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SARS-CoV-2: Current Therapeutics Human and Veterinary Medicine

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Abstract

The *Severe Acute Respiratory Syndrome Coronavirus 2*, SARS-CoV-2, was first reported in Wuhan City, China, in December 2019. Health and environmental risk factors are crucial in this current pandemic, yet it is essential to note that even though individuals of all ages are susceptive to this virus, there are risk factors associated with developing the severe disease. It is also eminent to establish the human-animal interaction by tackling important past pathogenic viruses such as SARS-CoV and MERS-CoV and its zoonotic links. In need of a clinically established management for this outbreak, approved drugs' therapeutic interventions could help treat this disease, targeting its replication. The need to resolve the current pandemic of COVID-19 epitomizes the need for a different approach, drug repurposing. Characterization of artificial intelligence created by predicted models and structures could alleviate COVID-19; it has been used not only in the development of drugs but also in tackling screening, treatment, and contact tracing. This review presents pathogenesis, transmission, and the analysis of drug repositioning in both human and veterinary medicine of SARS-CoV-2 to delve into practical approaches to manage this disease.

Introduction

Coronavirus (CoVs) belong to the order *Nidovirales*, including *Coronaviridae*, *Roniviridae*, and Arterivirdae families. *Coronavirinae* family is subdivided into four distinct genera: *alpha, beta, gamma, and delta coronavirus,* critical in both human and veterinary medicine. CoVs broadly infect vertebrates, including humans, birds, bats, snakes, mice, and other wild animals (Weiss, 2015). CoVs are highly transmissible and pathogenic positive-sense, single-stranded RNA enveloped viruses, with a genome ranging from 26 to 32kb in length. The 5'terminal two-thirds of the genome contain open reading frames (ORFs), ORF1 and ORF2 encoding two distinct polyproteins pp1a, which cleaves into 11 proteins and pp1b, cleaving into 16 proteins. These proteins serve an essential function in the genome, allowing maintenance and virus replication. The structural proteins, namely spike (S), an envelope protein (E), membrane protein (M), and nucleocapsid (N), are located at the one-third 3′ terminal of the genome. (Malik,2020). N complex along with RNA genome provides a helical capsid configuration located inside the viral envelope. The trimers of S contribute to the virion *corona* or crown arrangement. Furthermore, COVs have accessory proteins that aid in virus replication; the S gene aids in host

specificity and receptor binding. Some CoVs have hemagglutinin-esterase (HE) protein in its virion, which forms a smaller spike to destroy specific receptors found on the host cells.

Seven CoVs that infect humans have been identified; HCOV-229E and HCoV-NL63 belonging to Alphacoronavirus, HCoV-OC43, and HCoV-HKU1, belong to Betacoronavirus, as well as SARS-CoV, MERS-CoV, and SARS-CoV-2. The pandemic of severe acute respiratory syndrome (SARS) in 2002–2003, the emergence of the Middle East respiratory syndrome (MERS) in 2012, and the emergence of a new coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of the coronavirus disease 2019 pandemic, are all examples of human infections leading to significant fatality caused by coronaviruses (Guarner, 2020). The development of novel transmissible diseases epitomizes a liability to public health and a socio-economic impact on both humans and livestock. Analysis of the SARS-CoV2 (COVID-19) sequence indicated that it shows 77.2% amino acid identity with SARS-CoV (SARS) with the non-structural proteins (nsp's) 7–10 showing between 97.1% to 98.8% identity (Wu, 2020). Consequently, it is imperative to understand SARS-CoV-2 to implement a functional management strategy, decreasing both transmission and morbidity.

The subfamily of CoVs, as mentioned previously, comprises four genera *alpha*, *beta, gamma,* and *delta coronavirus*. The alpha and beta coronaviruses infect only mammals; gamma and delta coronaviruses infect birds, but some can also infect mammals (Decaro,2020). Coronaviruses like mouse hepatitis virus, rat sialodacryoadenitis CoVs, guinea pig CoVs, and rabbit CoVs are important viruses responsible for hepatitis, enteritis, and respiratory infections in lab animals.

Among large animals, bovine coronaviruses (BoCVs) have zoonotic potential as being isolated from asymptomatic children and also found affecting several domestic and wild ruminants, in which calf diarrhea in neonates, bloody diarrhea in adult cattle and respiratory form of shipping fever in all age groups of cattle are universal implications (Tiwari, 2020). Feline CoVs also affect the respiratory and gastrointestinal tract, producing enteritis and infectious peritonitis (Tekes, 2016). There is an understanding that the virus has a zoonotic origin, yet much remains unknown. Bats are critical natural hosts of alphacoronaviruses and beta coronaviruses; the discovery of diverse bat CoVs closely related to SARS-CoV-2 suggests that bats are potential reservoirs of the virus (Hu, 2020). According to WHO, identifying the zoonotic source of the virus and its introduction in the human population is vital to prevent SARS-CoV-2. Not only this but

identifying intermediate hosts and their roles. As of November 2020, WHO has become vigilant of infected minks as a potential reservoir host. Not only that, but mutations have been reported; however, these variants are not yet understood, but it could result in a promising outcome. To date, six countries, namely Denmark, the Netherlands, Spain, Sweden, Italy, and the United States of America, have reported SARS-CoV-2 in farmed minks to the World Organization for Animal Health (WHO,2020). The continual human-animal interaction potentiates distress, particularly without the proper environmental biosecurity methods that could pose a potential threat, spreading the virus.

SARS-CoV-2 pathogen was first reported in Wuhan City, China, in December 2019, after numerous patients presented pneumonia-like symptoms, including fever, dry cough, and shortness of breath followed by severe acute respiratory infections. In January 2020, it was announced that a new CoV had emerged named 2019-nCoV and later given the name of COVID-19 by the World Health Organization (WHO). The exponential spread of COVID-19 in January 2020 could be attributed mainly to Wuhan being the capital of China's Hubei province. According to Guarner, Wuhan has over 11,000,000 inhabitants, and it is a central transportation hub, which increased person-to-person contact, adding to the possibility of exported cases to other locations. The international spread of the virus accelerated by the end of February due to international travel. By March 2020, it was categorized as a pandemic. According to WHO, as of November 2020, over fifty million cases reported worldwide, and over ten million reported in the United States. Fatality obesity, high blood pressure as well as a weakened immune system.

Due to the viruses' novel nature and unavailability of vaccine or specific therapy, it is vital to understand SARS-CoV-2 pathogenesis, transmission, and clinical signs. As this topic is fast-changing, understanding the repurposing of drugs and human-animal interaction is fundamental to control this pandemic. This review presents pathogenesis and transmission and the analysis of current therapeutics in both human and veterinary medicine of SARS-CoV-2 to delve into practical approaches to manage this disease.

SARS-CoV-2 Pathogenesis and Transmission

Through accumulating data, the severity of Covid-19 is related to increase inflammatory cytokines and chemokines including (IL)-2, IL-7, IL-10, tumor necrosis factor (TNF), granulocyte colony-stimulating factor (G-CSF), monocyte chemoattractant protein-1 (MCP1; also known as CCL2), macrophage inflammatory protein one alpha (MIP1α; also known as CCL3), CXC-

chemokine ligand 10 (CXCL10), C-reactive protein, ferritin, and D-dimers in blood upon SARS-CoV-2 infection (Tay, 2020). In most of those severe cases of coronavirus infection, the clinical expression is characterized not only by a fever, cough, and other constitutional symptoms but also by a clinical constellation including a cytokine storm, respiratory failure, and eventually death (Baden, 2020).

SARS-CoV-2 spike binds to its receptor angiotensin-converting enzyme 2 (ACE2) through its receptor-binding domain (RBD) and is proteolytically activated by human proteases. (Shang,2020). COVID-19 can be divided into different phases corresponding to different disease clinical stages (Wu, 2020). The first stage is known as the asymptomatic stage; it encompasses the initial days of the virus. By numerous studies, asymptomatic infections make up a substantial percentage of confirmed COVID-19 cases. Asymptomatic infections are hidden and easily overlooked. However, their potential to spread the virus cannot be underestimated, as the viral load they carried and their ability to infect close contacts may be similar to those of symptomatic individuals. (Tan, 2020). Upper airway and conducting airway response correspond to the second stage. At this stage, the virus proliferates and continues down the respiratory tract; it also activates the innate immune response. The third and last stage is hypoxic, resulting in deprived oxygen supply leading to acute respiratory syndrome (ARDS). A systemic inflammatory response causes an unregulated immune response; a cytokine storm gives rise to the release of significant amounts of pro-inflammatory cytokines. This "intense attack" by the immune system promotes ARDS and multiple organ failure, leading to death in severe COVID-19 cases.

The distribution of ACE2 receptors in different tissues could explain the difference in patient symptoms. SARS-CoV-2 binds to ACE2, the host cell receptor, which is found on the epithelium of other organs such as the intestine and endothelial cells in the kidney and blood vessels explain gastrointestinal symptoms and cardiovascular complications (Cevik 2020). The stipulation of olfactory dysfunction has become of attention as numerous patients presented a temporary loss of taste and smell, which can be attributed to damage in the olfactory epithelium. Much remains unknown, yet the clinical outcomes of SARS-CoV-2 are associated with underlying risks such as obesity, cardiovascular disease, and older age. Also, increased pro-inflammatory cytokines correlate with severe pneumonia and increased ground-glass opacities within the lungs (Takahashi, 2020).

Since declaring COVID-19 as a pandemic, it has been crucial to combat this disease. It has been established that this disease characterizes by person-to-person transmission, performance being both symptomatic and asymptomatic. Droplet transmission occurs by the direct spray of large droplets onto conjunctiva or mucous membranes of a susceptible host when an infected patient sneezes, talks, or coughs (Jayaweera, 2020). Infectious aerosols can pose an infection risk, especially in poorly ventilated or prolonged exposures to it. Current evidence on SARS-CoV-2 has limitations but strongly indicates aerosols as one of several routes of COVID-19 transmission. It should be noted that the equivalent evidence for contact and large droplet transmission is not available but has been an unproven assumption from the outset (Tang S, 2020).

Health and environmental risk factors are crucial in this current pandemic, yet it is essential to note that even though individuals of all ages are susceptive to this virus, there are risk factors associated with developing the severe disease. Elderly individuals (aged > 60 years) and people with underlying chronic health conditions are more susceptible to severe disease (18.5%) as compared to children and younger healthy adults (6%) (Wang,2020) Recently, individuals with asymptomatic infection were also found to act as sources of infection to susceptible individuals. Both the asymptomatic and symptomatic patients secrete similar viral loads, which indicates that the transmission capacity of asymptomatic or minimally symptomatic patients is very high (Tan, 2020). Also, incubation time is a crucial factor in infectious diseases, determined by the time elapsed between infection and appearance of the disease's first symptoms. Detailed epidemiological investigation and contact follow-up have shown that the virus's incubation period is typically between 3 and 7 days and no more than 14 days. During the incubation period, patients appear normal, with no symptoms, but can still spread the disease (Zhonghua, 2020).

Drug Repurposing

Drug development is a strenuous process that involves aiming at biotic targets involving biological processes. Analyses across all therapeutic areas indicate that new medicine's development, from target identification through marketing approval, takes over 12 years, and is often much more prolonged (DiMasi et al., 2017). Not only this, but the development process is costly and uncertain as many issues come into consideration; toxicity, lack of efficacy and safety, dosing ranges, and irreversible adverse effects. It usually costs an average of US$2.6 billion for approximately 17 years of development from molecule to market. Even so, only 2.01% of all drug development initiatives finally make it to the market as a successful drug (Xue, 2018)

The need to resolve the current pandemic of COVID-19 epitomizes the need for a different approach, drug repurposing. In this tactic, an established drug utilized can treat other diseases aiming at new targets, decreasing the developmental period. Usually, there are three steps before considering repositioning a drug: (1) the identification of candidate molecules for the given indication; (2) the theoretical assessment of the drug effect in preclinical models; and (3) the evaluation of safety efficacy in phase II clinical trials (Pushpakom et al., 2019 Economically it lowers the overall developmental costs by approximately $300 million (Low et al., 2020). This is of interest as commercially available drugs such as antivirals, protease inhibitors, antibacterials, antibiotics, IL-6 blockers, Jak inhibitors, and antimalarials are utilized as potential treatments for COVID-19.

Different approaches within drug repositioning have become a significant complement in this pandemic. Computational Artificial Intelligence (AI) is defined as the mimicking of human intelligence demonstrated by machines, which entail reasoning, planning, learning, and perception to maximize the chances of achieving different goals under extreme load and urgencies like pandemics or diseases of unknown etiology (Low et al., 2020). Characterization of AI creates by predicted models and structures that could alleviate COVID-19. It has been used not only in the development of drugs but also in tackling screening, treatment, and contact tracing. Recent studies design an auxiliary tool to increase the accuracy of Covid-19 diagnosis with the new model Automatic COVID-19 detection based on a deep learning algorithm (Ozturk et al., 2020).

AI and its drug-disease relationship could exponentially grow shortly as it allows for a faster, efficient, and low-cost alternative process. Challenges remain in developing these AI tools, such as data heterogeneity and low quality, insufficient data sharing by pharmaceutical companies, and the security and interpretability of the models. (Zhou et al.). In this review, we would explore the proposed repositioning of drugs targeting COVID-19 as these attempts are crucial in alleviating symptoms in the disease. As there is no current approved treatment or vaccination for COVID-19, drug recycling is urgent.

Current Therapeutics

As of November 2020, numerous vaccine trials are taking place, including nucleic-based, inactivated, and vector trial vaccines. These considerable efforts would still need to meet the primary essential criteria, safety. Consequently, this review's primary aim is to evaluate current drugs' evidence and how it could target distinct stages of the SARS-CoV-2 replication cycle.

SARS-CoV-2 uses ACE 2 as the receptor and human proteases as entry activators; subsequently, it fuses the viral membrane with the cell membrane and achieves invasion (Hu, 2020). According to Zirui, the virus principally targets airway epithelial cells and alveolar epithelial macrophages, all expressing ACE 2. The virus reduces ACE-2 in the lungs, and therefore the downregulation would lead to inflammasome activation promoting pyroptosis. This cell death resulting from inflammation would enable the damage-associated molecular patterns. This cascade would trigger pro-inflammatory cytokines, promoting further inflammation by the promotion of monocytes and macrophages. After entering the cell through clathrin-mediated endocytosis, the transmembrane protease serine 2 (TMPRSS2) cleaves to the S protein facilitating cell entry and fusion between the endosomal membrane and viral S2 sequence (Hoffmann et al., 2020). After fusion concluded, viral RNA is released to the infected host cell, promoting pathogenic responses and replication. In a first step, the open reading frame 1a/b (ORF1a/b) of the viral genome translates to produce the replicate proteins, after which the replicase-transcriptase complex DMVs assemble. In a second step, the replication complex reverse-transcribes the positive RNA genome into full-length negative-sense RNAs, which template the production of full-length daughter genomes and a subset of translation-focused mRNAs. These translation-dedicated transcripts contain a standard 5′ leader sequence cytosolically spliced to downstream genes, added by a discontinuous synthesis of minus sense subgenomic RNAs templating the positive RNA genome (Nitulescu, 2020).

In need of a clinically established management for COVID-19, approved drugs' therapeutic interventions could help treat this disease, targeting its replication cycle. Not only this but understanding the animal-human interaction could expand current knowledge in prevention, control, animal CoVs evolution, as well as the adaption to humans due to zoonotic variations

Human Medicine

As continuously mentioned through this review, new data emergence and understanding of the virus increased the experimental drugs currently used. In the unavailability of treatment for COVID-19, market drugs are practical solutions in isolating a therapy for the disease. Consequently, lacking data on effectiveness and safety limits recommendation of treatment. Classification of drugs for the treatment of COVID-19 is generally classified; in this review, different drug classes are explored. Table 1 describes the drug classes, and the hypothesized mechanisms for SARS-CoV-2 discussed for the specific drugs in this review.

Drugs Class	Drug	Suggested Mode of Action in SARS-CoV-2
Antivirals	Remdesivir	Causes disintegration of NTP into replicating RNA by RdRp, preventing chain elongation after NTP plus three additional nucleosides, promoting premature RNA synthesis termination (Malin, 2020).
	Favipiravir	Selectively and potently inhibits the RNA-dependent RNA polymerase (RdRp).
	Ribavirin	Creates random mutation that reduces the viability of the virus, as a consequence the viral response decreases as well as transmission
	Umifenvoir	Blocks the virus-cell membrane fusion and virus-endosome fusion through incorporation into cell membranes and interference with the hydrogen bonding network of phospholipids (Villalain, 2010)
	Amantadine	Block early stages of viral replication, inhibiting virion release in cell.
	Elbasvir	Binds to RdRP, papain-like proteinase and helicases which are the main protein that SARS-CoV-2 replication is dependent on.
	Sofosbuvir	Suppresses SARS-CoV-2 RdRp.
	Daclatasvir	Binds to N terminus of nonstructural (NS5A) protein, inhibiting viral replication and assembly, whereas NS5B is an RNA-dependent RNA polymerase (RdRp) critical for RNA synthesis in HCV replication (Kumar, 2020).
Protease Inhibitor	Lopinavir/Ritonavir	Lopinavir is a protease inhibitor that impedes viral replication. Ritonavir hinders CYP3A4,enlarging concentration of lopinavir (Horby, 2020).
	Nafamostat	Prevents fusion of the envelope of the virus with host cell surface membrane (Jang and Rhee, 2020
	Nelfinavir	Binds to the SARS-CoV-2 protease as well as inhibit cell fusion caused by the SARS-CoV-2 S glycoprotein (Ianeyski et. al, 2020).
Antimalarials	Chloroquine & Hydroxychlorquine	Obstruction of post-translation modification E proteins, as well as suppressed IL-6 and downregulated TNFR (Shende, 2020).
Antibiotics	Azithromycin	Hinders viral reproduction and IL-6 assembly
	Doxycycline	Inhibit the replication of single-stranded RNA viruses via inhibiting the viral serine protease (Rothan et. al, 2020).
IL-6 Blockers	Tocilizumab	Selectively and competitively binds to soluble expressing the IL-6 receptor and then blocking the signaling caused by IL- 6 (Sing et. al, 2020)
	Lenzilumab	Blocks the GM-CSF pathway reducing cytokine-induced inflammation (Vijayvargiya et al, 2020)
Kinase Inhibitors	Ruxolitinib	Interact with SARS-CoV-2 and ACE 2 receptors could mitigate the cytokine storm by targeting critical cytokines
	Baricitinib	Acts as a JAK inhibitor interfering with the inflammatory process.
Corticosteroid	Dexamethasone	Activation of histone deacetylase may oppose the action of SARS-CoV-2 (Ortolani, 2020).

Table 1: Described the different drug classes as well as the hypothesized mode of action in SARS-CoV-2.

Antivirals

Remdesivir and Favipiravir

Drugs that have been tested or are still ongoing clinical trials for SARS-CoV-2 replication as subgenomic transcription include favipiravir (FPV) and remdesivir (RDV). FPV is an antiviral agent that selectively and potently inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses. (Furuta,2017). It does this by entering infected cells through endocytosis, which then targets RdRp by disrupting the nucleotide incorporation process during RNA replication. In Japan, FPV has been approved to manage pandemic influenza infection in 2014 (Agrawal, 2020).FPV is a nucleoside precursor which inhibits the broad range of influenza virus strains. However, it shows antiviral activity through its NTP form (converted into an active phosphoribosylated form, T-705 RTP) via direct inhibition of the RDRP activity of influenza A virus polymerase, and it has also shown lethal mutations within the viral genome. (Singh et al.). According to Wang et al., a higher concentration of FPV is needed to inhibit SARS-COV-2 in Vero cells. Clinical trials are still ongoing, yet safe and efficient treatment regarding dosing and severity of illness is needed to determine FPV effectiveness. Along these lines, a drug tackling the immune response and viral replication inhibition would be promising to counteract the SARS-CoV-2 replication cycle.

On October 22, 2020, FDA approved RDV for the treatment of COVID-19 requiring hospitalization. RDV is an antiviral nucleoside analog; it undergoes intracellular metabolic conversion to its active metabolite, nucleoside triphosphate (NTP). RDV causes disintegration of NTP into replicating RNA by RdRp, preventing chain elongation after NTP plus three additional nucleosides, promoting premature termination of RNA synthesis, which is needed for new generation virions (Malin, 2020). Its viral activities against SARS-CoV-2 have been shown in both *in vitro* and *in vivo* studies. Remdesivir has been used in several countries as an emergency drug for patients with COVID-19 (Frediansyah, 2020).

Ribavirin

Evaluating the role of ribavirin in treating the novel virus has also come into effect. The inability to tie zoonotic links influences the treatment currently studied. Ribavirin is a guanosine analog acting as a chain terminator by inhibiting RNA polymerase (Zhou et al., 2020). The earliest reported in vitro efficacy of five FDA-approved drugs with activity against WIV04 has been reported; ribavirin, penciclovir, nitazoxanide, and nafamostat and chloroquine (Khalili, 2020). Ribavirin creates random mutation that reduces the viability of the virus; consequently, the viral

response decreases as well as transmission. Ribavirin has also shown immune response properties as an anticancer agent; as an enhanced polarization of Th1, regulatory cells would suppress the immune response, an indirect mechanism (Li Z, 2016). Ribavirin is also very cheap compared to other drugs, allowing the medical product to be distributed readily to the public, challenging the pandemic. New clinical trials are currently in process, which will expand understanding of dosing, combination drugs, and its efficacy.

Umifenvoir

Umifenovir is a broad-spectrum antiviral agent that could effectively inhibit the virus's fusion with host cells and is already licensed for prophylaxis and influenza treatment (Huang, 2020). Its mechanism is to block the virus-cell membrane fusion and virus-endosome fusion by incorporating cell membranes and interference with the hydrogen bonding network of phospholipids (Villalain, 2010). This antiviral has been associated with a lower incidence of SARS-COV-2 infection but not hospitalization, yet much remains unknown; inconsistency in different studies concludes that randomized clinical trials should take place in order to confirm umifenovir effectiveness.

Amantadine

Amantadine has been utilized as an antiviral against the influenza A virus; the proposed mechanism is that the drug blocks the early stage of viral replication. When the viral particle enters the cell, an endosome is formed, with an acid pH of 5. The proton channel is formed by the M2 protein, which carries protons into the virion's interior (Abreu,2020). The drug can pass through the endosome membrane, inhibit the virion release into the cell, and break the hydrogen bridges formed by Ala 30 and Gly 34 (Thomaston,2018). It could be expected that amantadine could lessen the disease's effects when the first symptoms occur.

Elbasvir

This drug is approved for the treatment of hepatitis C, and it has been predicted that it could bind to RdRP, papain-like proteinase, and helicases, which are the main protein that SARS-CoV-2 replication depends on. In a recent study performed by Balasubramaniam et al., target-based computational analysis screening drugs that would target the virus's three main proteins were utilized. According to Balasubramaniam et al., several drugs are capable of a weak relationship with numerous viral proteins; elbasvir is characteristic in its probable high affinity for SARS-CoV-2 proteins, involving those in viral replication.

Sofosbuvir and Daclatasvir

Sofosbuvir is a pyrimidine nucleotide analog prodrug, has a hydrophobic masked phosphate group that enhances its ability to enter host cells (Jockusch et al., 2020). This antiviral has demonstrated evidence in vitro on viral RdRp and is hypothesized to suppress SARS-CoV-2 RdRp. Daclatasvir, as an antiviral, binds to the N terminus of nonstructural (NS5A) protein, inhibiting viral replication and assembly, whereas NS5B is an RNA-dependent RNA polymerase (RdRp) critical for RNA synthesis in HCV replication (Kumar, 2020). These direct-acting antivirals have shown in an *in vitro* (albeit non–peer-reviewed) study the inhibition of SARS-CoV-2 virus particles by daclatasvir in Vero cells, hepatoma cell line, and type II pneumocytes (Kumar, 2020). These drug's low-cost expense and treatment outcomes reported promising results in the near future, yet more extensive studies are needed to assess effectiveness.

Protease Inhibitors

Lopinavir/Ritonavir

Protease inhibitors employ competitive binding to the site of viral enzymes breaking down proteins and peptides. Lopinavir/ritonavir (LPV/r) combination has been widely recognized and used to inhibit the HIV protease enzyme. It hypothesized that the 3CL-pro-inhibiting activity of LPV/r influences anti-CoV effects (Zumla, 2016). As of November 2020, drugs counteracting the attachment to the virus' polymerase, LPV/r, have been discontinued. According to WHO, these drugs do not provide substantial evidence of a reduction in hospitalized patients' mortality. Additionally, allocation to lopinavir-ritonavir was not associated with reductions in hospital stay duration or the risk of being ventilated or dying for those not on ventilation at baseline. These results were consistent across subgroups of age, sex, ethnicity, duration of symptoms before randomization, amount of respiratory support at randomization, and baseline predicted risk of death at randomization (Horby, 2020).

Nafamostat

This drug has been utilized for the treatment of pancreatitis and disseminated intravascular coagulation in Japan. This drug shows the activity as an anticoagulant, anti-inflammatory, and antiviral activities in COVID-19. Nafamostat prevents the fusion of the virus's envelope with the host cell surface membrane (Jang and Rhee, 2020). In a study of 3 elderly patients with progressive pneumonia and at high risk based on age, Nafamostat was utilized, improving clinical status. According to Jang and Rhee, nafamostat can counteract disease advancement by manipulating the

immune system such as the complement cascade, hindering DIC, impeding virus invasion by hindering virus fusion on the cell membrane. Thus, it was observed that the antiviral drug improved clinical outcomes; a more significant sample size is essential for a better evaluation of this treatment.

Nelfinavir

Acts as an HIV-1 protease inhibitor, also it produces numerous influences on cellular processes as stimulation of apoptosis and necrosis. Molecular docking studies predict that nelfinavir binds to the SARS-CoV-2 protease and inhibits cell fusion caused by the SARS-CoV-2 S glycoprotein (Ianeyski et al., 2020). Preliminary experiments indicate that S-n and S-o may be cleaved in Vero cells in the presence of nelfinavir, although it is not currently known whether this cleavage occurs efficiently (Musarrat et al., 2020). Nelfinavir also studied in a combination of amodiaquine- host-directed- which has a similar action mechanism to chloroquine. It was noted to better efficacy and decreased toxicity for the treatment of SARS-CoV-2 and perhaps other viral infections (Ianeyski et al., 2020). This combination could have a crucial function in COVID-19 and should be furthered looked into.

Antimalarials

Chloroquine and Hydroxychloroquine

Chloroquine and its analog hydroxychloroquine have long been used worldwide as frontline drugs for treating and human prophylaxis of malaria (Tripathy et al., 2020). Inhibition of SARS-CoV-2 entry through the endocytic pathway or fusion with the host cell would be attributed to antimalarials. Chloroquine, as well as hydroxychloroquine, were proposed as a therapy for COVID-19 as it obstructed post-translation modification E proteins, as well as suppressed IL-6 and downregulated TNFR (Shende, 2020). Hydroxychloroquine should be cautiously used in patients with known hepatic or renal dysfunction. The co-administered drugs with hydroxychloroquine excreted via liver/kidney may interact with hydroxychloroquine and modulate its pharmacokinetics and toxicity (Singh et al., 2020). According to Agstam et al., hydroxychloroquine and chloroquine are associated with a high prevalence of QT prolongation. Subsequently, rigorous monitoring is advised. A protocol designed to study Remdesivir, Hydroxychloroquine, Lopinavir, and Interferon-β 1a and its effect on mortality was assessed in the Solidarity trial. In this trial, the primary objective was to assess effects on in-hospital mortality,

including numerous hospitals in different countries. From March 22 to October 4, 2020, 11,330 patients were entered from 405 hospitals in 30 countries in all 6 WHO regions (WHO,2020). According to WHO, on July 4, 2020, the international trial discontinued the hydroxychloroquine and lopinavir/ritonavir group receiving the intervention of these drugs as it showed no reduction in the mortality of COVID-19 in comparison to the standard of care. The overall findings also tackled hydroxychloroquine's cardiotoxicity, but there was no indication of excess mortality due to this concern.

Antibiotics

Azithromycin

This drug is a macrolide antibiotic used primarily to treat respiratory infections. Azithromycin has additional immunomodulatory effects and has been used in chronic respiratory inflammatory diseases for this purpose (McMullan and Mostaghim, 2015). In the COALITION II study, the efficacy of hydroxychloroquine and azithromycin was assessed. According to Oldenburg, azithromycin showed no benefit on clinical outcomes, including clinical status or mortality, when added to the standard of care regimen. The results emphasized the findings from COALITION I, yet azithromycin's role should be evaluated earlier in the disease as it is the most commonly prescribed outpatient therapy for COVID-19 (Oldenburg, 2020). Thorough analyses of this antibiotic and its use for the current pandemic is needed for accurate prescription rationale.

Doxycycline

Through literature identification, doxycycline has been reached to treat the SARS-CoV-2 virus. As demonstrated with the dengue virus *in vitro*, doxycycline may also inhibit the replication of single-stranded RNA viruses via inhibiting the viral serine protease (Rothan et al., 2020). Tetracyclines can also induce activation of Protein Kinase C apoptosis of mast cells, thus decreasing levels of circulating agents (Sandler et al., 2005). These conclusions facilitate the conclusions that this drug could aid in the cytokine storm prompted by the virus inhibiting Mpro.

Interleukin-6 (IL-6) Blockers

Tocilizumab

This drug is mostly used for rheumatoid arthritis and currently demonstrate potential treatment for the fatal patient with COVID-19, improving lung tissue inflammation. Tocilizumab selectively and competitively binds to soluble expressing the IL-6 receptor (IL-6) and then blocking the signaling caused by IL- 6 (Song et al., 2020). Low-dose tocilizumab was currently

associated with rapid recovery for hyper inflammation in the patient experiencing COVID-19 as an adverse effect such as liver toxicity has been explored. As a result, efficacy needs to be assessed to adjust dosing as this drug is under review. Thus, it could suggest a good alternative for the patient in a terminal state (Singh et al., 2020).

Lenzilumab

Lenzilumab, a recombinant monoclonal antibody against granulocyte-macrophage colony-stimulating factor, has been shown to reduce several inflammatory mediators, making it another suggested treatment for cytokine-release syndrome, CRS (Melody et al., 2020). In the current ACTIV-5 Big Effect Trial comprising over 40 U.S sites to accelerate the innovation for COVID-19, investigating lenzilumab in a combination of remdesivir against remdesivir and lenzilumab placebo. The extensive trial's purpose is to evaluate clinical efficacy regarding different therapeutics at day eight and the amount of time it takes for a patient to recover from the disease. The experimental arm intervention is 200-mg intravenous (IV) remdesivir loading dose on Day 1, followed by a 100-mg once-daily IV maintenance dose up to a 10-day full course while hospitalized and 600-mg IV lenzilumab infusion every 8 hours starting on Day 1 for a total of 3 doses. N=100 (NIH,2020). As the recognition of this drug has become apparent as an immunomodulator and remdesvir, thorough testing is needed to determine its efficacy.

Kinase Inhibitors

Ruxolitinib

This drug is a JAK1/JAK2 inhibitor showing anti-inflammatory properties. It has been approved for the use of myelofibrosis and polycythemia vera (Vannucchi et al. t, 2015). Ruxolitinib displays valuable proficiency in severe respiratory expression. It is also associated with coagulopathy regarding COVID-19. The triggering of the innate immune response needs to be further studied regarding hypercoagulability with complement-mediated microthrombotic expressions (Connors and Levy, 2020). Ruxolitinib's interaction with the virus and ACE 2 receptors could mitigate the cytokine storm by targeting critical cytokines. In a study, seven cytokines markedly decreased in the patient receiving the drug: IL-6, nerve growth factor β, IL-12(p40), inhibitory migration factor, MIP-1α, MIP-1β, and VEGF in comparison to the control group (Cao et al., 2020) This finding could instigate further studies to incorporate Ruxolitinib in a larger controlled trial, identifying its relationship to the virus.

Baricitinib

On November 19, 2020, the FDA approved the emergency use of baricitinib combined with remdesivir in the hospitalized patient needing oxygen. According to the FDA, patients using the combination of these drugs had a reduction in recovery compared to patients receiving placebo in the Adaptive COVID-19 Treatment Trial 2(ACTT-2). Baricitinib acts as a JAK inhibitor interfering with the inflammatory process. Its therapeutic dose of 2mg or 4mg once daily is enough to inhibit AP2-associated protein kinase 1 (AAK1), a regulator of the endocytosis process implicated in the cellular viral entry process, making it a potential drug for COVID-19(Corman, 2020).

Corticosteroid

Dexamethasone

This drug is a glucocorticoid with anti-inflammatory and immunosuppressive actions. On SARS-CoV-2, nsp5 inhibits HDAC2 transport into the nucleus, impeding how it mediates inflammation and cytokine response. Therefore, dexamethasone's activation of histone deacetylase may oppose the action of SARS-CoV-2 (Ortolani,2020). Due to the RECOVERY trial, it was concluded that a controlled dose of dexamethasone, 6 mg daily for ten days, lowered mortality in hospitalized patients with COVID-19 and respiratory failure who required therapy with supplemental oxygen or mechanical ventilation (Horby et al., 2020). The use of corticosteroids is inconclusive but based on the literature, it could potentially decrease the mortality rate in acute patients.

Numerous drugs are still under investigation; the understanding of this virus is still relatively new. The drug reviewed are part of the current, proposed, or discontinued therapies for the virus. Revising the drug's efficacy through different randomized, double-blind, and controlled trials are of utmost importance to understand and target COVID-19. At this time, further research is needed to tackle this global health threat. Figure 1 depicts some of the current therapies utilized and their mode of action.

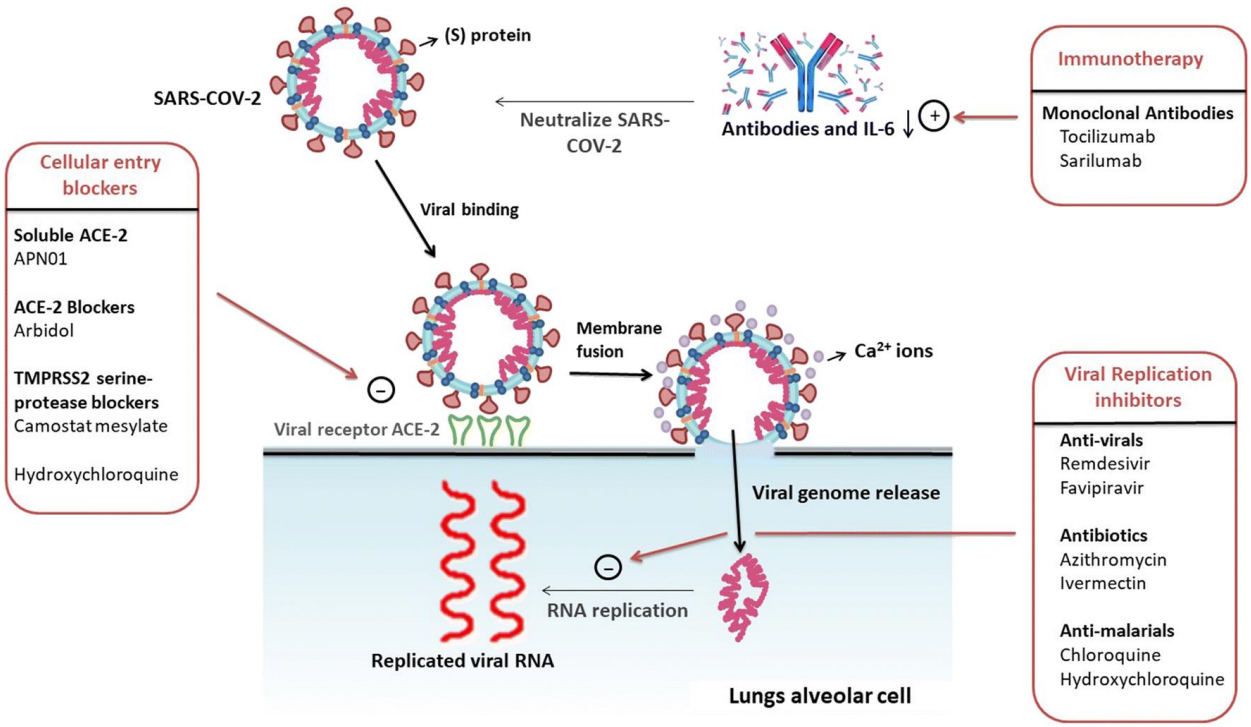

Fig 1: Mechanism of action of major repurposing agents against COVID-19. Jamshaid, H., Zahid, F., Din, I.u. *et al.* Diagnostic and Treatment Strategies for COVID-19. *AAPS PharmSciTech* **21,** 222 (2020). https://doi.org/10.1208/s12249-020-01756-3

Veterinary Medicine

Zoonotic links are vital to identify and understand its wide host range, especially with CoVs. The initial assumption with SARS-CoV-2 and its relation to animal source was from Wuhan Seafood Market. In Wuhan, Hubei Province, China, restaurants are famous for offering various small and large domestic animals, wild animals, and live animals, including poultry, rabbits, bats, snakes, pangolins, turtles, hedgehogs, badgers, and marmots for human consumption (Tiwari, 2020). According to Li et al., bats appear to be the natural reservoir or source of origin for SARS-CoV-2; the intermediate host is still in question. Amongst CoVs, recent zoonotic ones such as SARS-CoV, MERS-CoV, and SARS-CoV-2 gained higher importance due to the severity of disease in humans and their global spread (Rothan, 2020). In the current COVID-19 pandemic, laboratory findings confirmed that SARS-CoV-2 is also 96% identical to the bat CoV at the genomic level, and hence bats may be the primary source of this zoonotic spillover (Andersen, 2020).

Strains have been isolated from pangolins reporting that the E, M, N, and S genes encoding structural proteins between pangolin coronavirus (pangolin-nCoV) and SARS-CoV-2 showed 100,

98.6, 97.8, and 90.7% amino acid identity, respectively (Xiao et al., 2020). This finding could aid in further studies focusing on pangolins as intermediate hosts, yet at this point, it is uncertain. As mentioned earlier, minks have also brought attention as a potential intermediate host after outbreaks in the Netherlands' farms. The most probable explanation for the widespread infection on the mink farms is the transmission of the virus by humans and subsequent transmission among the minks. Ferrets, which are near related to minks, were also able to transmit the virus to other ferrets under experimental conditions; transmission was observed under direct and indirect contact (Oreshkova, 2020).

The human interaction with their pets could also possess a risk. Among the investigated animals, cats have the highest proportion of ACE2 and TMPRSS2 co-expressed cells regarded as SARS-CoV-2 target cells (Shi et al. 2020). Effective drugs have been evaluated in feline coronavirus inhibiting the main protease of SARS-CoV-2 Mpro. It autocleaves itself between nsp4 and nsp6 before processing the overlapping polyproteins pp1a and pp1ab at 11 cleavage sites (Muramatsu,2013). Mpro enzyme has crucial influence for SARS-CoV-2. In a recent study by Vuong et al., the prodrug GC376 and GC373 were examined to inhibit SARS-CoV-2. These drugs have been tested in feline infectious peritonitis (FIP), effectively inhibiting Mpro of feline coronavirus. Both GC373 and GC376 inhibit the SARS-CoV Mpro and the SARS-CoV-2 Mpro in vitro at nanomolar concentrations (Vuong et al., 2020). These findings denote that these drugs should be contemplated for treatment of COVID-19 in human trials.

Further studies of SARS-CoV-2 infection in diverse animal species are needed to understand the influences of transmission in different species. As of now, identification of the reservoir host is fundamental for the advancement of zoonotic links. As in minks' case, we learned human-animal reverse spread, which could lead to new antigenic types of SARS-CoV-2. Thus, the critical framework for future studies was initiated by Mpro and its inhibiting capacities by GC373 and GC376.

Conclusion

COVID-19 has spread rapidly in the past year, causing concern, uncertainty, and fear as it became a public health crisis. In this literature review, the repurposing of drugs was a tackle, and the identification of divergences still exists as this disease is relatively new. Interdisciplinary contributions in human and veterinary medicine should be promoted, and in so, the prevention of future outbreaks could be better assessed. Not only this, but the application of AI is innovative and

would enhance early detection, treatment as well as the development of new drugs by offering updated information at a faster rate. Numerous drugs are being approved, refuted, and reviewed to enable strategic interventions. As there is no approved drug to treat this disease, it is imperative to follow the general public guidelines, wear a mask, practice social distancing, and practice good hygiene. In the future, drugs reviewed and a combination of old or new drugs could potentially resolve this pandemic. Understanding basic pathogenesis driven by computational analysis could redirect drug recycling as the treatment for this pandemic.

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