared to controls (10 days vs 18 days) Lower 28-day mortality as compared to controls (5.1% vs 7.8%)</li> </ul>	<p><math>P = 0.03</math></p> <p>OR: 1.3; 95% CI: 1.0–1.6 Rate ratio for recovery: 1.51; 95% CI: 1.10–2.08 HR: 0.65; 95% CI: 0.39–1.09</p>	[28]

TABLE 2: (Continued).

Drug or drug combination	Clinical trial status	Study site	Patient number and characteristics	Outcome	Statistical analysis	Ref.
Tocilizumab**	Phase 2 (NCT04317092)	Multicenter in Italy	301 hospitalized COVID-19 patients with SpO <sub>2</sub> ≤ 93% or required oxygen support or mechanical ventilation (all ages)	Lower lethality rates at 14 days (15.6%) and at 30 days (20.0%) compared to overall lethality (at 14 days – 18.4%; at 30 days - 22.4%)	NA	[32]
	Phase 2 (NCT04346355)	24 centers in Italy	126 hospitalized adult patients with COVID-19 pneumonia presented with Pao <sub>2</sub> /Fio <sub>2</sub> 200-300 mmHg	Primary outcome: • A total of 28.3% of tocilizumab-treated patients showed clinical worsening within 14 days as compared to controls (27.0%) Secondary outcomes: • No differences between both arms in ICU admission (10.0% vs 7.9%), mortality (1.7% vs 1.6%), and discharge rate (56.7% vs 57.1%)	P = 0.87  NA	[35]
	Phase 2 (NCT04331808)	9 university hospitals in France	131 hospitalized COVID-19 patients with moderate to severe pneumonia	Primary outcomes: • At day 4, 19% tocilizumab-treated patients had a WHO-CPS score >5 as compared to 28% in the control group • At day 14, fewer patients needed NIV or MV or died in tocilizumab-treated group as compared to controls (24% vs 36%)	90% CrI: -21.0 – 3.1  95% CI: -28 – 4	[34]
	Phase 2 (NCT04331795)	University of Chicago Medicine, United States	32 nonintubated hospitalized adult patients with COVID-19, radiographic pulmonary infiltrate, fever, and CRP ≥ 40 mg/L	Primary outcome: • A total of 75% patients experienced fever resolution within 24 hr following tocilizumab treatment Secondary outcome: • Total of 86% patients achieved CRP decrease of ≥ 25% • 28-day mortality was 16% • Mean time to recovery was 3 days and associated with severity of disease at enrollment	NA  NA	[33]
	Phase 3 (NCT04381936)	National Health Service hospitals in United Kingdom	4116 hospitalized adult COVID-19 patients with hypoxia (SpO <sub>2</sub> < 92%) and systemic inflammation (CRP ≥ 75 mg/L)	Primary outcome: • Lower mortality within 28 days in tocilizumab-treated group as compared to control group (31% vs 35%) Secondary outcomes: • Shorter time to discharge (57% vs 50%) • Less likely to reach composite endpoint of invasive MV and death with tocilizumab among those who were not receiving MV at baseline	P = 0.0028  P < 0.0001  P < 0.0001	[40]

TABLE 2: (Continued).

Drug or drug combination	Clinical trial status	Study site	Patient number and characteristics	Outcome	Statistical analysis	Ref.
	Phase 3 (NCT04372186)	Multicenter in United States (27), Peru (5), Brazil (3), Kenya (1), South Africa (1) and Mexico (2)	377 hospitalized adult patients with Covid-19 pneumonia who were not receiving supplemental oxygen or MV	Primary outcome: • Less likely to receive MV or died by day 28 (12% vs 19.3%) Secondary outcomes (not significant): • Median time to hospital discharge: 6 days vs 7.5 days • Median time to clinical improvement: 6 days vs 7 days • Mortality by day 28: 10.4% vs 8.6%	$P = 0.04$  HR: 1.16; 95% CI: 0.91–1.48 HR: 1.15; 95% CI: 0.90–1.48 95% CI: -5.2 – 7.8	[31]
	Phase 3 (NCT04320615)	62 hospitals in Europe and North America (Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, United Kingdom, and United States)	438 hospitalized adult patients with severe COVID-19 pneumonia	Primary outcome: • No significant improvement in clinical status at day 28 (1.0 vs 2.0) Secondary outcome: • No significant difference in mortality at day 28 (19.7% vs 19.4%)	$P = 0.31$  $P = 0.94$	[36]
	Terminated Phase 3 (NCT04403685)	9 hospitals in Brazil	129 adults with confirmed covid-19 who were receiving supplemental oxygen or MV and had abnormal levels of at least two serum biomarkers	Primary outcome: • No significant difference for the need on MV or mortality at day 15 Secondary outcomes: • No significant differences in mortality at day 28 and in-hospital mortality • No significant differences in clinical status at day 8 and day 29	$P = 0.32$  $P = 0.07$  $P = 0.79; 0.10$	[37]
	Phase 4 (NCT02735707)	Multicenter in Australia, Belgium, Canada, Croatia, Finland, France, Germany, Hungary, Ireland, New Zealand, Portugal, Romania, Saudi Arabia, Spain, United Kingdom, United States, India, Nepal, Pakistan	353 critically ill adult patients with COVID-19 who were admitted to ICU and receiving respiratory or cardiovascular organ support	Primary outcome: • Lower median number of organ support-free days (10 days vs 0 day) Secondary outcomes: • Improve 90-day survival • Improve time to ICU discharge • Improve time to hospital discharge	OR: 1.64; 95% CrI: 1.25–2.14  OR: 1.59; 95% CrI: 1.24–2.05 OR: 1.42; 95% CrI: 1.18–1.70 OR: 1.41; 95% CrI: 1.18–1.70	[39]
Sarilumab	Phase 3 (NCT04327388)	45 hospitals in Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russia, and Spain	420 hospitalized adult COVID-19 patients presented with pneumonia and required supplemental oxygen or intensive care	Primary outcome: • No significant difference in median time to clinical improvement for both 200 mg and 400 mg of sarilumab as compared to placebo (10 days, 10 days vs 12 days) Secondary outcome: • No significant differences in survival at day 29	$P = 0.96, 0.34$  $P = 0.25$	[38]
	Phase 4 (NCT02735707)	Multicenter in Australia, Belgium, Canada, Croatia, Finland, France, Germany, Hungary, Ireland, New Zealand, Portugal, Romania, Saudi Arabia, Spain, United Kingdom, United States, India, Nepal, Pakistan	48 critically ill adult patients with COVID-19 who were admitted to ICU and receiving respiratory or cardiovascular organ support	Primary outcome: • Lower median number of organ support-free days (11 days vs 0 day) Secondary outcomes: • Improve 90-day survival • Improve time to ICU discharge • Improve time to hospital discharge	OR: 1.76; 95% CrI: 1.17–2.91  OR: 1.82; 95% CrI: 1.22–3.38 OR: 1.64; 95% CrI: 1.21–2.45 OR: 1.60; 95% CrI: 1.17–2.40	[39]

TABLE 2: (Continued).

Drug or drug combination	Clinical trial status	Study site	Patient number and characteristics	Outcome	Statistical analysis	Ref.
Lopinavir/ritonavir	Phase 3 (NCT04381936)	176 hospitals in United Kingdom	5040	Primary outcome: • No significant difference in mortality within 28 days (23% vs 22%) Secondary outcomes: • No significant difference in time to discharge from hospital (11 days vs 11 days) • No significant difference in risk of progressing to invasive MV or death	$P = 0.60$ $P = 0.53$ $P = 0.092$	[44]
Lopinavir	Phase 3 (NCT04315948)	405 hospitals in 30 countries	2771 hospitalized adult patients with diagnosis of COVID-19	Primary outcome: • No significant effect in reducing mortality (10.6% vs 10.6%) Secondary outcomes: • No effect on initiation of ventilation and hospitalization duration	$P = 0.97$	[24]
Danoprevir/ritonavir	Completed phase 4 (NCT04345276)	China	11 hospitalized Chinese adult patients with COVID-19 pneumonia (moderate)	Primary outcome: • No patient had composite adverse outcome Secondary outcomes: • First negative real-time PCR test at a median of 2 days • Obvious absorption in lung imaging at a median of 3 days	NA NA NA	[47]
Hydroxy-chloroquine	Terminated Phase 3 (NCT04381936)	176 hospitals in United Kingdom	4716 hospitalized adult patients with COVID-19 infection and no medical history	Primary outcome: • No significant difference in all-cause mortality (27% vs 25%) Secondary outcome: • Less likely to be discharged from hospital (59.6% vs 62.9%) • Higher frequency of invasive MV or death (30.7% vs 26.9%)	$P = 0.15$ RR: 0.90; 95% CI: 0.83–0.98 RR: 1.14; 95% CI: 1.03–1.27	[53]
	Phase 3 (NCT04315948)	405 hospitals in 30 countries	1853 hospitalized adult patients with diagnosis of COVID-19	Primary outcome: • No significant effect in reducing mortality (11% vs 9%) Secondary outcomes: • No effect on initiation of ventilation and hospitalization duration	$P = 0.23$	[24]
Dexamethasone	Phase 3 (NCT04327401)	41 trial sites in Brazil	299 hospitalized adult patients with COVID-19 and moderate to severe ARDS	Primary outcome: • Significant increase in the number of ventilator-free days over 28 days Secondary outcomes: • No significant difference in all-cause mortality at 28 days (56.3% vs 61.5%) • No significant improvement in clinical status (5 vs 5-6) • No significant difference in ICU-free days (2.1 days vs 2.0 days) • No significant difference in MV duration (12.5 days vs 13.9 days)	$P = 0.04$ $P = 0.85$ $P = 0.07$ $P = 0.50$ $P = 0.11$	[61]

TABLE 2: (Continued).

Drug or drug combination	Clinical trial status	Study site	Patient number and characteristics	Outcome	Statistical analysis	Ref.
	Phase 3 (NCT04381936)	176 trial sites in United Kingdom	6425 hospitalized adult patients with COVID-19 and no medical history	Primary outcome: • Reduced all-cause mortality within 28 days (22.9% vs 25.7%) among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support Secondary outcomes: • Shorter hospitalization duration (12 days vs 13 days) and greater probability of discharge alive within 28 days • Reduced number of patients who progressed to invasive MV and death	$P < 0.001$  RR: 1.10; 95% CI: 1.03–1.17  RR: 0.93; 95% CI: 0.85–1.01	[59]
Methyl-prednisolone	EUCTR2020-001934-37	5 hospitals in Spain	64 hospitalized adult patients with moderate to severe COVID-19.	Primary outcome: • No significant effect on composite of death, admission to ICU or requirement for noninvasive ventilation (40% vs 48%) Secondary outcome: • Significant lower risk of experiencing the composite endpoint in the per protocol analysis	$P = 0.25$  $P = 0.043$	[64]
Hydrocortisone	Phase 4 (NCT02735707)	121 sites in Australia, Canada, France, Ireland, Netherlands, New Zealand, United Kingdom, and United States	384 hospitalized adult patients with severe COVID-19 infection	Improvement in organ-support free days (11.5 days with fixed dose hydrocortisone and 9.5 days with shock-dependent hydrocortisone vs 6 days with no hydrocortisone)	OR: 1.43; 95% CrI: 0.91–2.27; OR: 1.22; 95% CrI: 0.76–1.94;	[62]
	Terminated Phase 3 (NCT02517489)	Multicenter in France	149 patients admitted to ICU for COVID-19 related acute respiratory failure	Primary outcome: • No significant reduction in treatment failure at day 21 (42.1% vs 50.7%) Secondary outcomes: • The need of tracheal intubation: 50% vs 75% • Cumulative incidences of prone positioning 47.4% vs 53.4%	$P = 0.29$  NA $P = 0.47$	[63]
Ivermectin/doxycycline	Phase 3 (NCT04403555)	2 hospitals in Egypt	164 hospitalized adult patients with mild to moderate COVID-19 infection	Primary outcome: • No significant difference in mortality (3.7% vs 4.9%) Secondary outcomes: • No significant difference in length of hospital stay (8.82 days vs 10.97 days) • No significant difference in the need for MV (3.7% vs 3.7%)	$P = 1.00$  $P = 0.085$ $P = 1.00$	[67]
	Phase 2 (NCT04431466)	Single center in Brazil	32 hospitalized adult patients with COVID-19 infection	High proportion of patients had undetectable level of viral load within 7 days (71% vs 63.3%)	NA	[68]

\*FDA-approved drug for COVID-19 treatment; \*\*Emergency Use Authorization. Abbreviations: OR, odds ratio; CI, confidence interval; HR, hazard ratio; CrI, credible interval; CRP, C-reactive protein; LDH, serum lactate dehydrogenase; ICU, intensive care unit; ARDS, acute respiratory distress syndrome; NIV, non-invasive ventilation; WHO-CPS, WHO 10-point Clinical Progression Scale; MV, mechanical ventilation; NA, not available; Pao<sub>2</sub>/Fio<sub>2</sub>, partial pressure of arterial oxygen to fraction of inspired oxygen; SpO<sub>2</sub>, oxygen saturation.

TABLE 3: Pharmacology of clinically repurposed drugs to treat COVID-19 [100, 101].

Drug indication)	(Original	Mechanism of action	Pharmacokinetic profile	Side effect
Remdesivir* (Broad spectrum antiviral agent against Ebola, hepatitis B and C, HIV infections.)		Acts as an adenosine triphosphate analog and competes for incorporation into RNA chains by the SARS-CoV-2 RdRp, resulting in delayed chain termination during viral RNA replication. Inhibits viral RNA synthesis due to incorporation into the viral RNA template	Protein binding: 88 – 93.6% Half-life: Prodrug: 0.89 hr Active forms: 27 hr Excretion: urine (~ 74%)	Bradycardia, cardiac arrest, reversible transaminase elevations, worsening of underlying chronic kidney disease, headache, lightheadedness, anaphylaxis, infusion related reactions
Baricitinib (Rheumatoid arthritis)		Inhibits JAK enzymes, which are intracellular enzymes involved in stimulating hematopoiesis and immune cell function through a signaling pathway. In response to extracellular cytokine or growth factor signaling, JAKs activate STATs, which regulate gene expression and intracellular activity. Inhibition of JAKs prevents the activation of STATs and reduces serum IgG, IgM, IgA, and CRP.	Metabolism: hepatic, primarily via CYP3A4 Bioavailability: ~ 80% Elimination half-life: ~12 hr	Infection, upper respiratory tract infection, nausea, increased serum ALT and AST, herpes zoster infection
Tocilizumab (Cytokine release syndrome)		Binds to IL-6 receptor which leads to a reduction in cytokine and acute phase reactant production	Elimination half-life: 8-14 days	Upper respiratory tract infection, nasopharyngitis, headache, high blood pressure
Sarilumab (Rheumatoid arthritis)		Binds to both soluble and membrane-bound IL-6 receptors which leads to a reduction in CRP levels	Bioavailability: 80% Elimination half-life: 21 days	Neutropenia, thrombocytopenia, infections of upper respiratory tract, oral herpes, hyperlipidemia, reaction at injection site
Lopinavir/Ritonavir (HIV infection)		Lopinavir component binds to the site of HIV-1 protease activity and inhibits the cleavage of viral Gag-Pol polyprotein precursors into individual functional proteins required for infectious HIV which results in the formation of immature, noninfectious viral particles. The ritonavir component inhibits the CYP3A metabolism of lopinavir, allowing increased plasma levels of lopinavir.	Absorption: lopinavir has poor bioavailability, yet boosted by low dose ritonavir Distribution: Lopinavir: plasma protein binding 98-99% Ritonavir: high concentrations in serum and lymph nodes. Enters breast milk. Metabolism: Lopinavir: metabolized by CYP3A4 Ritonavir: metabolized by CYP3A4 and CYP2D6 Excretion: Lopinavir: feces (83%, 20% as unchanged drug), urine Ritonavir: feces (~86%; 34% as unchanged drug), urine	GI disturbance, dyslipidemia, diabetes mellitus, pancreatitis, hepatic disorders
Chloroquine (Malaria)		Binds to and inhibits DNA and RNA polymerase Interferes with metabolism and hemoglobin utilization by parasites Inhibits prostaglandin effects Concentrates within parasite acid vesicles and raises internal pH resulting in inhibition of parasite growth	Absorption: Rapid and complete oral absorption Distribution: well-distributed including CNS Metabolism: metabolized by CYP2C8 and CYP3A4 Excretion: urine (60%)	Nausea, vomiting, dyspepsia, dysgeusia, rashes, itching, headache, tinnitus, retinopathy, QT prolongation
Hydroxychloroquine (Malaria)		Interferes with digestive vacuole function within sensitive malarial parasites by increasing the pH and interfering with lysosomal degradation of hemoglobin Inhibits locomotion of neutrophils and chemotaxis of eosinophils Impairs complement-dependent antigen-antibody reactions	Complete oral absorption 55% protein bound Metabolism: metabolized by CYP450 enzymes Excretion: urine (60%)	Quite well tolerated, ocular effects, QT prolongation, nausea, vomiting, diarrhea, anorexia, abdominal cramps, rash, itching, alopecia, headache
Dexamethasone (Immunosuppressant)		A long-acting corticosteroid with minimal sodium-retaining potential. It decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response	Bioavailability: 80-90% Metabolism: liver Excretion: urine (65%)	Adrenal suppression, CNS and psychiatric/behavioral effects, Cushingoid features, GI effects, hyperglycemia

TABLE 3: Pharmacology of clinically repurposed drugs to treat COVID-19 [100, 101].

Drug (Original indication)	Mechanism of action	Pharmacokinetic profile	Side effect
Hydrocortisone (Immunosuppressant)	Short-acting corticosteroid with minimal sodium-retaining potential; decreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability	Elimination half-life: 1.5 h	Adrenocortical insufficiency, Cushingoid features, GI effects, hyperglycemia
Ivermectin (parasitic infections)	Binds selectively and with strong affinity to glutamate-gated chloride ion channels which leads to increased permeability of cell membranes to chloride ions and hyperpolarization of the nerve or muscle cell, and death of the parasite.	Distribution: widely distributed Metabolism: liver by CYP450 Excretion: feces, urine (<1%) Half-life: 18 h	Lethargy, drooling, encephalopathy, confusion, stupor, coma

\*FDA-approved drug for COVID-19 treatment. Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; RdRp, RNA-dependent RNA polymerase; RNA, ribonucleic acid; JAK, Janus kinase; STAT, signal transducers and activators of transcription; Ig, immunoglobulin; CYP, cytochrome P450; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; IL-6, interleukin-6; HIV, human immunodeficiency virus; GI, gastrointestinal; DNA, deoxyribonucleic acid; CNS, central nervous system; ACE-2: angiotensin-converting enzyme 2; RBD, receptor binding domain.

## 1.5. Baricitinib

Baricitinib, a Janus kinase (JAK) inhibitor approved for rheumatoid arthritis (RA), possesses anti-inflammatory properties, and can prevent cytokine release [26]. Richardson and colleagues reported an exciting finding that baricitinib reduced viral transmissibility by disrupting endocytosis regulators; AP2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase, which led them to propose a trial to study the inhibition of COVID-19 viral entry and inflammation in infected patients treated with a therapeutic regimen of baricitinib (2 mg or 4 mg once daily) [27]. Since then, this drug has been evaluated in clinical trials for its safety and efficacy in moderate COVID-19 pneumonia patients [27]. Owing to this, a trial was proposed by the research group to study the inhibition of COVID-19 viral entry and inflammation in infected patients treated with a therapeutic regimen of baricitinib (2 mg or 4 mg once daily) [27]. In a study conducted by Cantini *et al.* (2020), baricitinib was evaluated with lopinavir-ritonavir as a combination therapy in moderate COVID-19 pneumonia patients [26]. Baricitinib-treated patients showed significant improvement compared to baseline in terms of clinical characteristics and respiratory function. After two weeks of baricitinib intervention, 58% of the patients were discharged, which was higher than the control group (8%). Baricitinib was well tolerated in all the patients without an incidence of severe adverse event [26]. Nevertheless, the findings of this trial were limited due to the small sample size, lack of randomization, and blinding. On the other hand, another large scale, randomized, double-blinded controlled trial concluded that patients receiving baricitinib in combination with remdesivir achieved shorter recovery (7 days) compared to those who received remdesivir and

placebo (8 days) [28]. However, grade 3 or 4 adverse events such as hyperglycemia, anemia, lymphocytopenia, and acute renal injury were reported in at least 5% of the patients. Despite the discontinuation of the trial due to the reported significant side effects, it should be noted that the overall adverse events were much lesser in the combination-treated group in comparison to the control group [28].

## 1.6. Interleukin-6 inhibitors

Interleukin (IL)-6 is believed to be the key mediator of cytokine storms in COVID-19 patients. IL-6 can bind to the membrane-bound IL-6 receptors (mIL-6R) and soluble IL-6 receptors (sIL-6R), triggering intracellular signaling mechanisms such as MAPK and STAT signaling pathways, which further intensify inflammation and causes other damages [29]. Tocilizumab and sarilumab are FDA-approved humanized anti-IL-6 receptor monoclonal antibodies for RA and cytokine release syndrome. Upon binding to mIL-6R and sIL-6R, these drugs inhibit the IL-6-mediated signal transduction, which in turn decreases the inflammatory response in a cytokine storm. The incidence of acute respiratory distress syndrome (ARDS) will be minimized, thus achieving a better clinical outcome with a decreased mortality rate [30]. As earlier studies have established the role of IL-6 in COVID-19, IL-6 inhibitors have been evaluated in severe to critical COVID-19 patients. However, due to the small sample size and different study designs of the clinical trials, it is difficult to compare the outcomes of these studies.

The EMPACTA trial demonstrated that treatment of COVID-19 patients with tocilizumab reduced the probability of disease progression (the need for mechanical ventilation or death) on day 28. Still, it did not improve the survival rate compared to placebo [31]. In addition, the use of tocilizumab decreased the lethality rate on day 30 without causing significant toxicity [32]. On the other hand, a low dose of tocilizumab was associated with rapid improvement of hyperinflammation in clinical and laboratory status among hospitalized COVID-19 patients [33]. Controversially, the use of tocilizumab did not reduce World Health Organization Clinical Progression Scale (WHO-CPS) scores lower than five on day five and mortality on day 28, although it might have reduced the risk of noninvasive ventilation, intubation, or death on day 14 [34]. Other trials reported no beneficial outcomes with the use of tocilizumab in COVID-19 patients [35-37]. For sarilumab, the clinical study showed that it did not improve the outcomes for hospitalized COVID-19 patients [38]. Interestingly, the REMAP-CAP trial, which enrolled a narrowly defined population of critically ill patients, found that the IL-6 receptor antagonists were more effective than the current standard of



care [39]. The RECOVERY trial consistently reported that the ARDS patients with inflammatory response benefited from tocilizumab treatment [40]. Observations also pointed out that the use of tocilizumab had contributed to a higher percentage of patients discharged in 28 days, a lower probability of progressing to death, or the need for invasive mechanical ventilation. These two clinical trials provided evidence that severely ill patients obtained a modest mortality benefit from the treatment of tocilizumab, especially when coadministered with corticosteroid.

Despite the positive outcomes from several trials in the previous year, the specific group of COVID-19 patients who may benefit from this treatment is yet to be ascertained. Hence, the risk-benefit ratio of IL-6 inhibitors should be carefully evaluated in patients with critical conditions [41]. In June 2021, FDA authorized the emergency use of tocilizumab for the treatment of hospitalized adults and pediatric patients ( $\geq 2$  years old), who were receiving systemic corticosteroids and required supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation [42]. This Emergency Usage Authorization (EUA) is mainly supported by data from well-controlled clinical trials, which suggested that tocilizumab may improve clinical outcomes in patients receiving corticosteroids and requiring supplemental oxygen or breathing support where the benefit of the treatment outweighs the risk in this authorized population of patients.

## 1.7. Lopinavir/Ritonavir

Lopinavir is a protease inhibitor used as an antiretroviral drug for the treatment of human immunodeficiency virus (HIV). Recently, it has become a candidate for COVID-19 treatment, as a combination with ritonavir (another protease inhibitor). Lopinavir is given as combination therapy due to its low-oral bioavailability owing to the extensive CYP3A4 enzyme metabolism. Coadministration of lopinavir with ritonavir can increase the half-life of lopinavir, as ritonavir is CYP3A4 enzyme inhibitor [43]. In the event of COVID-19 infection, SARS-CoV-2 makes its way into the host cell and produces multiple copies of its RNA with enzyme 3-chymotrypsin like protease (3CLpro). These newly formed RNA accumulates at the periphery of the cell and are subjected to cleaving, packaging, and releasing from the host cell. Lopinavir is believed to inhibit the effect of 3CLpro, thus halting the viral replication process [43]. Yet, there are some doubts on the potential efficacy of protease inhibitor against this virus as SAR-CoV-2 proteases comprise of 3Cpro that is lacking C2 symmetric pocket, which is the target of HIV protease inhibitors. The doubt seems to be further verified by the negative outcomes reported by several clinical trials. The use of lopinavir-ritonavir was

not associated with reduced 28-day mortality, duration of hospitalization, or risk of advancing to invasive mechanical ventilation or death among hospitalized COVID-19 patients [44]. Other clinical trials demonstrated that there were no advantages observed with lopinavir/ritonavir combination treatment compared to standard care [45]. Thus, further investigation is required to confirm the potential benefits of this drug combination.

### 1.8. Danoprevir/Ritonavir

Danoprevir is a NS3/4A hepatitis C virus (HCV) protease inhibitor with favorable effects against diverse HCV genotypes. It has a potent and broad-spectrum antiviral effect on hepatitis C. Recently, danoprevir has been reported to have strong inhibitory effect against SARS-CoV2 with a strong interaction with the active site on main protease of SARS-CoV2 [46] whereby ritonavir increases the blockade effect of danoprevir on the main protease and eventually halts the multiplication cycle. This combination has shown promising outcomes in improving the health condition of patients with moderate COVID-19 and increasing the discharge rate without adverse outcomes [47]. In terms of the comparison of efficacy of danoprevir/ritonavir and lopinavir/ritonavir, recent study reported that danoprevir/ritonavir is superior to lopinavir/ritonavir in treating COVID-19 patients where shorter time is required to achieve negative nucleic acid testing and shorter duration of hospitalization [48].

### 1.9. Chloroquine/Hydroxychloroquine

Chloroquine (CQ) and hydroxychloroquine (HCQ) have a long-standing history in the management of malaria, RA, and systemic lupus erythematosus. Both drugs also display antibacterial, antifungal, and antiviral properties [49]. CQ and HCQ have shown their potential for COVID-19 treatment in preclinical models via three main pathways: (i) hindrance of receptor recognition process; (ii) interference in the endocytic pathway, and (iii) inhibition effect on T-cell activation and cytokine production. The CQ and HCQ can inhibit glycosylation of ACE-2 receptors, thus preventing the virus from entering the host. In addition, both drugs can bind to sialic acids and gangliosides with high affinity, preventing the binding of SARS-CoV-2 to the gangliosides [50]. On the other hand, CQ/HCQ acts as a weak base and accumulates in endosomes and lysosomes to neutralize the pH. This leads to the hindrance of lysosomal proteases effects, thus preventing the fusion of virus and host membranes during receptor-mediated endocytosis

[51]. These drugs prevent MHC Class II expression and inhibit T-cell activation, resulting in a decrease in cytokine production by T and B cells. The changes in endosomal pH induced by CQ/HCQ also decreases the production of cytokines by interfering the toll-like receptor (TLR) signaling. Further, a weakened cyclic GMP-AMP (cGAMP) synthase (cGAS) activity reduces the generation of interferon-1 [51].

The CQ/HCQ appeared to exert a favorable efficacy in some initial studies with a smaller sample size. Due to the critical situation, FDA had granted the EUA of these agents in the treatment of COVID-19 in March 2020. However, this EUA was then revoked due to the latest data from the RECOVERY and WHO Solidarity trial which confirmed that CQ or HCQ did not provide any clinical benefit for COVID-19 patients [52]. In a large randomized controlled trial of hospitalized patients in the United Kingdom (RECOVERY trial), it was found that HCQ-treated patients did not demonstrate a lower incidence of death on 28th day, had a longer duration of hospitalization, and had low probability of discharge than those who received standard care [53]. Similarly, another randomized and controlled WHO Solidarity trial also indicated that there is no difference in mortality among hospitalized COVID-19 patients with HCQ treatment compared to the usual care [24]. While the ongoing clinical trials are still evaluating the use of CQ/HCQ, the existing data suggest that it is unlikely that clinical benefits will be identified for this regimen. Hence, CQ/HCQ should not be recommended for widespread use in COVID-19 and these two drugs are currently used in the context of clinical trial.

### 1.10. Corticosteroids

One of the deleterious responses to SARS-CoV-2 infection is an overactivation of innate immune system. In response to that, neutrophils and pro-inflammatory cytokines including IL-1, IL-2, IL-6, TNF- $\alpha$ , and prostaglandins will be highly produced resulting in “cytokine storm.” The excessive release of these pro-inflammatory cytokines exposes COVID-19 patients to ARDS, multiple dysfunctions, and death [54, 55]. As potent anti-inflammatory drugs, corticosteroids are used to overcome the deterioration of cytokine storm [56]. Glucocorticoids bind to the glucocorticoid receptor on the cell membrane to form a complex which leads to translocation of corticosteroids into the cell. Upon entering the nucleus, the complex will then interact with specific sites of DNA which will then stimulate or suppress a variety of genes, thereby lowering the production of pro-inflammatory cytokines [56]. Glucocorticoids also stimulate the synthesis of glucocorticoid response element and reduce the expression of MHC class II and suppress the presenting of antigens to T cells [57].

According to a prospective meta-analysis, there is an overall lower odd of mortality with corticosteroid treatment compared to the standard therapies [58]. In the RECOVERY trial, dexamethasone reduced the mortality rate of COVID-19 patients who required invasive mechanical ventilation or oxygen support, yet it has no beneficial effect for patients who did not require any respiratory support [59]. Based on the trial's earlier outcome, WHO quickly recommended the use of systemic corticosteroids therapy for 7-10 days in patients with severe and critical COVID-19 [60]. Another two clinical trials, CoDEX and REMAP-CAP reported that moderate to severe COVID-19 patients treated with corticosteroid (dexamethasone or hydrocortisone) showed better outcomes, in terms of survival rate and oxygen-support free days compared to patients with standard care alone [61, 62]. In contrast, the CAPE COVID trial showed that critically ill patients with low doses of hydrocortisone did not have a lower rate of mortality after 21 days of treatment, and were more likely to require high-flow oxygen therapy or undergo mechanical ventilation for survival [63]. Unfortunately, these three studies were then proven to be underpowered due to the small sample size and were then terminated following the publication of RECOVERY report. GLUCOCOVID trial evaluated the effect of methylprednisolone in COVID-19 patients and showed that patients on methylprednisolone were not significantly impacted when analyzed through intention-to-treat analysis. In contrast, when analyzed by per-protocol analysis, methylprednisolone demonstrated beneficial effect. As the GLUCOCOVID trial was also underpowered, the results should be interpreted with caution [64].

The evidence from clinical trials alluded that corticosteroid therapy can provide beneficial outcome to moderate or severe-critical COVID-19 patients as the findings from clinical trials demonstrated superiority of corticosteroid therapy in primary clinical outcomes when compared to the standard therapy. Dexamethasone is identified to be one of the few therapies that reduce the mortality among hospitalized patients with COVID-19. The stage of disease at the time of treatment is crucial in determining the success of corticosteroid treatment in COVID-19 patients. Corticosteroid has modest efficacy during the hyperinflammatory stage of COVID-19 as it can reduce the C-reactive protein (CRP) levels and has a superior clinical outcome in patients with elevated CRP levels at baseline [65]. For now, there is still limited data available to comment on the efficacy of corticosteroid treatment in the early phase of the disease and therefore ongoing clinical trials are still needed to provide evidence regarding the clinical benefit of steroids in this phase. However, the use of corticosteroids, at a higher dose for long term is often followed with a subsequent risk of side effects.

## 1.11. Ivermectin

Ivermectin was a well-known anti-helminthic drug used in veterinary medicine in the late 1970s that could stimulate GABA-gated-Cl<sup>-</sup> channels, causing hyperpolarization and paralysis of parasitic organisms. Another mechanism considered to have the same effect is immune regulation of host response. This is achieved through neutrophil activation and elevated levels of interleukin-6 and C-reactive protein. Ivermectin has been reported to act against Chikungunya virus and some flaviviruses (dengue fever and tick-borne encephalitis virus) in *in vitro* studies [66]. The publication of ivermectin in eradicating SARS-CoV-2 *in vitro* has been highlighted. It is hypothesized that inhibiting importin protein  $\alpha/\beta$  1, which mediates viral protein transport inside and outside the nucleus, contributes to its effect against SARS-CoV-2. [66]. Importins are one of the karyopherins (i.e., nuclear transporters) involved in the nucleocytoplasmic transport of various substrates.

In a randomized controlled trial, both ivermectin group and placebo group did not exhibit significant differences in their clinical outcome [67]. Albeit not significant, there was a reduction in duration of hospital stay in ivermectin-treated group. The lack of significant association may be brought by the low dosage of ivermectin used in the clinical trial. A pilot trial conducted by Pott-Junior *et al.* suggested that a larger dose of ivermectin is required to reduce SARS-CoV-2 viral load and improve clinical symptoms in COVID-19 patients [68]. However, larger follow-up studies are required to further validate the use of ivermectin. Based on WHO therapeutics and COVID-19 living guideline, ivermectin is not recommended in patients with COVID-19, except in the context of clinical trial [60]. Indeed, the potential toxic effects of ivermectin, including severe episodes of confusion, ataxia, seizures, and hypotension should be a concern [69].

## 1.12. Potential new drug for treatment of COVID-19

### 1.12.1. Bamlanivimab and etesevimab

Bamlanivimab (ly3819253 or ly-cov555) and etesevimab (ly3832479 or ly-cov016) are effective neutralizing monoclonal antibodies against the spike protein of SARS-CoV-2, which aim to prevent the virus from attaching and entering human cells. These antibodies were recovered from 2 independent COVID-19 patients in North America and China, respectively. The FDA has issued an EUA for the use of bamlanivimab and etesevimab in combination for the treatment of mild-to-moderate COVID-19 and

postexposure prophylaxis (prevention) in adults and pediatric patients [70]. In pre-clinical experiments, etesevimab binds to different epitopes from bamlanivimab, and neutralizes drug-resistant variants through bamlanivimab bound epitope mutations. The monotherapy of bamlanivimab was found to reduce the COVID-19 infection incidence, hospitalization, and death among individuals with elevated risk of SARS-CoV-2 exposure [71]. However, among mild to moderate COVID-19 patients, the combination of the two neutralizing monoclonal antibodies enhances the reduction of viral load and reduces the drug resistance variation in treatment, but no reduction in viral load was observed for bamlanivimab monotherapy [72]. In addition, among high-risk ambulatory patients, the combination therapy of etesevimab and bamlanivimab resulted in lower incidence of hospitalization and death with greater reduction of SARS-CoV-2 viral load [73].

### 1.12.2. Imdevimab/Casirivimab

Casirivimab (previously REGN10933) and imdevimab (previously REGN10987) are recombinant human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2, which eventually block the viral attachment and entry into the human cells [74].

The investigational antibody cocktail of casirivimab and imdevimab had significantly reduced the viral loads among non-hospitalized COVID-19 patients particularly in those whose immune response had not yet been initiated or those with a high-viral load at baseline when compared to placebo [75]. Initial data from phase II of this study also indicated that casirivimab and imdevimab decreased the medically attended visits in non-hospitalized COVID-19 patients. Another trial which enrolled subjects who had household contact with infected individuals revealed that administration of subcutaneous casirivimab and imdevimab were shown to prevent the symptomatic SARS-CoV-2 infection and overall infections, either symptomatic or asymptomatic among the exposed subjects [76]. This anti-SARS-CoV-2 monoclonal antibody combination: casirivimab plus imdevimab has been granted the EUA by FDA for treatment of mild-to-moderate COVID-19 patients and postexposure prophylaxis treatment for COVID-19 [77]. In addition, the RECOVERY trial found that the treatment of casirivimab and imdevimab improved the survival of hospitalized COVID-19 patients who lacked the anti-SARS-CoV-2 antibodies at baseline, compared to the usual care [78].

Up to date, there is still limited information known about the safety and effectiveness of casirivimab and imdevimab in treating patients with COVID-19 or preventing COVID-19 in people who are at high risk of being exposed to someone who is infected with

SARS-CoV-2. Hence, more clinical trials need to be conducted to address the clinical efficacy and possible risks of this combination.

### 1.12.3. Cepharanthine

Cepharanthine is an alkaloid extracted from *Stephania cepharantha* Hayata, which is a Chinese medicinal plant. It has been used in Japan since 1951 for the treatment of various conditions, including leukopenia, exudative middle-ear catarrh, alopecia areata, and viper bite. It is also reported to have a unique antiviral property against various viruses, such as HCoV-OC43, HIV, and SARS-CoV. Additionally, it was shown to have other properties, such as anti-oxidative, anti-inflammatory, and anti-parasitic effects [79]. Its mechanism of action remains unclear, but its activity is postulated to be associated with inhibition of nuclear factor-kappa B activation, lipid peroxidation, nitric oxide production, cytokine production, and expression of cyclooxygenase [79]. These components are key mediators in viral replication and inflammatory responses. Therefore, cepharanthine has become a drug of interest for many researchers as a potential treatment for COVID-19.

Ohashi and colleagues reported that the combination of cepharanthine and nelfinavir (a HIV protease inhibitor) exhibited synergistic effect to limit SARS-CoV-2 proliferation *in vitro* [80]. This synergistic effect was postulated to be contributed by their different mode of actions where nelfinavir was identified as a replication inhibitor which inhibits the main viral protease while cepharanthine inhibited viral entry by blocking the ability of the virus to attach to its target cell. Monotherapy with either nelfinavir or cepharanthine decreased viral RNA load to 5.8% or 6.3% respectively; however, combination therapy significantly diminished the viral RNA load to 0.068% [80].

Cepharanthine possessed potent antiviral activity at low IC<sub>50</sub> (0.73 µmol/L) and CC<sub>50</sub> (39.30 µmol/L) [81, 82]. It was previously reported to have inhibitory effects on both SARS-CoV and HCoV-OC43. Furthermore, there was a significant reduction in viral RNA yield during entry, post-entry and full-time assays by 2.17-fold, 1618-fold, and 12459-fold respectively, in comparison to negative control group [81]. Therefore, the data suggested that cepharanthine can inhibit SARS-CoV-2 infection at entry and post-entry phases. The evidence of anti-SARS-CoV-2 activity of cepharanthine was further supported by Jeon *et al.* using human lung cells (Calu-3 cells) which were more appropriate compared to Vero cells [83].

On the other hand, Ruan and colleagues proposed that the antiviral activity of cepharanthine was due to its interaction with NSP [84]. Cepharanthine was able to block both NSP12-NSP7 interface and NSP12-NSP8 interface of SARS-CoV-2, and NSP12-NSP8

interface of SARS-CoV through Van der Waals forces and hydrogen bonds involving ARG-215 [84]. The NSP12 subunit is the architecture of the viral RdRp [85]. Thus, inhibition of NSP12-NSP7-NSP8 complex by cepharanthine could prevent SARS-CoV-2 from replication and protein synthesis.

Based on the evidence from *in vitro* studies, cepharanthine is proven to have antiviral and inhibitory effects against the virus. Therefore, it could be one of the potential drug candidates to combat COVID-19 infection.

#### 1.12.4. Sotrovimab

The emerging SARS-CoV-2 variants such as B.1.351 lineage have resistance toward antibody neutralization [86]. This growing concern has fueled the need for effective therapeutics as evolution of the virus takes place. One of the plausible solutions is by using a monoclonal antibody targeting a fixed epitope which lies outside the evolving receptor-binding motif. Sotrovimab is an investigational human engineered monoclonal antibody IgG1k. It was granted EUA by FDA for the treatment of mild to moderate symptoms of COVID-19 on May 26, 2021 [87]. It has been proposed that its mechanism in preventing the entry of viruses into human cells is by binding to the conserved epitope on the spike protein of COVID-19 [88]. Sotrovimab consists of two amino acid Fc modifications which enhances its bioavailability in respiratory mucosa and improve its therapeutic duration with longer overall half-life [87].

According to the findings from clinical trial, patients who received sotrovimab had an 85% reduction in incidence of hospitalization over 24 h, or death [9]. In terms of the safety profile of sotrovimab, 17% patients who received sotrovimab and 19% individuals who received placebo had experienced adverse effects. Additionally, there were noticeably lower number of grade 3 or 4 adverse events reported in the sotrovimab group [9]. Current findings from clinical trials supported the fact that sotrovimab could prevent further advancement of COVID-19 in high-risk patients. Therefore, it is indeed one of the potential drugs of choice in managing COVID-19.

#### 1.12.5. XAV-19

XAV-19 is a glycol-humanized polyclonal antibody (GH-pAb) developed by Xenothera, a biotechnology company in France. The XAV-19 possesses a neutralizing action against the SARS-CoV-2, thus blocking the interaction between the spike S1 molecules and



ACE-2 molecules found in the respiratory tract. Phase 2 and Phase 3 clinical trials of this drug are currently in progress [88].

The XAV-19 is derived from genetically engineered pigs, which are also known as double-knocked out (DKO) pigs. This procedure is necessary to eliminate two enzymes: cytidine monophosphate-N-acetylneuraminic acid hydroxylase (CMAH), and  $\alpha$ 1,3-galactosyltransferase enzyme (GGTA1), which are responsible for the synthesis of N-glycolyl form of the neuraminic acid (Neu5Gc) and Gal alpha 1,3-galactose ( $\alpha$ -Gal) epitopes. Besides, the antibodies of pigs, whether normal or DKO, are incapable of interacting with the human Fc $\gamma$  receptor. In contrast, several experiments have demonstrated that the antibodies of other animals, such as rabbits, horses, and goats, exhibit interaction with at least one of the Fc receptors [88]. These two unique traits are beneficial as they prevent serum sickness disease and antibody-dependent enhancement (ADE), which is an event where interaction between virus and immunoglobulins promotes the viral entry into cells, leading to replication of the virus [88, 89]. A plaque reduction neutralization test (PRNT) and cytopathogenic effect (CPE) assay were used to investigate the neutralizing effect of XAV-19. The results of PRNT presented an end titer of greater than 12.5 folds as recommended by the European Commission, while the results of the CPE assay presented an end titer of more than 15 folds as compared to COVID-19 convalescent plasma [88]. These indicate that the swine serum contains a high concentration of SARS-CoV-2 antibody. Another study was carried out using CPE assay to investigate the efficacy of XAV-19 against Alpha and Beta variants by isolating live viruses from COVID-19 patients. Bamlanivimab was used as a comparator due to its evidence of protection against serious COVID-19. When the concentration was increased to higher than 5  $\mu$ g/mL, XAV-19 demonstrated 100% effectiveness against the original Wuhan strain, Alpha strain, and Beta strain. In contrast, bamlanivimab, although possessing a higher potency against the original Wuhan strain and Alpha variant as compared to XAV-19, does not show any effect against the Beta variant at any concentrations [90].

A double-blinded randomized controlled trial was conducted on 18 hospitalized COVID-19 patients suffering from moderate pneumonia to study the safety and pharmacokinetics profile of XAV-19 [91]. The recruited subjects exhibited clinical improvement and were discharged from the hospital, except for 1 patient who passed away due to comorbidities. The analysis of quantitative viral load by comparing treatment group and placebo group also presented evidence of faster SARS-CoV-2 viral clearance with the treatment of XAV-19. As for the adverse events, there were no occurrences of severe adverse events associated with XAV-19, and no notable differences in adverse events

were observed between the placebo and study drug. In addition, no allergic reactions were reported, and treatment was not discontinued [91]. This indicates that the drug was safe among COVID-19 patients. Nevertheless, this trial only involved a small sample size for the adverse effects to be significant.

In short, XAV-19 displayed a complete neutralizing effect through *in vitro* studies. However, further studies are required to be conducted in a greater sample size to validate the efficacy and safety of XAV-19.

## 2. Conclusion

COVID-19 has affected millions of people around the world and thus designing a novel specific drug to effectively treat COVID-19 is of utmost importance. Although vaccination is considered as one of the most effective ways to decrease the COVID-19 transmission, there is still a need for effective treatment. However, the traditional drug discovery and development involves long, complex, and expensive process which may not be possible during an ongoing pandemic. Therefore, drug repurposing may offer an alternative route toward discovering effective treatments for COVID-19 based on existing FDA-approved drugs. Some of the drugs which have the potential to be repurposed include antiviral drugs, antimalarial drugs, and monoclonal antibodies. The antiviral drug, remdesivir is the first FDA-approved drug to treat COVID-19 in adults and pediatric patients of 12 years of age and older. However, with the recent findings from Solidarity trial, the use of this drug may need to be reviewed again. On the other hand, there are drugs listed in FDA EUA for the treatment of COVID-19, including casirivimab and imdevimab, baricitinib (in combination with remdesivir), and bamlanivimab. Recently, tocilizumab, the IL-6 inhibitor, is also authorized for emergency use under an EUA for the treatment of COVID-19 in hospitalized COVID-19 patients. In this review, several drugs with the potential to be repurposed have been highlighted. Given the urgency for potent therapies for the treatment and prophylaxis of COVID-19, more studies are warranted to validate the findings to immediately translate them into clinical settings.

## Acknowledgements

The authors are thankful to Taylor's University, Malaysia for the support.

## Ethical Considerations

Not applicable.

## Competing Interests

The authors declare that they have no conflict of interest regarding this paper.

## Availability of Data and Material

Not applicable.

## Funding

The authors would like to acknowledge the Malaysia Ministry of Higher Education (MOHE) for the funding support under the Fundamental Research Grant Scheme (FRGS/1/2019/SKK09/TAYLOR/03/1).

## Authors' Contribution

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. FJB, SH, RS and YHY developed the concept and idea to conduct this review. CSM, KSY, LJQ, GPW, HKRS, and TTZZ performed the literature search and organized the finding under supervision of FJB, SH, RS, and YHY. The manuscript was written by CSM, KSY, LJQ, GPW, HKRS and reviewed by FJB, SH, RS, and YHY. CSM, FJB, SH, RS, and YHY critically revised the manuscript. All authors read and approved the manuscript.

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