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Coronavirus Disease 2019 (COVID-19): Origin, Impact, and Drug Development

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Abstract

At the end of December 2019, in Wuhan, China, a rapidly spreading unknown virus was reported to have caused coronavirus disease of 2019 (COVID-19). Origin linked to Wuhan's wholesale food market where live animals are sold. This disease is caused by SARS Coronavirus-2 (SARS-CoV-2), which is closely related to the Severe Acute Respiratory Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). This virus shares a high sequence identity with bat-derived SARS-like Coronavirus, which indicating its zoonotic origin. The virus spread globally, provoking widespread attention and panic. This Coronavirus is highly pathogenic and causes mild to severe respiratory disorders. Later, it was declared a global pandemic by the World Health Organization (WHO) due to its highly infectious nature and worldwide mortality rate. This virus is a single-stranded, positive-sense RNA genome, and its genome length about 26 to 32 kb that infects a broad range of vertebrates. The researchers worldwide focus on establishing treatment strategies on drug and vaccine development to prevent this COVID-19 pandemic. A drug repurposing approach has been used to identify a rapid treatment for the people affected by COVID-19, which could be cost-effective and bypass some Food and Drug Association (FDA) regulations to move quickly in phase-3 trials. However, there is no promising therapeutic option available yet. This book chapter addresses current information about the COVID-19 disease, including its origins, impacts, and the novel potential drug candidates that can help treat the COVID-19.

Keywords: COVID-19, Zoonotic virus, SARS-CoV-2, Epidemiology, Drug discovery, Therapeutics

1. Introduction

Nowadays, there is growing concern and perceived threat due to the outbreak of the novel coronavirus disease, COVID-19, as named by the World Health Organization (WHO), which poses a peril of pandemic to the global public health. The epicenter of the novel Coronavirus was located in Wuhan province of China, where the outbreak originated in December 2019 due to Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) [1]. This disease has spread to 220 countries, with over 158 million confirmed coronavirus cases of 3.3 million confirmed

deaths with 136 million recoveries worldwide as of May 10, 2021 [2]. Also, millions of people's lives have been affected as mandatory isolations/quarantines instructed. The adverse effect of the COVID-19 outbreak could bring significant challenges to the health system globally and could have far-reaching consequences on the global economy if the virus's spread is not effectively curtailed [3, 4].

Coronaviruses (CoVs) are encapsulated within a membrane envelope containing a single-stranded positive-sense RNA genome. Spikes of glycoprotein that give coronaviruses their crown-like appearance are studded with the viral membrane. Coronaviruses infect humans as well as animals such as bats that host the widest range of coronaviruses [5]. There are four types of alpha, beta, gamma, and delta-designated coronaviruses. Extreme acute respiratory syndrome virus (SARS-CoV), Middle East respiratory syndrome (MERS-CoV), and SARS-CoV-2 are included in the beta coronavirus class [6, 7]. SARS-CoV-2 targets the lower respiratory system to induce viral pneumonia, similar to SARS-CoV and MERS-CoV, but may also affect the heart, kidney, liver, and central nervous system, resulting in multiple organ failure [8]. New evidence suggests that SARS-CoV-2 is more contagious/transmissible than SARS-CoV and MERS-CoV [9]. Glycosylated spike (S) protein acts as a significant inducer of host immune responses, which mediates both SARS-CoV and SARS-CoV-2 host cell invasion by binding with angiotensin-converting enzyme 2 (ACE2) located on the host cells of the surface membrane [1].

With the onset of the second wave of COVID-19 infection, developing countries like India seem to be reeling in the most catastrophic damages. Since late March of 2021, the emergence of COVID-19 infected patients has skyrocketed to more than 22 million people and have touched a record number of 4000 deaths per day in the first week of May 2021. The outbreak has left the country struggling hard to cope with the healthcare needs of patients. This silent killer disease creates havoc on earth, yet the upcoming course of this virus is unpredictable. Therefore, necessary measures are needed to control and eradicate this alarming problem to save the people's precious life and the country's economy [4, 10]. However, significant steps have been taken by the government of different countries. Many countries such as Italy, Germany, and India have "lockdown" the whole country to break the chain by quarantine and confinement of people to the homes. To date, there is no clinically approved antiviral drug or vaccine available to be used against COVID-19; therefore, it has posed a public health emergency and a global threat to the entire world. Repurposing existing medications is an affordable and effective therapeutic technique. The scientific community reacted quickly with a suggested list of current drugs with therapeutic potential for COVID-19, based on genomic sequence knowledge. This chapter examines the source of infection, the SARS-CoV-2 transmission pathway, and the medications currently being clinically tested for COVID-19 management to include references for follow-up research, prevention, and treatment that may help readers gain the latest understanding of this emerging infectious disease.

2. History

The first case of Coronavirus infection was detected in 1960. Twice in the past two decades, history has seen incidences where β -coronavirus has cross over from animal to humans in severe infectious diseases. Till 2003, coronavirus infection was considered to be a non-fatal disease. However, with many mortally affecting cases of severe acute respiratory syndrome cropping up in Hong Kong, the United States of America, Vietnam, Taiwan, and Thailand culminated in the deciphering of the deadly pathogenesis of this disease and led to the declaration of disease as a state emergency by World health organization (WHO) in 2004 [10–13]. In 2012, almost a decade later,

the Middle East respiratory syndrome coronavirus, also known as MERS-CoV, arose in Saudi Arabia, killing 858 and affecting 2494 people. This virus also originated from bats, and dromedary camels were possibly its intermediate host [14].

3. Origin and prevalence of COVID-19

It all started in the Hubei province's capital city, Wuhan, in December 2019, when several adults with severe pneumonia were admitted to the nearby hospitals. The surveillance team was triggered and collected the samples of respiratory patients for the etiologic study. It was investigated that numerous patients had contact with the Huanan wholesale seafood, where dead and live animals were sold and traded. At the end of December 2019, China declared the outbreak of this disease to the WHO. This virus had more than 95% homology with bat coronavirus (SARS-like bat CoVs) and more than 70% resemblance with SARS-CoV, and hence the virus was recognized as Coronavirus on January 7, 2020. The environmental samples obtained from the Huanan seafood market were also tested positive, which indicated that the virus took origin from the Huanan seafood market [15]. Though the Coronavirus originated from bats, the existing possibility of an intermediary animal that gets transferred to humans may be snakes or pangolins. Xu. Et al. have isolated SARS-CoV-2 from pangolin and found pangolin to be the potential intermediate host of the SARS-CoV-2 as it shows high similarity (99%) between the coronaviruses affecting the humans [16]. However, these current results are not sufficient to prove the potential host and intermediate of COVID-19. **Figure 1** shows a schematic view of crucial reservoirs and the mode of transmission of COVID-19.

According to Wu, JT, Leung et al. of York University, the estimated Basic Reproduction Number (R_0), which means the average amount of secondary infection that patients may develop without intervention in a completely susceptible population, varies with several research groups [17]. Utilizing the Susceptible-Exposed-Infectious-Recovered (SEIR) model and Incidence Decay with Exponential Adjustment (IDEA) model, the estimated R_0 value of novel COVID-19 was found to be 2.47–2.86 [18] and 2.0–3.3 [19] respectively, which is higher than other viruses of β -coronaviruses such as MERS-CoV (2.0–6.7) [20] and SARS-CoV (2.2–3.6) [21]. This elevated value of R_0 points towards the fact that COVID-19 has a comparatively high transmission rate. It is also indicated from the overall case-fatality rate (CFR) that elderly male citizens are more prone to this Coronavirus, especially those with chronic health issues (heart disease, diabetes, hypertension) than other groups of the viruses. Thus, SARS-CoV-2 shows a high prevalence, and the population is easily susceptible to this virus. Among the RNA viruses, Coronavirus contains the most extensive genome sequence of about 26 to 32 Kilobases with 14 Open Reading Frames (ORFs). These ORFs code for 27 structural and non-structural proteins of the virus [22, 23]. Spike protein, membrane protein, envelope, and nucleocapsid, along with eight accessory proteins, lie in the 3' end of the SARS-CoV-2 genome. A very high sequence resemblance is shared between structural proteins of SARS-CoV-2 and its predecessor human coronaviruses (hCoVs) (82%) (except in the 8a, 8b, and 3b accessory protein); suggests common molecular pathophysiology and pathogenesis among COVID-19, SARS, and MERS [24]. Genomic analysis has surmised the relevance of the Sans N gene in coronaviruses. Positive selection, mutation, and adaptation affect the pathogenicity and stability of the virus and might play an essential role in widespread infection in a large population [25]. This also poses a threat to the generation of newer strains of the virus that may result from mutation and adaptation, making the threat of transmission even more potent [26].

Figure 1.
Schematic view of the critical reservoirs and mode of transmission of coronaviruses.

4. Drug repurposing

Drug repurposing is an old weapon in the arsenal for new drug development strategies. This approach identifies new therapeutic indications for available marketed drugs making it time-efficient in a cost-effective manner [27, 28]. It has been assumed that about 75% of existing drugs could be repurposed for various diseases [29]. Global pandemic like novel coronavirus disease 2019 (COVID-19) has an urgent need to select appropriate therapeutic options with limited time to discover the new drug candidates [30]. It takes 10–15 years to develop a new drug, and the actual cost would be more than a billion dollars, with only 2.01% of its success rate

[31, 32]. Existing drug compounds, including Raltegravir, Paritaprevir, Bictegravir, and Dolutegravir, identify promising inhibitors against 3C-like protease 2'-O-ribose methyltransferase from COVID-19 is cost-effective and a drug repurposing approach [33, 34]. A recent in-silico study suggested that natural compounds like guggulsterone and drug rifampicin can be repurposed for COVID-19, insights from the molecular docking analysis [35, 36]. Thus, the concept of drug repurposing could be utilized as a novel drug discovery process to discover an effective therapeutic option against COVID-19. Recent examples of drug repurposing against COVID-19 are given in **Table 1**.

Based on previous experiences in the treatment of previous coronavirus diseases like SARS-CoV and MERS-CoV, drugs currently being implemented in the management of this disease are entry or inhibitors of SARS-CoV-2, RNA mutagens that stop replication, host inflammatory response inhibitors, viral protease inhibitors, monoclonal antibodies (mAbs), and convalescent plasma-based immunogenicity, blockers of the release of mature virion and glucocorticoids based cell tissue and organ injury management apart from necessary ventilation for support [54]. It is an urgent need to perform more prospective, rigorous population studies and further preclinical and clinical trials to gain a perspective on the safety and therapeutic effect of new and potential therapeutic agents that may help contain the spread and enhance recovery from SARS-CoV-2 infection.

S.No.	Drug name	Primary use	Description	Ref.
1.	Remdesivir	Ebola Virus Disease	Viral RNA polymerase inhibitor	[37, 38]
2.	Chloroquine & Hydroxychloroquine	Malaria	Antimalarial; interferent with protein post-translational processes; Mitogen-activated protein kinase (MAPK) inhibitor; pro-inflammatory cytokines inhibitor	[39–41]
3.	Arbidol and Oseltamivir	Treatment of influenza virus infections	Blocks virus entry into the cell	[40, 42–45]
4.	Danoprevir	Hepatitis C virus (HCV)	Nonstructural protein 3 (NSP3) inhibitor	[46]
5.	Xiyanping	Antibacterial and antiviral	Blocks virus entry into the cell	[47]
6.	Darunavir	HIV protease inhibitor	Using among the COVID-19 pneumonia patients	[48]
7.	Thalidomide	Anti-inflammatory action	Reduce tumor necrosis factor- α (TNF α), increase interleukins secretion, and activate natural killer cells	[49, 50]
8.	Methylprednisolone	Corticosteroid therapy	Prolongs the survival time among the severe stage COVID-19 patients	[51, 52]
9.	Lopinavir-Ritonavir	HIV treatment	Viral Protease inhibitors	[40, 43]
10.	Ribavirin	Viral RNA synthesis inhibitor	Viral RNA-dependent RNA polymerase (RdRp) inhibitor	[53]

Table 1.
Recent examples of drug repurposing against COVID-19.

5. Drugs under clinical trials for COVID-19

As the epidemic spreads more and more, scientists worldwide are in a quest to explore drugs that may be potentially effective in combating COVID-19. During a pandemic that causes morbidity and mortality to grow exponentially, well-structured, randomized, controlled trials are necessary to evaluate new or repurposed drugs' safety and efficacy to protect the community from ineffective, unnecessary, or unsafe drugs [55]. World Health Organization and partners have launched an international clinical trial – Solidarity trial, to assist in the accelerated search for a therapeutic regimen for COVID-19. Solidarity trial is one of the most extensive international randomized trials for COVID-19 to evaluate drugs on three essential outcomes that were needed for assisted ventilation, mortality, and duration of hospital stay. Solidarity Trial also aims to assess the chances of drugs improving survival or reducing the need for ventilation or hospital stay duration [56]. Currently, repurposed antiviral therapies are under significant scrutiny in clinical trials as disease-specific and designated antiviral therapy may have a maximum impact on disease progression and optimized treatment of COVID-19 [57].

5.1 RNA mutagens

RNA and DNA viruses encode RNA-dependent RNA polymerase (RdRp) core, which is requisite for RdRp catalytic function and viral replication. Hence, it is one of the prime targets for intervention infection. RdRp facilitates the elongation of the RNA strand and genome replication [7, 58]. RNA mutagens are nucleotide analogs that halt RNA elongation by RdRp by inserting themselves into the RNA chain. RdRp has no host cell homolog making this antiviral drug development superior as it reduces the risk of affecting human cells or protein. Thus, mutagenic nucleoside analog inhibitors like remdesivir, favipiravir, and ribavirin targeting RdRp are explored for their function to block viral RNA synthesis against human coronaviruses [7].

Remdesivir is a known antiviral against SARS-CoV and the MERS-CoV and has been a drug choice for SARS-CoV-2 due to its proven activity to inhibit SARS-CoV-2 in vitro [59]. A randomized, placebo-controlled, double-blind trial of intravenous remdesivir in hospitalized adults suffering from lower respiratory tract infection due to COVID-19 shows an average recovery day of 14 days and clinical improvement at day 15, emphasizing that remdesivir abbreviate time to recovery among COVID-19 patients. The trial also suggested that a remdesivir treatment regimen may prevent disease progression to more severity and a lower incidence of respiratory support requirement [60]. Another randomized, open-label trial among patients with severe COVID-19 who required oxygen support showed recovery among patients with both 5- and 10-day courses of remdesivir [61]. In another randomized phase 3 clinical trial, compared to standard of care treatment, the period of 5 days of remdesivir had significant improvement in patient's clinical status [62]. Prompted by such conclusive evidence, the US Food and Drug Administration has granted remdesivir a status of Emergency Use Authorization for SARS-CoV-2 infected patients of about 12 years of age and with pneumonia [57].

Favipiravir is a broad-spectrum oral RNA-dependent RNA polymerase (RdRp) currently under study in numerous clinical and preclinical trials for its role in inhibiting the viral replication phase of SARS-CoV-2. Glenmark Pharmaceuticals evaluates Favipiravir in Phase 3 clinical trial for COVID-19 among mild to moderately infected patients of COVID-19 and has observed a marked 40% faster recovery of patients by day 4 [63].

In another prospective, randomized, controlled, open-label multicentered trial involving adult patients with COVID-19 in china, Favipiravir, compared to Arbidol, significantly improved the viral clearance, relief for pyrexia and cough with mild and manageable adverse effects [64]. Such promising results have cast the attention of healthcare providers to use RNA mutagens in treatments for SARS-CoV-2 infection [65].

5.2 Protease inhibitors

Lopinavir/Ritonavir is a combination therapy used as a potent inhibitor of the human immunodeficiency virus protease. Lopinavir is a protease inhibitor that inhibits the protease enzyme necessary for the virus to catalyze the cleavage of polyprotein essential for completing the viral infectious cycle. In contrast, ritonavir is used in combination with Lopinavir to inhibit cytochrome P450 and increase its half-life for a longer duration of action [66]. Lopinavir/ritonavir was also employed in the treatment of MERS. In vitro experiments have shown lopinavir/ritonavir potential in limiting replication of Coronavirus. 400 mg Lopinavir with 50 mg Ritonavir (Kaletra) is an efficacious oral anti-HIV drug [67]. A study on SARS-CoV demonstrates the inhibitory activity of Lopinavir (4 µg/mL) in plaque reduction assay.

In contrast, combination therapy of Lopinavir (400 mg) and Ritonavir (100 mg) two times a day for 14 days in SARS-CoV infected patients exhibited lessening of viral load in patients [68]. Subsequently, a randomized control trial known as the MIRACLE trial (MERS-CoV Infection Treated With A Combination of Lopinavir/Ritonavir and Interferon Beta-1b) was started to establish the therapeutic efficacy of combination therapy of interferon β -1b along with lopinavir/ritonavir among MERS-CoV infected patients [69]. Whereas in a retrospective case-control study, treatment by a combination of Lopinavir/Ritonavir (LPV/r) and Ribavirin yielded depreciated Acute Respiratory Distress Syndrome (ARDS) as well as mortality in SARS patients [70].

Darunavir (DRV), another protease inhibitor that shares a similar mechanism for inhibiting HIV replication, like Lopinavir, is in phase III studies. In combination with Cobicistat, Darunavir showed better efficacy and tolerability among Covid-19 patients with less diarrhea and dyslipidemia and fewer adverse reaction compared with LPV/r [71].

5.3 Virus entry and fusion blockers

S proteins of Coronavirus interact with angiotensin-converting enzyme 2 (ACE2) to initiate entry into the host cell, and hence ACE2 is a critical molecular target for drugs aiming to inhibit cellular access of SARS-CoV-2 [72]. Several drugs have been known to inhibit ACE2, and they are under significant scrutiny for clinical studies.

Chloroquine and Hydroxychloroquine are the drugs from natural sources being employed as the first line of drugs, potential broad-spectrum antiviral drugs. Both are also being used to treat infection by SARS-CoV [73–75]. In Simian Vero cells, both chloroquine phosphate and Hydroxychloroquine have shown inhibition of replication of SARS-CoV-2, and in a physiologically-based pharmacokinetic model, 400 mg twice daily was established as the necessary dose [76, 77]. A pilot trial in about ten hospitals from Wuhan, Guangzhou, Jinzhou, Shanghai, Beijing, Chongqing, and Ningbo emphasizes Chloroquine phosphate's superior ability to inhibit pneumonia, reduce viral load, and improving pulmonary findings, and reducing the duration of COVID-19 disease [77]. An open-label non-randomized

clinical trial demonstrated that in 57% of patients, COVID-19 patients who underwent treatment with a daily dose of 600 mg Hydroxychloroquine for six days showed virological clearance. In contrast, in another randomized clinical trial in Wuhan, sixty-two COVID-19 patients showed improvement in 5 days of treatment by a daily dose of 400 mg hydroxychloroquine [39, 78]. This confirmation from the above smaller studies has propelled many prospective studies to investigate Chloroquine and Hydroxychloroquine efficiency in patients of SARS-CoV-2 infection [79, 80].

Umifenovir (Arbidol) is a drug that blocks virus entry inside the host cell by inhibiting endocytosis. It halts viral membrane from fusing into the host cell and subsequent viral entry and has been used in prophylaxis of influenza A and B viruses and inhibits numerous viruses, including Ebola virus, Hepatitis C virus, Lassa virus making it a critical antiviral [81–83]. Arbidol has been tested for its efficiency against COVID-19 conducted in Wuhan, China, where patients receiving 400 mg Umifenovir showed reduced viral load and decreased mortality [84]. A retrospective cohort study among Umifenovir-treated patients showed malicious SARS–COV-2 detection by RT-PCR was, and 69% of patients had improved chest computed tomography scans [85]. These promising results have led to the clinical trial investigation of Umifenovir to be recently initiated [85–88].

Immunotherapy has proven to be effective against infectious diseases such as influenza, SARS, MERS, and Ebola, using monoclonal antibodies (mAbs) to mitigate contagious diseases [89]. Monoclonal antibodies bind to a specific target in the body, enabling it to mimic, block, or cause changes and provide a therapeutic effect for the particular diseases [90]. SARS-CoV-2 and SARS-CoV show many similarities among them, and this suggests the use of SARS antiviral monoclonal antibodies that can identify Receptor Binding Domain (RBD) in subunit S1 in SARS-CoV-2. mAbs can block RBD interaction and its ACE2 receptor, making it anti-spike protein therapy [91, 92]. A cocktail of monoclonal antibodies that can target S-proteins in SARS-CoV and detect different epitopes can potentially destroy viral cells. For example, a cocktail of monoclonal antibodies (MAB)- CR3022 show CR3022, and CR3014 showed neutralization in laboratory setup [92, 93]. Combination of Casirivimab and Imdevimab, popularly known as REGN-COV2 is a monoclonal antibody that can bind to SARS-CoV-2 spike protein and prevent it from entering healthy cells and is under scrutiny for the same. LY3819253- a mAb isolated from a recovered COVID-19 patient, is also under evaluation that has been sponsored by Eli Lilly and Company of Indianapolis, Indiana [94].

5.4 Virus-release blockers

Oseltamivir, branded as Tamiflu, is Food and Drug Admission (FDA) approved drug that acts as a neuraminidase inhibitor and has since been used popularly in treating influenza A and B [95]. Oseltamivir is being tried as a first-line antiviral drug in symptomatic patients with COVID-19 posts its successful use in SARS-CoV in 2003. A study by Zhang et al. brings light to the fact that the active site of the Spike (S) 1 Protein of SARS shows a striking similarity to neuraminidase, making use of neuraminidase inhibitors useful to treat SARS-CoV [96]. Clinical trials are currently evaluating Oseltamivir in combination with favipiravir and Chloroquine in treating SARS-CoV-2 infection [97].

5.5 Non-virus-targeting treatments

Tocilizumab is a humanized mAb employed in Rheumatoid Arthritis treatment, and numerous studies have included tocilizumab for consideration as

anti-SARS-CoV-2 therapy. A larger multicentred clinical trial of tocilizumab has been launched in China and had about 500 patients treated already enrolled [98, 99]. Anakinra is an FDA-approved modified human IL-1 receptor antagonist (IL-1RA) for RA treatment, which blocks innate immune response associated with cytokine storm resultant inflammation [100, 101].

Dexamethasone is a glucocorticoid that curbs lung injury resultant from inflammation, respiratory failure, and death in ARDS by decreasing ventilator days and mortality. World Health Organization has put Dexamethasone on the list of essential medicines. National Institutes of Health has recommended glucocorticoids in patients hospitalized with Covid-19 in the United States [102]. Randomized Evaluation of COVID-19 Therapy (RECOVERY Trial) - a large human study was initiated in the United Kingdom by Oxford University in March 2020 to test the utility of several previously known drugs against the COVID-19 trial. The initial report announced that Dexamethasone at a dose of 6 mg once daily for up to 10 days could bring down mortality significantly in critically ill COVID-19 patients validating the use of Dexamethasone for COVID-19 patients [103]. In another recent trial, dexamethasone therapy given to patients showed 15% lower mortality in ARDS patients [104].

CD24Fc, also known as Cluster of differentiation 24, is a recombinant fusion protein and a biological immunomodulator comprising the Fc region of human Immunoglobulin G1 (IgG1) attached to the nonpolymorphic areas of CD24, making it an innate checkpoint against the inflammatory responses against tissue injuries associated with cytokine storm. The protection and biological activity of CD24Fc in suppressing the expression of multiple inflammatory cytokines have been demonstrated in preclinical and clinical studies carried out. A Phase II clinical trial in patients with leukemia indicates that three doses of CD24Fc effectively eliminated the appearance of extreme acute Graft vs. Host Diseases (GVHD) due to overreacting immune system and recipient target attacking transplanted T cells. CD24Fc may therefore be investigated as a prime candidate for non-antiviral COVID-19 therapy intervention for the control of cytokine storms in affected cells [105].

Dapagliflozin (Farxiga), a sodium-glucose co-transporter-2 (SGLT-2) inhibitor, has currently been assessed under “Dapagliflozin in Respiratory Failure in Patients with COVID-19” or DARE-19 in a phase-3 randomized trial designed to evaluate its efficacy as a treatment option for COVID-19 at risk of developing comorbidity such as organ failure [106]. SGLT-2 inhibitors play a role in instigating the renin-angiotensin-aldosterone pathway through the expression of angiotensin-converting enzyme type-2 (ACE2). Renin-angiotensin-aldosterone system (RAAS) pathway is essential in the pathophysiology of SARS-CoV-2. Organ-protective effects are provided by SGLT-2 inhibitors complementary to its glycaemic benefits and hence may afford additional vital organ protection to the patients [107, 108]. Patients in DARE-19 are to be treated with a daily dose of 10 mg Dapagliflozin once a day.

6. Future prospective

The evolution of Zoonotic Chinese Coronavirus SARS-CoV-2 needs to be better monitored through implementing better surveillance and precautionary steps. Due to this COVID-19 pandemic, scientists worldwide were encouraged to search for novel therapeutic options, including vaccines, drugs, and diagnostics. However, until now, there is no effective treatment approved and recommended for COVID-19 globally. Utilization of such computer-aided-drug design (CADD) and bioinformatics tools such as Immune Epitope Database (IEDB) software to predict a computational vaccine and target drug compounds for COVID-19 is

also encouraging [109]. In this way, drug repurposing emerged as a promising therapeutic approach in a time-saving and cost-effective manner. There are many drugs repurposed in the case of COVID-19 treatment. Drugs like Remdesivir, Dexamethasone, and a combination of Lopinavir-Ritonavir, reported positive outcomes to treat COVID-19.

Similarly, there are currently more than 100 vaccine candidates under development for the COVID-19, and it will likely be ready by early/late 2021. 38 Vaccines are in the first stage for the testing safety and dosage, 17 Vaccines are in their second phase and expanded safety trials, 12 Vaccines are in the third phase comes in large-scale efficacy tests, and 6 Vaccines approved for first or limited use. None of the vaccines are approved for full use. The safety issue is concerning and the most significant challenge when tested in diverse populations, especially in countries like India and China. Large-scale production, storage, and distribution of vaccines are also another challenge. However, further investigations and experiments are needed to discover an effective treatment option.

7. Conclusion

The Zoonotic Chinese Coronavirus SARS-CoV-2 outbreak likely started in the seafood market in Wuhan, China, where live animals are sold. The spread of this disease has been declared a global pandemic by WHO as it rapidly expanded worldwide and still infecting people exponentially. However, it is suggested that bats are the natural hosts for SARS-CoV-2. Bat-derived coronavirus identified from a sequence analysis shares 93.3% nucleotide identity with SARS-CoV-2 complete virus genome and 97.2% identity in the 1ab gene. However, the origins of the virus remain unclear. There is no effective therapeutic option available against human coronaviruses. This pandemic may get worsened soon if no effective therapeutics or vaccine is developed to combat COVID-19.

Nevertheless, researchers and scientists are searching for the vaccines or/and drugs used against this deadly virus. Different broad-spectrum medications, including repurposed antiviral drugs, either alone or in combinations, are evaluated for their efficacy to treat COVID-19 patients. Few drugs give positive results to block the COVID-19 infection, including Remdesivir, Oseltamivir, Lopinavir, and Ritonavir. A predictive analysis says that more such viral pandemic could emerge shortly and cause deadly outbreaks. Therefore, to prevent the emergence of a new viral pandemic, strategies should be developed to minimize its consequences.

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References

- [1] Jalandra, R., et al., Strategies and perspectives to develop SARS-CoV-2 detection methods and diagnostics. *Biomedicine & Pharmacotherapy* 2020; 110446.
- [2] Organization, W.H., Novel Coronavirus (2019-nCoV): situation report, 3. 2020.
- [3] of the International, C.S.G., The species Severe acute respiratory syndrome-related Coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nature Microbiology* 2020; 5(4) 536.
- [4] Kupferschmidt, K. and J. Cohen, *Will novel virus go pandemic or be contained?* 2020, American Association for the Advancement of Science.
- [5] Anthony, S.J., et al., Global patterns in coronavirus diversity. *Virus evolution* 2017; 3(1).
- [6] Chan, J.F.-W., et al., Interspecies transmission and emergence of novel viruses: lessons from bats and birds. *Trends in microbiology* 2013; 21(10) 544-555.
- [7] Zhu, N., et al., A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine* 2020.
- [8] Zhang, Y., et al., New understanding of the damage of SARS-CoV-2 infection outside the respiratory system. *Biomedicine & Pharmacotherapy* 2020; 110195.
- [9] Tang, B., et al., An updated estimation of the risk of transmission of the novel Coronavirus (2019-nCoV). *Infectious disease modelling* 2020; 5 248-255.
- [10] Tsang, T., et al., Update: outbreak of severe acute respiratory syndrome-worldwide, 2003. *MMWR: Morbidity & Mortality Weekly Report* 2003; 52(12) 241-241.
- [11] Update, W., 31-Coronavirus never before seen in humans is the cause of SARS. *Unprecedented Collaboration Identifies New Pathogen in Record Time* 2003; 16.
- [12] Organization, W.H., Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. http://www.who.int/csr/sars/country/table2004_04_21/en/index.html 2003.
- [13] Peiris, J., et al., Coronavirus as a possible cause of severe acute respiratory syndrome. *The Lancet* 2003; 361(9366) 1319-1325.
- [14] Memish, Z.A., et al., Middle East respiratory syndrome. *The Lancet* 2020.
- [15] Singhal, T., A review of coronavirus disease-2019 (COVID-19). *The Indian Journal of Pediatrics* 2020; 1-6.
- [16] Xu, X., et al., Evolution of the novel Coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Science China Life Sciences* 2020; 63(3) 457-460.
- [17] Remais, J., *Modelling environmentally-mediated infectious diseases of humans: transmission dynamics of schistosomiasis in China*, in *Modelling parasite transmission and control*. 2010, Springer. p. 79-98.
- [18] Wu, J.T., K. Leung, and G.M. Leung, Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *The Lancet* 2020; 395(10225) 689-697.

- [19] Majumder, M. and K.D. Mandl, Early transmissibility assessment of a novel coronavirus in Wuhan, China. China (January 23, 2020) 2020.
- [20] Lipsitch, M., et al., Transmission dynamics and control of severe acute respiratory syndrome. *Science* 2003; 300(5627) 1966-1970.
- [21] Majumder, M.S., et al., Estimation of MERS-coronavirus reproductive number and case fatality rate for the spring 2014 Saudi Arabia outbreak: insights from publicly available data. *PLoS currents* 2014; 6.
- [22] Wu, A., et al., Genome composition and divergence of the novel Coronavirus (2019-nCoV) originating in China. *Cell host & microbe* 2020.
- [23] Lu, R., et al., Genomic characterisation and epidemiology of 2019 novel Coronavirus: implications for virus origins and receptor binding. *The Lancet* 2020; 395(10224) 565-574.
- [24] Lau, Y.L. and J.M. Peiris, Pathogenesis of severe acute respiratory syndrome. *Current opinion in immunology* 2005; 17(4) 404-410.
- [25] Chen, N., et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet* 2020; 395(10223) 507-513.
- [26] Liu, S., et al., Genetic spectrum and distinct evolution patterns of SARS-CoV-2. *Frontiers in Microbiology* 2020; 11 2390.
- [27] Ahn, D.-G., et al., Current status of epidemiology, diagnosis, therapeutics, and vaccines for novel coronavirus disease 2019 (COVID-19). 2020.
- [28] Ke, Y.-Y., et al., Artificial intelligence approach fighting COVID-19 with repurposing drugs. *Biomedical Journal* 2020.
- [29] Huang, F., et al., Identification of amitriptyline HCl, flavin adenine dinucleotide, azacitidine and calcitriol as repurposing drugs for influenza A H5N1 virus-induced lung injury. *PLoS Pathogens* 2020; 16(3) e1008341.
- [30] Dyal, J., et al., Repurposing of clinically developed drugs for Treatment of Middle East respiratory syndrome coronavirus infection. *Antimicrobial agents and chemotherapy* 2014; 58(8) 4885-4893.
- [31] Wong, H.-H., et al., Examination of clinical trial costs and barriers for drug development final. 2014.
- [32] Yeu, Y., Y. Yoon, and S. Park, Protein localization vector propagation: a method for improving the accuracy of drug repositioning. *Molecular BioSystems* 2015; 11(7) 2096-2102.
- [33] Khan, R.J., et al., Targeting SARS-CoV-2: a systematic drug repurposing approach to identify promising inhibitors against 3C-like proteinase and 2'-O-ribose methyltransferase. *Journal of Biomolecular Structure and Dynamics* 2020; 1-14.
- [34] Harrison, C., Coronavirus puts drug repurposing on the fast track. *Nature biotechnology* 2020; 38(4) 379-381.
- [35] Mishra, A., et al., Natural compounds as potential inhibitors of novel coronavirus (COVID-19) main protease: An in silico study. 2020.
- [36] Pathak, Y., A. Mishra, and V. Tripathi, Rifampicin may be repurposed for COVID-19 Treatment: Insights from an in-silico study. 2020.
- [37] ClinicalTrials.gov. A Trial of Remdesivir in Adults With Severe COVID-19. ClinicalTrials.gov Identifier: NCT04257656. National Library of MedicineDate. Published. <https://clinicaltrials.gov/ct2/show/NCT04257656>

- [38] ClinicalTrials.gov.Mild / Moderate 2019-nCoV Remdesivir RCT. NCT04252664.Published. <https://clinicaltrials.gov/ct2/show/NCT04252664>
- [39] Gautret, P., et al., Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International journal of antimicrobial agents 2020; 105949.
- [40] ClinicalTrials.gov.A Prospective/ Retrospective,Randomized Controlled Clinical Study of Antiviral Therapy in the 2019-nCoV pneumonia. ClinicalTrials.gov Identifier: NCT04255017.National Library of Medicine (US); Date. Published. <https://clinicaltrials.gov/ct2/show/NCT04255017>
- [41] ClinicalTrials.gov.Chloroquine/ Hydroxychloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting (COPCOV). ClinicalTrials.gov Identifier: NCT04303507.National Library of Medicine (US).Date. Published. <https://clinicaltrials.gov/ct2/show/NCT04303507>
- [42] ClinicalTrials.gov.Clinical Study of Arbidol Hydrochloride Tablets in the Treatment of Pneumonia Caused by Novel Coronavirus. ClinicalTrials.gov Identifier: NCT04260594.Published. <https://clinicaltrials.gov/ct2/show/NCT04260594>
- [43] ClinicalTrials.gov.The Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection (ELACOI). ClinicalTrials.gov Identifier: NCT04252885.National Library of Medicine (US); Date. Published. <https://clinicaltrials.gov/ct2/show/NCT04252885>
- [44] ClinicalTrials.gov.The Clinical Study of Carrimycin on Treatment Patients With COVID-19. ClinicalTrials.gov Identifier: NCT04286503.National Library of Medicine (US)Date. Published. <https://clinicaltrials.gov/ct2/show/NCT04286503>
- [45] ClinicalTrials.gov.Favipiravir, Protease Inhibitors, Oseltamivir -Gpo, Hydroxychloroquine for Treatment of COVID-19 (FIGHT-COVID-19). ClinicalTrials.gov Identifier: NCT04303299.National Library of Medicine (US). Date. Published. <https://clinicaltrials.gov/ct2/show/NCT04303299>
- [46] Markham, A. and S.J. Keam, Danoprevir: first global approval. Drugs 2018; 78(12) 1271-1276.
- [47] Tang, T., Application of Xiyanping in Treatment of infantile rotavirus diarrhea. J Hainan Med Univ 2016; 22(13) 113-5.
- [48] ClinicalTrials.gov.Efficacy and Safety of Darunavir and Cobicistat for Treatment of COVID-19 (DC-COVID-19). ClinicalTrials.gov Identifier: NCT04252274.National Library of Medicine (US)Date. Published. <https://clinicaltrials.gov/ct2/show/NCT04252274>
- [49] ClinicalTrials.gov.The Efficacy and Safety of Thalidomide Combined With Low-dose Hormones in the Treatment of Severe COVID-19. ClinicalTrials.gov Identifier: NCT04273581.National Library of Medicine (US)Date. Published. <https://clinicaltrials.gov/ct2/show/NCT04273581>
- [50] ClinicalTrials.gov.The Efficacy and Safety of Thalidomide in the Adjuvant Treatment of Moderate New Coronavirus (COVID-19) Pneumonia. ClinicalTrials.gov Identifier: NCT04273529.National Library of Medicine (US)Date. Published. <https://clinicaltrials.gov/ct2/show/NCT04273529>
- [51] ClinicalTrials.gov.Glucocorticoid Therapy for COVID-19 Critically Ill

Patients With Severe Acute Respiratory Failure. ClinicalTrials.gov Identifier: NCT04244591. National Library of Medicine (US) Date. Published. <https://clinicaltrials.gov/ct2/show/NCT04244591>

[52] Long, Y., et al., Clinical recommendations from an observational study on MERS: Glucocorticoids was benefit in treating SARS patients. International Journal of Clinical and Experimental Medicine 2016; 9(5).

[53] Hung, I.F.-N., et al., Triple combination of interferon beta-1b, Lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. The Lancet 2020; 395(10238) 1695-1704.

[54] Li, H., et al., Updated approaches against SARS-CoV-2. Antimicrobial agents and chemotherapy 2020; 64(6).

[55] Rome, B.N. and J. Avorn, Drug evaluation during the Covid-19 pandemic. New England Journal of Medicine 2020.

[56] Organisation, W.H. “Solidarity” clinical trial for COVID-19 treatments. 2020 October 16 2020; Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments>.

[57] Sanders, J.M., et al., Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. Jama 2020; 323(18) 1824-1836.

[58] Gorbalenya, A.E., et al., The palm subdomain-based active site is internally permuted in viral RNA-dependent RNA polymerases of an ancient lineage. Journal of molecular biology 2002; 324(1) 47-62.

[59] Sheahan, T.P., et al., Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nature communications 2020; 11(1) 1-14.

[60] Beigel, J.H., et al., Remdesivir for the treatment of Covid-19. New England Journal of Medicine 2020.

[61] Goldman, J.D., et al., Remdesivir for 5 or 10 days in patients with severe Covid-19. New England Journal of Medicine 2020.

[62] Spinner, C.D., et al., effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. Jama 2020; 324(11) 1048-1057.

[63] Games, A., et al., Glenmark also continues its Phase 3 clinical trials on antiviral Favipiravir monotherapy for COVID-19 patients in India.

[64] Chen, C., et al., Favipiravir versus Arbidol for COVID-19: a randomized clinical trial. MedRxiv 2020.

[65] Cai, Q., et al., Experimental Treatment with favipiravir for COVID-19: an open-label control study. Engineering 2020.

[66] Benson, C.A., et al., Safety and antiviral activity at 48 weeks of lopinavir/ritonavir plus nevirapine and 2 nucleoside reverse-transcriptase inhibitors in human immunodeficiency virus type 1-infected protease inhibitor-experienced patients. The Journal of infectious diseases 2002; 185(5) 599-607.

[67] Corbett, A.H., M.L. Lim, and A.D. Kashuba, Kaletra (lopinavir/ritonavir). Annals of Pharmacotherapy 2002; 36(7-8) 1193-1203.

[68] Chu, C., et al., Role of lopinavir/ritonavir in the Treatment of SARS:

initial virological and clinical findings. Thorax 2004; 59(3) 252-256.

[69] Arabi, Y.M., et al., Treatment of Middle East respiratory syndrome with a combination of lopinavir-ritonavir and interferon- β 1b (MIRACLE trial): study protocol for a randomized controlled trial. Trials 2018; 19(1) 1-13.

[70] Chan, J.F.-W., et al., treatment with lopinavir/ritonavir or interferon- β 1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. The Journal of infectious diseases 2015; 212(12) 1904-1913.

[71] Chen, J., et al. *Antiviral activity and safety of darunavir/cobicistat for the Treatment of COVID-19*. in *Open forum infectious diseases*. 2020. Oxford University Press US.

[72] Li, W., et al., Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003; 426(6965) 450-454.

[73] Ben-Zvi, I., et al., Hydroxychloroquine: from malaria to autoimmunity. Clinical reviews in allergy & immunology 2012; 42(2) 145-153.

[74] Savarino, A., et al., New insights into the antiviral effects of Chloroquine. The Lancet infectious diseases 2006; 6(2) 67-69.

[75] Vincent, M., et al., *Chloroquine is a potent inhibitor of SARS coronavirus infection and spread*. Virol J2: 69. 2005.

[76] Keyaerts, E., et al., In vitro inhibition of severe acute respiratory syndrome coronavirus by Chloroquine. Biochemical and biophysical research communications 2004; 323(1) 264-268.

[77] Gao, J., Z. Tian, and X. Yang, Breakthrough: Chloroquine phosphate has shown apparent efficacy in

Treatment of COVID-19 associated pneumonia in clinical studies. Bioscience trends 2020.

[78] Chen, Z., et al., efficacy of Hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. MedRxiv 2020.

[79] Zhang, Q., et al., Clinical trial analysis of 2019-nCoV therapy registered in China. Journal of medical virology 2020; 92(6) 540-545.

[80] Cortegiani, A., et al., A systematic review on the efficacy and safety of Chloroquine for the Treatment of COVID-19. Journal of critical care 2020.

[81] Boriskin, Y.S., E.-I. Pécheur, and S.J. Polyak, Arbidol: a broad-spectrum antiviral that inhibits acute and chronic HCV infection. Virology journal 2006; 3(1) 56.

[82] Blaising, J., et al., Arbidol inhibits viral entry by interfering with clathrin-dependent trafficking. Antiviral research 2013; 100(1) 215-219.

[83] Pécheur, E.-I., et al., The synthetic antiviral drug arbidol inhibits globally prevalent pathogenic viruses. Journal of virology 2016; 90(6) 3086-3092.

[84] Wang, Z., et al., Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clinical infectious diseases 2020.

[85] Deng, L., et al., Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. Journal of Infection 2020.

[86] Li, Y., et al., An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or Arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI). MedRxiv 2020.

- [87] Wen, C., et al., Real-world efficacy and safety of lopinavir/ritonavir and Arbidol in treating with COVID-19: an observational cohort study. *Zhonghua nei ke za zhi* 2020; 59 E012.
- [88] Huang, H., et al., Chloroquine, Arbidol (umifenovir) or lopinavir/ritonavir as the antiviral monotherapy for COVID-19 patients: a retrospective cohort study. 2020.
- [89] Cutino-Moguel, M.T., et al., Immunotherapy for infectious diseases in haematological immunocompromise. *British journal of haematology* 2017; 177(3) 348-356.
- [90] Lu, R.-M., et al., development of therapeutic antibodies for the treatment of diseases. *Journal of biomedical science* 2020; 27(1) 1-30.
- [91] Wong, S.K., et al., A 193-amino acid fragment of the SARS coronavirus S protein efficiently binds angiotensin-converting enzyme 2. *Journal of Biological Chemistry* 2004; 279(5) 3197-3201.
- [92] Duan, J., et al., A human SARS-CoV neutralizing antibody against epitope on S2 protein. *Biochemical and biophysical research communications* 2005; 333(1) 186-193.
- [93] Sheikhshahrokh, A., et al., Frontier therapeutics and vaccine strategies for sars-cov-2 (COVID-19): A review. *Iranian Journal of Public Health* 2020; 49 18-29.
- [94] Marovich, M., J.R. Mascola, and M.S. Cohen, Monoclonal antibodies for prevention and Treatment of COVID-19. *Jama* 2020; 324(2) 131-132.
- [95] Hayden, F.G., et al., use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized controlled trials for prevention and treatment. *Jama* 1999; 282(13) 1240-1246.
- [96] Zhang, X.W. and Y.L. Yap, The 3D structure analysis of SARS-CoV S1 protein reveals a link to influenza virus neuraminidase and implications for drug and antibody discovery. *Journal of Molecular Structure: THEOCHEM* 2004; 681(1-3) 137-141.
- [97] Rosa, S.G.V. and W.C. Santos, Clinical trials on drug repositioning for COVID-19 treatment. *Revista Panamericana de Salud Pública* 2020; 44 e40.
- [98] Fu, B., X. Xu, and H. Wei, Why tocilizumab could be an effective treatment for severe COVID-19? *Journal of translational medicine* 2020; 18(1) 1-5.
- [99] Registry, C.C.T., A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19). 2020.
- [100] Dinarello, C.A., Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunological reviews* 2018; 281(1) 8-27.
- [101] Wu, R., et al., An update on current therapeutic drugs treating COVID-19. *Current Pharmacology Reports* 2020; 1.
- [102] Moazzam, M., et al., Understanding COVID-19: From Origin to Potential Therapeutics. *International Journal of Environmental Research and Public Health* 2020; 17(16) 5904.
- [103] Juszczak, E. and A. Montgomery, Dexamethasone in Hospitalized Patients with Covid-19—Preliminary Report. *New England Journal of Medicine*.
- [104] Villar, J., et al., Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *The Lancet Respiratory Medicine* 2020; 8(3) 267-276.

[105] ClinicalTrials.gov.CD24Fc as a Non-antiviral Immunomodulator in COVID-19 Treatment (SAC-COVID). ClinicalTrials.gov Identifier: NCT04317040.Published. <https://ichgcp.net/clinical-trials-registry/NCT04317040>

[106] Bonnet, F. and A. Scheen, Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: The potential contribution to diabetes complications and cardiovascular disease. *Diabetes & metabolism* 2018; 44(6) 457-464.

[107] Kawanami, D., et al., SGLT2 inhibitors as a therapeutic option for diabetic nephropathy. *International journal of molecular sciences* 2017; 18(5) 1083.

[108] Cheng, H., Y. Wang, and G.Q. Wang, Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. *Journal of medical virology* 2020.

[109] Ibrahim, H.S. and S.K. Kafi, A Computational Vaccine Designing Approach for MERS-CoV Infections. *Immunoinformatics* 2020; 39-145.